93

THE EVOLUTION OF DOMINANCE

BY R. A. FISHER.

(Received February 25, 1931.)

CONTENTS.

I. EARLY SPECULATIONS ON DOMINANCE.

It was recognised early in the discussion of genetic phenomena that the two great facts demonstrated by Mendel's breeding experiments in the garden pea *(Pisum)*, segregation and dominance, had very different bearings upon our interpretation of genetic and evolutionary phenomena. Segregation, due to the particulate nature of the hereditary elements, was a primary and essential fact in the hereditary mechanism; dominance was an additional fact, not essential for explaining the hereditary mechanism, but rather an obstacle to its understanding, as is shown by the frequent use of the blue Andalusian fowl, a heterozygote quite unlike either the black or the flecked white homozygote, in explaining the Mendelian theory. Nevertheless, its immediate practical importance appears from the universal recognition of the 3 : 1 ratio, rather than the genetic 1:2:1 ratio, in the offspring of selfed or interbred heterozygotes. And, just because it is a fact logically independent of the factorial system of inheritance, it has exerted a very important influence on the evolutionary speculations of the early writers.

The first general statements respecting dominance referred dominance to certain characters rather than to certain genes. Thus, numerous cases in which the recessive was white, or of a lighter colour, or of a simpler pigmentation, than the dominant, suggested, in spite of exceptions, a general notion that pigmentation is dominant to absence of, or less, pigmentation. To this stage in genetical concepts belong such statements as that tallness is dominant to shortness, not in reference to a particular pair of allelomorphic genes studied by Mendel in *Pisum*, but as a biological

principle already proved in *Pisum*, the general applicability of which would be explored by further research. While dominance was thought of in this way, the available examples formed a general impression that the dominant characters were more positive, or complete, than the recessive characters, an idea which seems to have influenced later speculations a good deal.

Facts, however, soon headed off speculation as to the dominance of characters, as opposed to that of particular genes. Both dominant and recessive whites were found in fowls, both dominant and recessive piebalds in mice. Breeding tests showed that the different Mendelian factors involved had no genetic connection; they merely manifested themselves by the same or similar somatic contrasts. Nevertheless, dominance or recessiveness were evidently not assigned at haphazard; knowing the effect of a factor, one could make a shrewd guess as to which phenotype would be the dominant. On what were such guesses based? What rules did the incidence of dominance appear to obey? Two criteria were prominent:

(i) The recessive was often defective. Deficiency of pigmentation, of chlorophyll in plants, or of the banded structure of the hairs in the wild or "agouti" pattern in rodents, were clearly of this type; also such structural defectiveness as is shown by the inner ears of "waltzing" mice, and in many cases of malformation so gross as to be classed as monstrous. The defects of the wings and bristles of *Drosophila* added a number to the list of recessive defects.

(ii) Novelties were usually recessive. In such a plant as the Sweet Pea *(Lathyrus odoratus),* the Mendelian analysis of the numerous cultural varieties showed in every case that the characteristic of the dominant genotype was that of the presumptive wild ancestor. With the study in *Drosophila* of mutants certainly arising in culture, it appeared clearly that these were generally recessive to the genes of the wild type of fly; and this in spite of the fact that dominants were more easily and more quickly detected, and were much valued by the geneticists.

A theory which connected some of these facts, and, in spite of its inherent difficulties, has, in the absence of satisfactory alternatives, exerted a considerable influence, was put forward by Bateson and Punnett, as the "Presence and Absence Hypothesis." According to this view the recessive genotype was totally lacking in a gene which was present in the dominant genotype. Dominance was due to the supposed fact that a single gene in the zygote was capable of exerting the same influence as if the normal pair had been present. The recessive genotype, lacking these genes altogether, displayed its genetic deficiency by a visible somatic defectiveness. Mutation consisted, usually if not always, of the loss of a pre-existent gene. The evolutionary consequence was boldly drawn by Bateson that the genetic outfit of existing animals and plants was a residue or remainder of the complete genetic outfit of their primordial ancestors. Evolution consisted in "unpacking" the germ plasm, all the possibilities of which had been present from the first. A somewhat comprehensive process of creation was relegated to the distant past.

The fact that some mutations were at least partially dominant was met by the ingenious, but dangerous, hypothesis that they were due to the loss of "inhibitors." In cases where dominance is absent or incomplete, it was supposed that for some

special reason the single gene could not produce the same effects as a homologous pair. These special explanations of the rarer types of relationship damaged a good deal the general plausibility of the theory; and in the case of the dominant characteristics of several breeds of poultry, to which the wild type is recessive, Punnett was willing to consider the view that "something new had been added."

The "Presence and Absence Hypothesis" became untenable when it was shown that not two only but three or more different allelomorphs often existed belonging to the same Mendelian factor. Not more than one of these could be postulated as an "absence," and the admission, in some cases, of two different kinds of "presence," one completely dominant to the other, greatly strengthened the view that in other cases also the recessive gene was not a mere "absence." That mutations do not consist simply of losses was decisively contradicted by the occurrence of reverse mutations, and though for a time many of the earlier reports of these could be explained away, their occurrence has recently been fully demonstrated by Patterson and Muller (1930) by the use of X-rays. If a mutation is a "loss," its reversal must be counted a "gain," and once such gains are admitted the ground for supposing that mutations in general are frequently of so simple a character as a mere loss falls away.

In view of these facts, the original presence and absence hypothesis has been replaced in practice by the more tenable, though perhaps too simple, view that a series of multiple allelomorphs may differ only quantitatively in respect of some one physiological or biochemical function, so that in such a case as the white-eye series in *Drosophila*, we should think of the wild red-eyed fly as containing fully active genes, and the various mutant allelomorphs as containing, in order of the depth of pigmentation, genes of the same kind, only less and less active. That this may in some cases really be true is strongly suggested by the fact that a mutation such as Notch 8, which may be regarded on good evidence as really due to the absence of a small tract of chromatin, containing the white eye locus, behaves in conjunction with the allelomorphs of white eye as though it contained the most extreme member of the series. The supposed connection, however, between such inactivation and recessiveness has been challenged by Ford (1930), who points out that this very series are not recessive to the wild type in respect of certain internal characters.

II. GENERAL EVIDENCE AS TO DOMINANCE.

Setting aside the suppositions:

(i) that Mendelian allelomorphs are always pairs which can be formally identified as the presence or absence of something;

(ii) that mutations are always or usually merely losses or inactivations of nuclear material; and

(iii) that such loss or inactivation is in itself a sufficient cause of recessiveness; we are in a position to reconsider what the evidence available really has to tell us as to the incidence, and causes, of the phenomenon of dominance.

It should be emphasised at the outset that dominance is an observational fact, involving a comparison of the somatic characters of three different genotypes, two

homozygotes and the heterozygote formed by crossing them. In such a comparison it is evident that the three genotypes compared should, properly, differ only in the one factor under consideration, otherwise the effects of other factors, or of dominance in other factors, will be involved. If the heterozygote is found to be indistinguishable from one of the homozygotes, that homozygote is said to be completely dominant and the other completely recessive. If the heterozygote were equally different from both homozygotes, dominance would be absent, and neither gene should be said to be dominant to its allelomorph. Between these extreme cases we may recognise cases of incomplete dominance in which the heterozygote resembles one homozygote perceptibly more than the other, while resembling neither completely. The phenomenon is not a genetic one in the sense that further experimental breeding can throw light on an ambiguous observation, but is purely somatic and observational. In view of the fact that all three genotypes are usually variable, increased precision may be obtained by observing groups of the three genotypes to be compared, and observations made in this way are susceptible to any degree of biometrical refinement.

The terms as above defined have not been used very strictly in the literature. For example, many lethal genes have visible effects; that is to say, one homozygote is inviable while the heterozygote differs visibly from the viable homozygote. Such genes are usually spoken of as dominants, or sometimes as lethal dominants. They should, I think, be called visible lethals in contradistinction to the recessive lethals which have no visible effect when heterozygous. Even the elusive class of lethal genes which cause death both in the homozygous and the heterozygous condition should, I suggest, only be regarded as dominant lethals if the two lethal phases are known to be similar up to the time of death. Again, where, as in *Drosophila*, a definite wild type is available as a basis for comparison, it is usual to speak of all mutants which are not completely recessive as dominants, merely to indicate that the heterozygote is distinguishable from the wild type, without reference to whether the heterozygote is more like to the wild fly, or to the homozygous mutant.

The factors, the behaviour of which has been studied by experimental breeding, fall broadly into three classes:

(a) Mutations arising in culture, which in the past have been principally available in non-domesticated animals such as the fruit flies *Drosophila* and the shrimp *Gammarus chevreuxi*, which are bred as convenient genetic material. Such mutations, induced by X-rays, will, it is to be supposed, soon become abundantly available in many other animals and plants.

(b) Differences between different varieties of domesticated animals and plants, which have originated presumably by mutations in the past, but whose effects have often been modified, by combination with other factors, to a large extent in the course of human selection.

(c) Differences between the various forms of species which are polymorphic in nature.

The evidence as to the incidence of dominance provided by these three classes is naturally very different in character, and it was especially the simplicity of the

rules followed by the mutants that first led me to speculate on the subject. The conditions for studying dominance are here much better than with domesticated races, for the mutant will usually differ from other members of the stock in which it arose only in one factor affecting the characteristics to be observed.

The great majority of mutations in *Drosophila* are lethals, nearly all completely recessive, though a minority have visible effects. With respect to the non-lethal mutations in *Drosophila melanogaster* I found, on classifying the 221 different mutations reported by Morgan, Bridges and Sturtevant (1925), that 208 were classified as recessives and thirteen as dominants. The recessives were in fact sixteen times as numerous as those classed as dominant, and of the thirteen cases of dominance recorded the dominance was in every case incomplete; that is to say, the homozygous mutants were always distinguishable from the heterozygotes, which, indeed, showed all degrees of intermediacy between the wild type and the homozygous mutant.

The second fact of importance, which seems to be general in the *Drosophila* mutations, is that in the many cases of multiple allelomorphism, where several distinguishable mutant genes have arisen from the same gene of the wild fly, the wild-type gene is completely dominant to all its mutants, while these give with each other heterozygotes of an intermediate character. Dominance is, in fact, conspicuously absent from the genes of such allelomorphic series with the single exception of the particular allelomorph which prevails in the wild population.

The phenomenon of recessiveness to the wild type is also very generally observable in the domesticated races of animals and plants, though crosses between different varieties of these provide generally far less suitable material for the study of dominance than do the mutants that arise in culture. It is particularly fortunate therefore that a very thorough study of the albino series of multiple allelomorphs, which occurs in most rodents, has been carried out by Sewall Wright (1925) in the guinea-pig. Using five allelomorphs of this series, Wright bred the five homozygous and the ten heterozygous types, in which they may be combined, in sufficient numbers to study both the average depth of pigmentation of the red and the black parts of the animal and its variability between different individuals of the same genotype. The results of this investigation were perfectly clear-cut and decisive. The five homozygous genotypes were all easily distinguishable. Of the ten heterozygotes four, which contained the wild gene, were indistinguishable from the wild homozygote, showing its full pigmentation in both respects. The remaining six heterozygotes, containing two different mutant genes, were, in each case, intermediate in appearance between the two corresponding homozygotes.

This remarkable, and uniform, behaviour of the allelomorphic series, supplies, I believe, a direct clue to the interpretation of dominance phenomena generally, for if we are to assume that in the course of evolutionary change individual genes have been replaced, for whatever reasons, by mutant allelomorphs, it is evident that the member of an allelomorphic series which was prevalent in the wild population at one stage must have been in the past, and, by reverse mutation, might come to be in the future a mutant member of the same series. The rule that the wild-type gene must be dominant to all its competitors could only continue to hold if, in the course of

evolutionary change, it became dominant to them. The cause of dominance should on this view be sought as a by-product of the causes which lead one gene rather than its allelomorphs to prevail in the wild population. It becomes necessary at this point to enquire into the possibility of the modification of dominance by selective agencies.

III. SELECTIVE MODIFICATION OF THE EFFECTS OF MENDELIAN FACTORS.

Evidence of the selective modification of the effects of Mendelian factors is, in fact, when looked for, exceedingly abundant. Anyone who has bred, for example, mice, for genetic purposes, knows with what contempt his productions would be viewed by the judge at a fancier's show. He knows that the show "Dutch" mice are recessive pied, but their shoulder patches have been suppressed, the head markings have been confined to two beautifully symmetrical ovals round the eyes and ears, and the rump markings confined to a broad straight band across the body. The ideal prize-winner may be a rare product of its own genotype, and probably has to be heterozygous for one or more special factors. Its genetic production would certainly require a very detailed study of the factors which modify the pied pattern. And the same is true of the show product in nearly all the fancy breeds of animals; the geneticist can only recognise the gross differences caused by those factors whose effect is pronounced enough for him to study. The showman, by selecting a multitude of modifying factors, has modified the crude genetic type almost out of recognition.

More immediately to the point is the spontaneous modification which has frequently been observed in mutant strains soon after their isolation. Several workers with Drosophila have reported cases in which a mutation, having well-marked bodily effects, has been set aside to be bred in stock bottles until it could be used. After several generations of breeding in this way the mutant has appeared to be less distinctive and more normal than it was at first; it seems to have reverted somewhat towards the wild type. Such mutations often show, from the first, some degree of reduced viability, besides some variability in the intensity with which the mutant character is manifested, or, in other words, in the violence of their reaction to the mutant gene. The modification of the mutant genotype which has taken place is apparently due to the selection of modifying factors, which mitigate to some extent the effect of the mutation. That this is the true explanation has been verified by out-crossing the modified mutant to unrelated wild flies, and recovering the mutant by inbreeding the offspring. The mutant type so recovered has been partially de-modified, and shows a return towards the extreme condition originally observed.

A very similar case has been reported by Prof. F. E. Weiss, of a mutant nasturtium, which had modified leaves and was very sterile. It was in consequence propagated with considerable difficulty, and by the time that a satisfactory strain was obtained the leaves were found to have reverted, to a considerable extent, towards the normal nasturtium form. Mr E. B. Ford also informs me that it is the general rule among the mutants he has studied in Gammarus that they have at first an extremely low

viability, and that only after considerable modification by natural selection are healthily viable stocks obtained.

It has, of course, long been known that genes which have a pronounced effect in the presence of some other gene may have none in its absence. Terms such as epistatic factors, complementary factors, specific modifiers, etc., have only been introduced in recognition of particular cases of the general fact that the effect of any one genetic substitution depends upon the gene complex, or genetic background, in which the substitution is made. What the particular cases cited demonstrate is that, even in small isolated stocks, a sufficient variety of modifying factors is usually present to produce, in a few generations, a considerable effect upon the appearance of a homozygous mutation subjected to direct selection. It would be astonishing if such selection were in any degree less effective in modifying the appearance of the heterozygote, had the heterozygote been the phase subjected to the selective action.

IV. SELECTIVE ACTION ON THE HETEROZYGOTES OF RECURRENT MUTATIONS.

Now it is certain that many of the *Drosophila* mutations occur with mutation rates of about one in a million, that is to say, that in each generation one in every million of a particular kind of gene undergoes the transformation in question. There is no reason to suppose that the mutation rates in the wild population are, or have been, lower than those observed in culture. As to the length of time during which the same mutation has been occurring, we have direct evidence that the mutations of different species in *Drosophila* are frequently homologous; many mutations therefore certainly antedate the fission of these species. This, moreover, is only a lower limit, for the direct proof cannot be extended beyond the range of species crosses. The close analogy, however, between the different allelomorphic series found in rabbits, rats, mice and guinea-pigs, indicates strongly that the same mutations have here been occurring through a great part of the period occupied by the differentiation of the rodents, and makes it seem less improbable that a mutation such as albinism, which occurs in the most diverse orders of mammals, has been occurring throughout the history of the class. It seems, indeed, impossible to set an upper limit to the antiquity of the oldest mutations which may be now occurring, for a lethal factor causing the death of the zygote in the one-celled stage might, for aught we know, have persisted in occurring throughout the whole history of the metazoa. It is probable, however, that the genetic changes which have brought about the evolutionary transformation of species have been accompanied by corresponding changes in the frequency and kind of the deleterious mutations to which their germplasms are prone, so that, although many mutations are undoubtedly enormously ancient, there is no reason to regard them as more ancient than those morphological features of animals which are regarded as of systematic importance.

If such a mutation has persisted in occurring among the ancestry of an existing population, and has been constantly kept rare by counter-selection, it is a matter of some importance to calculate the average frequency, in each generation of this ancestry, of the heterozygous and of the homozygous mutant; for these frequencies

should measure the efficacy of natural selection acting upon the modifying factors, in mitigating the reaction of the existing population to the mutation in question. It appears that the heterozygote will, in such cases, be so enormously more frequent than the homozygote that, except when its viability is within a very minute fraction equivalent to that of the wild type, and except in the case of sex-linked factors, the modification of the homozygous mutant need not be considered. With respect to the heterozygote, the case is very different. Its frequency will be, of course, proportional to the mutation rate, but will depend also greatly upon its viability, or frequency of parenthood. If, for example, this differs from the normal by only one per cent., with a mutation rate of one in a million, the proportion of heterozygotes in each generation in the ancestry of the existing population will have been about one in five thousand. With a viability of ninety per cent. the fraction has fallen to about one in sixty thousand, and at fifty per cent. to one in seven hundred and fifty thousand. These fractions should, in my view, represent the rates of modification of the heterozygotes in nature, in comparison to the rate of modification which could be brought about by selection applied to a population consisting entirely of mutants. Since this, even when applied to homozygotes, is certainly capable of producing noticeable effects in a short period, it appeared to me, and I can see no reason to doubt the soundness of the conclusion, that natural selection of the heterozygotes must be an agency in causing them more and more to resemble the non-mutant homozygotes, acting with a combined intensity and duration which cannot safely be neglected.

Since, however, the efficacy of such minute selective actions has been questioned, not on the ground that the time available is insufficient, but that they would be ineffective however long the time available, and since it is manifestly impossible to prove experimentally that a selective intensity one ten-thousandth of another will really produce the same effect in ten thousand times the time, it will be better, as in the other cases indicative of the modification of dominance, to which this objection does not apply, to follow out the qualitative consequences of the theory, and compare them with such known facts as are relevant.

If we suppose that at its first appearance the mutant heterozygote was intermediate in appearance and viability between the normal form and the mutant homozygote, its subsequent fate would depend greatly upon its initial viability. We have seen that as the viability improves, the intensity of selection is greatly accelerated, consequently those with an initially high viability would have time to become completely normal in appearance, before others, more heavily handicapped at the start, had made any appreciable progress. After the heterozygote has become completely normal, and the mutation in question has become completely recessive, a second process of modification will commence, this time in the homozygote, which as calculation shows (Fisher, 1928 *a)* can now be maintained at a sufficient frequency in the population for this process to be effective. In the case of the homozygote, the initial disadvantage will probably be considerably greater, and the initial rate of improvement enormously slower. Nevertheless, in favourable instances it, too, may attain a high level of viability, in which case it also will probably be modified to an extent

which renders it indistinguishable from the normal type. Such factors would, in themselves, necessarily be overlooked, for they produce no visible effects. They may, however, occasionally be brought to light as specific modifiers of other factors which are being studied.

In the case of lethals in which the homozygote invariably perishes, the second stage of modification is of course impossible, and the pause when the heterozygote becomes normal is indefinitely prolonged. Consequently we should expect the greatest number of factors to be accumulated at this stage, and it is noteworthy that by far the most numerous class of mutations occurring in Drosophila, either naturally or under the influence of X-rays, are completely recessive lethals. The heterozygotes of lethal genes might be expected to be more heavily handicapped than those of non-lethal genes, and we accordingly have a considerable class of visible or "dominant" lethals. Of the non-lethals, as we have seen, sixteen out of seventeen are classed as recessives, and may be regarded as having completed the first stage of their modification. The few that remain as incomplete dominants might conceivably be mutations of sufficiently recent origin as to have made, as yet, but little progress in modification. The fact that they have appeared in culture does make it probable, however, that their mutation rate is fairly high, and, unless mutation rates can change suddenly, which seems improbable, this in itself would seem to imply that they are probably not recent. The alternative view that they are on the whole somewhat heavily handicapped in respect of viability seems completely to fit this group of cases.

V. THE ABSENCE OF DOMINANCE IN CASES WHERE SELECTION CANNOT BE POSTULATED.

We have seen that a general view of the dominance phenomena exhibited by the mutants in Drosophila accords well with the opinion that recurrent mutations having deleterious somatic effects have become gradually recessive to the prevalent wild genes; and that the facts suggest further that the selective action has been sufficiently rapid to have effected a considerable change in the majority of those cases which come under observation. Important evidence is, however, also available from cases in which, in the absence of such counter-selection, dominance is likewise found to be absent, and these classes of observations, which we shall now consider, make it difficult to believe that explanations of dominance, which rely upon special assumptions as to the biochemical situation in the nucleus, can have more than occasional applications.

We have already mentioned the absence of dominance which is usual between the different mutant allelomorphs of the same gene. In this case it is evident that although one allelomorph may well be more advantageous than another, the extreme rarity in nature of heterozygotes carrying in the same locus two different mutant genes, and the low probability of such individuals contributing to the ancestry of the existing population, will have precluded the modification of these heterozygous types by natural selection.

Mr E. B. Ford (1930) has called attention to the extremely important fact that many of the Drosophila mutations such as the white-eye series, and the body-

colour mutants "sooty" and "ebony," while recessive in their effects upon the colour of the body and the eyes, are yet not recessive in the minute constant effects which they exert, as was shown by Dobzhansky (1927), upon the shape of the spermatheca. Ford points out that the intensity of selection upon such a character as body colour is probably considerable, as is, with equally high probability, that on the pigmentation of the eyes, but that in the case of a small change in the proportions of an internal organ we have exceptionally good grounds for presuming the absence of selective action. Consequently recessiveness would only have been produced if the genetic changes needed to modify the external characteristics had also modified the internal organs towards the normal shape. It is difficult to reconcile a series of cases of this kind, which, apart from special investigations, would inevitably have been overlooked, with the view that there is anything in the intrinsic nature of mutations, as such, which makes for recessiveness.

(c) Many cases are known in which a mutant is completely recessive to its wild allelomorph when these are compared in animals otherwise of the wild type, but in which the recessiveness becomes incomplete when they are compared in the presence of other mutant factors.

G. D. Snell, in a recent summary (1931) of the mutants which have been studied in mice, supplies several instances of this. Thus, in the *albino* series he notes that full colour is normally completely dominant to all other members of the series, but that., in the presence of "pink-eye," heterozygotes carrying the albino gene, or even chinchilla, another allelomorph of this series, are appreciably lighter than those homozygous for colour. He further mentions that mice heterozygous for albinism have been reported by more than one worker to develop large patches of white or silvered hair as they grow older, and that when treated at ten to fourteen days of age with just sufficient X-rays to cause the hair to fall, they regenerate a semi-white coat. Again, "brown" or "chocolate" is usually entirely recessive to its allelomorph "black," but pink-eyed non-agouti mice heterozygous for brown are distinguishable from those homozygous for black. Still more striking is the effect of "silver"; for silver mice heterozygous for brown show a greatly intensified silvering, the underfur being practically white. Chocolate-silvers, despite the two chocolate genes, are stated to be often darker than the heterozygotes, though distinguishable from them by the colour of the unsilvered hairs. With *recessive pied* the incomplete recessiveness is so frequent that Snell describes it as an imperfectly recessive character. In the presence of the lethal "dominant pied," heterozygotes carrying "recessive pied" are undoubtedly distinguishable by their more restricted pigment; in my own experience, however, litters sired by wild mice on recessive pied mothers show no sign of white spotting; recessive pied seems thus to be completely recessive when examined in conjunction with the wild gene complex.

In *Drosophila* the case of "forked" and "semi-forked" is of interest as showing that a modifier of dominance may be almost without effect upon either homozygote. In the wild fly forked is an ordinary recessive which produces a shortening, twisting and thickening of the bristles. It is sex-linked, so that dominance can only be examined in the female. In the course of Dr Lancefield's experiments with this

factor in 1918 the mutant semi-forked was discovered; this mutant has no distinguishable effect upon the homozygous forked females, or upon the forked males. It produces, but rarely, a slight shortening of the bristles in normal flies. Females heterozygous for forked, however, are modified by it into clear intermediates. In this connection we may recall also that the white-eye mutant in *Drosophila*, which, by itself, is a typical recessive, has, when heterozygous, a distinct diluting effect on flies homozygous for any of several other light eye-colour mutants. The fact that genetic combinations can be made up, in which the heterozygote differs from the non-mutant homozygote, is again difficult to reconcile with any general biochemical explanation of dominance, and indicates that we should look for some other explanation of the fact that these genotypes resemble one another so closely, when the effect of the gene is examined against a wild background.

(d) A case of very particular interest was brought to my knowledge by Mr J. B. Hutchinson, and arose in the investigations into the genetics of the cotton plant, which Dr S. C. Harland has been carrying out in Trinidad. The interest of the case in the present connection has led to a number of further experiments, and to consequent delay in publication, so that the original facts I can now give are subject to the confirmation or reinterpretation afforded by the later experiments.

It appears that a mutant form known as "Crinkled Dwarf," which occurs in the Sea Island cottons, is, in that species, a simple recessive, while in other New World species it is not known to occur. It has been identified with the "wrinkled-leaf" mutant which is known in Egypt in varieties closely allied to Sea Island. Dr Harland has crossed crinkled-dwarf mutants in Sea Island cottons with two other New World cottons of the Upland and Peruvian groups respectively. Substantially the same results were obtained in each case. The F_1 plants were slightly modified by the mutant, showing even at this stage some incompleteness of dominance. In the F_2 formed by self-fertilisation every degree of dominance seems to have appeared in a quite unclassifiable series. It would appear therefore that the Sea Island cottons, among which this mutant occurs, differ from other New World species in a number of modifying factors which function together to render it dominant to the mutant. Dominance in this case must have been evolved since the separation of Sea Island from the other New World cottons. The case is of special interest in opening up the possibility of examining the genetical behaviour of the actual modifiers by which dominance has been produced.

VI. FACTORS DISTINGUISHING DOMESTIC RACES.

The genetic analysis of the factors distinguishing the different races of animals and plants which have arisen under domestication is at present in a very imperfect condition. The influence of man on these species has been, broadly speaking, of two kinds; he has enhanced for his own use certain qualities, such as fleetness, fecundity, milk yield, docility and so on, which constitute the utilitarian characteristics of our domesticated species. He has on the other hand persistently favoured novelties of all kinds, oddities in form and coloration, or in movement, as in the tumbler pigeon or

"waltzing" mice. It is with this latter class of variations, almost exclusively, that genetic analysis has been successful, and there can be but little doubt that we are dealing here with the results of mutations similar to those which have been known to occur as such, and which had been, in all probability, occurring occasionally in the wild population for ages prior to domestication. It is not surprising, therefore, that the aggregate of available genetic results in this field should add little that is new, and should, broadly speaking, merely confirm the results obtained from the study of known mutations. That portion of the inherited variability from which new knowledge is to be expected, and which is from all points of view of the greater value to mankind, is apparently beyond the reach of Mendelian research as currently practised, and must await the development of more efficient and comprehensive quantitative methods.

In almost all species in which the peculiarities of domesticated forms have been investigated, a number of recessives, and but very few dominants, have been found. Of these dominants the great majority either show incomplete dominance or are in reality visible lethals. A single exception occurs in mice where, while the "dominant pied" and the "yellow" genes are lethals, yet the "white-bellied agouti" is a viable and apparently complete dominant to the wild, dark-bellied form. The white-bellied agouti is, however, scarcely a domesticated race, since it has been repeatedly caught wild, and we should perhaps more properly regard the wild mouse as possessing two forms, suited perhaps to different ecological situations, but distinguished only by a unifactorial difference. In rabbits, too, the dominant black, and the dominant, or English, white, are incompletely dominant, but one exceptional case occurs to the rule ordinarily governing allelomorphic series, in that the Himalayan breed seems to be completely dominant to the albino, with which it is allelomorphic. In guinea-pigs the reversed or rosetted fur is dominant to the wild form, but in this case there is no doubt that the condition has been much enhanced by human selection, for the basic gene for reversed fur, when alone, seems only to affect a small area in the hind leg. Whether this basic gene is really a dominant when introduced into the wild cavy has, I believe, not yet been determined.

In contrast to such rather equivocal exceptions as have been mentioned, the domestic fowl supplies in its various breeds a large number of non-lethal genes which are dominant to those of the presumed ancestor, *Gallus gallus*. These include a dominant white and a dominant black affecting the plumage, the sex-linked dominant "barred" which introduces a white bar or bars on the feathers, and a factor which replaces the black breast of the wild cock by buff or chestnut, a factor for black internal pigment, and among structural characters factors for polydactyly, feathered feet, and crest, and for the comb characters rose, pea, and duplex. The evidence for dominance is in many of these cases somewhat vague, being usually derived from crosses between breeds in which many other factors are involved, and several of them, for example both pea and duplex combs, are recorded as showing very variable degrees of dominance in different breeds. Moreover, in some cases, such as the sex-linked gene for silver, which are generally spoken of as dominants, the term has evidently been used extremely loosely, since the heterozygote is usually,

if not invariably, of quite intermediate appearance. Nevertheless, looking at the mutant genes in domesticated poultry in the aggregate there can be no doubt that cases of regular and apparently complete dominance do occur with a frequency entirely unparalleled in any other domesticated plant or animal.

It should be noted that in poultry ordinary recessives, such as recessive white, and silky feathers, are quite frequent, as also are visible lethals; what is exceptional and what, on any view, must require a special explanation, is the high frequency of fully viable and complete, or nearly complete, dominance of the domesticated over the wild character, which is found in this species. The phenomenon is not found in other domesticated birds; it is also noteworthy that none of the factors under discussion is known to have arisen from a recorded mutant; all are characteristic of existing breeds, some of which must be extremely ancient. These facts suggest that the cause of the phenomenon may usefully be sought in the early history of the domestication of this species.

I formerly thought that the theory of the selective modification of dominance had no solution to offer of this particular problem. On considering, however, the facts which suggest that special causes may have been active during the earlier stages of domestication, I have come to see (1928 *b)* a possible explanation which seems at the moment not improbable, and which has the advantage of being susceptible of experimental verification. It is evident that many mutations, which in the wild state were kept rare by counter-selection, have been in domestication not merely sheltered from competition, but favoured by man for their novelty. The mutant forms are valued by man, and are regarded by him with interest, and in some historical cases with superstitious veneration. In most species the novelties appear as recessive segregates, and can at once be bred true. It appears to me that the exceptional circumstance needed to explain the case of *Gallus* lies in the fact that the domestic hen is, in its own country, constantly liable to be mated by the wild cocks; this is known to be frequent in India at the present day, and must have been the prevalent condition in the early stages of domestication by jungle tribes. In these circumstances the only mutant novelties which could be established in the domestic flocks would be those in which the heterozygote differed somewhat from the wild type. The selected mutations must, in fact, be not completely recessive. Moreover, the distinctions of the breed could only be maintained by human selection, and such selection would necessarily favour those individuals which differed most clearly from the wild type, or, in fact, those in which the mutation was least recessive or most dominant.

This case of human selection for dominance of the mutant differs from natural selection for dominance of the wild type in that, whenever the brood is half-wild, the whole population exposed to selection consists of heterozygotes, instead of only one in some five or ten thousand. Its evolutionary effect in the absence of inbreeding will, therefore, be correspondingly rapid, and it would not be surprising that great changes should be produced in a thousand generations, or even much less; especially if we give weight to the statements, respecting several of these mutants, that very variable degrees of dominance are shown in different breeds. It should be possible

to put this explanation to an experimental proof, for, if the existing wild population has not been appreciably contaminated by inter-mixture with domesticated breeds, there is no reason to think that its reaction to these mutants should not be in its primitive condition. In this case we should expect that, if any of these mutants were introduced by continual back-crossing into a strain of genuinely wild Gallus, the historical process of modification would more or less rapidly be undone, and the mutant would be found to be neither dominant nor recessive, but one having a distinctly intermediate heterozygote, as in the case of the "blue" Andalusian. Even in the most favourable circumstances, this process would take several generations, and might be greatly retarded by linkage. It has, however, been possible to commence the experiment with a number of the most pronounced cases of dominance, and in four or five years it should be possible to decide whether the reaction of the wild Gallus to these mutants is or is not decisively different from that observed in the domesticated breeds.

VII. SELECTION AMONG MULTIPLE ALLELOMORPHS.

It has been pointed out by both Wright (1929) and Haldane (1930) that, in certain cases, the recessiveness of a mutation might be the inevitable consequence of the biochemical role played by a gene, or its immediate products; for, if we imagine these to act as enzymes, or, in general, as components of a series of chemical reactions proceeding at a certain rate, it may well be that this rate is controlled by components of the system other than the one under consideration, and that this one is always present in saturation, in the sense that no appreciable effect would be produced by increasing the activity of the gene in question, or by decreasing it to a small extent, although a more considerable diminution might largely retard the whole chain of reactions concerned, and so produce the visible effects of a mutation. If, moreover, the genes normally present in the wild species possessed at least double the activity necessary to produce their normal effects, then the complete inactivation of one of the pair of homologous genes would be attended by no noticeable consequences ; whereas, if both were replaced by inactive allelomorphs, an appreciable change, such as the suppression of a particular pigment, might ensue. Slender as the knowledge, which we at present possess, appears to be for judging of the plausibility of such a situation, it does not seem to the writer improbable that many genes do in fact act in this way; though, since the system requires us to identify the maximal possible activity of a gene with its optimal activity, the existence of such systems would seem to require rather an evolutionary than a purely biochemical explanation. An example of such a system has been elucidated by Stern (1929), who has shown that the normal dominant condition of the mutant "bobbed" can be built up by accumulating a number of recessive allelomorphs carried in additional *Y*-chromosomes. The mutant bobbed gene is thus seen to be not the absence of its normal allelomorph, but a particle capable of exercising the same effects, though acting with considerably lower intensity.

Both Wright (1929) and Ford (1930) have noted that such systems could have been brought about by the action of selection upon modifying factors; for the parti-

cular saturation value beyond which further activity is ineffective must be determined by other components of the system, and can therefore be changed to a higher or lower value by the modification of these components. Haldane (1930) has further put forward the valuable suggestion that many different allelomorphs of the wild-type gene may exist, which, if they all act up to the saturation intensity, would in such cases be indistinguishable. When, however, any of these come to be combined with an inactivated mutant allelomorph, only those with a "factor of safety" of at least two would produce the normal effect. Consequently, in such heterozygotes the more potent members of the allelomorphic series would possess a selective advantage, and would thus come to prevail throughout the wild population. By these two processes of modification it seems not improbable that many genes may have come to play the role of a component in excess in the chains of chemical reactions, through which their more important effects are brought about; though it should be noted that such a process seems merely to allow certain genes to throw on to other components of the system the responsibility for regulating the speed of biochemical reactions. Haldane's suggestion, however, of selection among multiple allelomorphs seems to be especially relevant to some of the cases of polymorphic animals which will be discussed in the following sections.

VIII. STABILITY OF THE GENE RATIOS IN POLYMORPHIC SPECIES.

The consideration of the dominance phenomena exhibited by polymorphic species has led to a very great extension of the theory of the evolution of dominance, beyond its scope as originally put forward. It has, however, resulted in so many and detailed verifications of the consequences implied by that theory, in addition to setting the genetic situation in these species in a clearer light, that no account of the theory would be complete without bringing them also into discussion. It should, however, be borne in mind that the conclusions arrived at are only on firm ground in those comparatively few cases in which preliminary genetical research has already been accomplished, and that in these cases much more decisive evidence may be looked for in the future, now that the observations of critical importance can be more clearly indicated.

Some few years ago (1927) I was led to the conclusion that polymorphism in certain butterflies, where it had been shown to depend on the segregation of one or more Mendelian factors, must imply the somewhat special conditions needed to ensure the stability of the frequencies of the different genes. Such stability, although subject to many possible influences, would find its simplest explanation if the heterozygotes could be postulated to be at a selective advantage compared to both of the alternative homozygotes. In the case of *Papilio polytes,* Fryer (1913) had shown that the two recognised mimetic types of female differed from the non-mimetic male-like female by a single dominant gene, while a second dominant determined whether the female, if mimetic, should be a mimic of P. *aristolochiae* or, in the case of the double dominant, a mimic of P. *hector*. Without in the least appreciating the significance of dominance in the interpretation of the case, I was struck by the observation of Fryer that in his experiments numerous cases of sterile unions occurred, which

suggested to him the possibility of the existence of "illegitimate" pairings, analogous to "illegitimate" pollination in heterostyled plants. The observation suggested the possibility that the selective advantage of the mimetic coloration was in nature counterbalanced by an inferior fertility of the homozygous dominants, so establishing that stability of the gene ratio on which the continued polymorphism must depend. The further possibility at once suggested itself that the selective advantage of a physiological factor, such as viability, or fertility, might be capable of numerical evaluation in culture, and that by observing the relative frequencies of the different forms in the wild population we should, in such cases, have a unique opportunity of evaluating the bionomic advantage in nature of one coloration over another.

A somewhat similar but equally obscure situation is revealed by Gerould's work (1923) on the dominant white observed in the female of several species of the butterflies *Colias*, which also reveals some peculiar features suggestive of a stability mechanism governing the yellow-white gene ratio. Gerould reports that great difficulties were encountered in obtaining the homozygous white types, these difficulties being evidently connected with the occurrence of a closely linked lethal factor. When pure white broods had been obtained, in a strain apparently freed from the lethal, the failure of the males to mate caused the introduction of wild males, and these were found to bring in the lethal factor. The conclusion that this particular lethal is not apparently rare in nature, although we should expect it to die out somewhat rapidly, suggests strongly that a stabilising system must be present, and that the heterozygous white female must enjoy some selective advantage over the yellow form, although in this case the mutant cannot be recognised as mimetic. The situation is, however, much obscured by the frequent occurrence of abnormal ratios.

Cases of polymorphism permanently maintained in a species by the stability of the frequency ratio of a pair of allelomorphs supply opportunities peculiarly favourable to the selective evolution of dominance, for in these cases the heterozygotes are not extremely rare, but usually constitute a perceptible percentage of the population, instead of something like one in ten thousand, as in the case of the heterozygotes of the ordinary deleterious mutations. The development of dominance by the phase having the more advantageous appearance would be expected, therefore, in the absence of special obstacles, to be particularly rapid. It is therefore highly suggestive that in both these cases we should have inferred on other grounds that the dominant form possesses a selective advantage.

Very extensive genetical experiments carried out by Nabours in the grouse locusts *Paratettix* and *Apotettix* (1925) have shown that the very highly developed polymorphism of this group is determined by a number of genes or gene complexes which, if not allelomorphic, are very closely linked in inheritance. Each species has a relatively common form which is completely recessive to all the others, but the dominant forms, if allelomorphic, show no mutual dominance, but have heterozygotes combining the characteristics of the two dominant homozygotes. As early as 1920, Haldane suggested with respect to the grouse locusts, that the close linkage and frequent apparent allelomorphism observed was due not only to the infrequency of crossing-over in their chromosomes, but to several chromosomes received from

the same parent being generally transmitted in a group to the same offspring. A similar interpretation was later put forward by Demerec (1928) with respect to the large group of closely sex-linked factors found by Winge (1927) to determine the striking polymorphism in the fish *Lebistes reticulatus.* Haldane later (1930), with the support of C. D. Darlington and C. L. Huskins, suggested that such linkage between chromosomes may be accounted for by sectional translocations, and that the dominant genotypes are themselves due to the duplication of such translocated segments. Some explanation of this kind appears to the writer extremely attractive in respect of the very close and frequent linkage observed, but not by itself as sufficient to account for the dominance, for while it is extremely probable that the addition of a translocated segment to the normal germinal outfit should produce a visible effect, one would certainly expect the effect to be intensified if the additional segment had been received from both parents. In such a case the heterozygote would be of intermediate appearance and would not closely resemble either homozygote.

If on the contrary we deduce from the observed fact of dominance the inference that the dominant colour patterns enjoy a selective advantage over the recessive, then we must postulate further, in order to maintain the equilibrium in gene frequency, that the dominant homozygotes are in some way at a selective disadvantage compared to the heterozygote. These two types are indistinguishable in appearance, and the difference between them is therefore probably of a physiological nature displaying itself in differences in viability or fertility.

It is particularly fortunate that, although the great bulk of Nabours' extensive experiments were devoted to the examination of linkage, using tests in which dominant homozygotes do not occur, yet there remains a sufficient number of cases in which insects which have received one dominant from each parent have been interbred with mates of like constitution. In such cases, apart from the rare recombinations, we should expect to obtain a number of heterozygotes equal to the sum of the numbers of the two dominant homozygotes. Results from no less than forty types of mating of this kind have been given by Nabours for *Apotettix iexanus.* After assigning to their proper class all recombinations capable of separate classification, we find that in the aggregate 4309 homozygotes and 4617 heterozygotes survived to be classified. This is a very considerable deficiency of homozygotes, since it exceeds three times its standard error. The viability of the homozygous dominants appears from these data to be only about 92.9 per cent. of that of the heterozygotes.

These aggregates are of course extremely composite, since many different dominants, or compounds of dominants, have entered into the tests. If these are examined separately, and the four cases for which only a few offspring are recorded are set aside, there remain fourteen different dominants, or compounds, for which from 200 to 2300 offspring have been recorded. Of these six show an individually significant departure from expectation, and in every case this departure is in the direction of a deficiency of homozygotes. Of the remaining eight cases, six show a similar deficiency, and two an excess; the departure from expectation being, in these eight cases, no more than, on the numbers recorded, should be ascribed to random fluctuations.

There is therefore a substantial experimental basis for asserting that the homozygous dominants, or a large number of them, suffer from some degree of inviability. The data presented, it must be remembered, are only a by-product of researches not especially intended to study viability; only the extent of the observations, and the completeness of publication, has made it possible to verify the theory so far. A more deliberate investigation would necessarily include a consideration of the age up to which differential viability shows itself, whether it is to any considerable extent conditioned by environmental circumstances, and whether it is accompanied by differential fertility. The data for other species, which have not so far been fully published, should also be of value. As far as the available facts go, however, it is clear that, unless countervailing influences are at work, the dominant genes are at a selective disadvantage in the homozygotes, and that selective equilibrium can only be maintained by the bionomic advantage conferred in nature by the dominant colour patterns. If it should prove that the physiological disadvantage of the homozygote can be measured in culture, it should further be possible, from the natural frequencies of the different forms, to evaluate this bionomic advantage numerically.

IX. SEX-LINKED DOMINANTS IN *LEBISTES*.

In the fish *Lebistes reticulatus* Winge (1927) has recorded a situation in some respects remarkably parallel to that found by Nabours in the grouse locusts. Here also we find the features of polymorphism, close linkage, and a series of dominant variants. In two respects, however, the cases are sharply contrasted. In the grouse locusts the polymorphism is equally displayed in both sexes, and the pattern genes, though so closely linked among themselves, are not genetically associated with sex determination. In *Lebistes* seventeen out of the eighteen variants studied are sex-linked, and the polymorphism is almost completely confined to the male. Since in this fish the male is heterogametic, it would be impossible to study dominance in the sex-linked factors, but for the circumstance that crossing over occurs between the *X* and the *Y*-chromosome. Certain genes therefore can be introduced into the male either in the *X*, or in the *Y*-chromosome, or in both. The coloration produced being the same in all three cases, those genes which have been tested are properly classed as dominants. With respect to the autosomal gene *(zebrinus)* this also is dominant in the male, though in the female it should be classed as recessive, for in certain homozygous females the barring has manifested itself; otherwise, save in certain intersexes, the pattern genes produce no effect upon the female.

Dr Winge has informed me of the very important conclusion that whereas in the cultivated races one or more dominants are commonly found in the *X*-chromosome, yet in wild specimens this chromosome is usually "empty," that is, recessive in respect of all factors. This observation seems to place beyond doubt the conclusion, which could only have been guessed from the incidence of dominance, that in nature the variant genes are advantageous in the male but deleterious in the female fish. For, since germinal interchange undoubtedly takes place between the *X* and *Y-chromosomes* at a small but measurable rate, the difference of gene ratio observed in

nature can only be maintained by the constant elimination of dominant genes in the X-chromosome, and their constant multiplication in the Y-chromosome. On this view, taking into account the fact that the gene ratios established in nature must in fact be stable, the theory of the evolution of dominance by selective agencies leads to consequences in very complete accord with the facts ascertained by genetical research. First, we should expect the variant forms to become dominant in the male, and recessive in the female fish; next, that continued counter-selection in the female should obliterate entirely, in this sex, the effects of those genes which were capable of crossing into the X-chromosome, and there giving rise to occasional homozygous females. The close sex-linkage of these genes is also a natural consequence of the same situation, for favourable selection in the Y-chromosome with counter-selection in the X must constantly favour those genotypes in which linkage with the sex-determining portion of the Y-chromosome is closest. Such selection may thus have built up the system of close sex-linkage which is now found. Moreover, close linkage with sex may have enabled certain variants, beneficial in the male, to have established genetic stability, for, had they been autosomal, their deleterious effect in the female might have definitely outweighed their genetic advantages, and thus have prevented them from contributing to the natural polymorphism. It is moreover striking, though it is perhaps a coincidence, that the one variant whose effect has not been entirely suppressed in the female is the only one that still stands outside the sex-linked system. Apart, however, from this fact, which might be interpreted as indicating that zebrinus is the latest addition to the collection of mutant genes by which polymorphism is determined, it is clear that the hypothesis of dominance modification enables us to interpret the remarkable genetic situation in this species as flowing from a few relatively simple causes; and it is difficult to imagine how the observed facts could more closely simulate those to be anticipated from the theory. The male in culture swims in constant attendance upon the female; and it is natural to interpret the brilliant spots and markings produced by the dominant genes as epigamic.

X. THE ASSOCIATION OF POLYMORPHISM, CLOSE LINKAGE AND DOMINANT VARIANTS.

It is sufficiently remarkable that the two cases of polymorphism hitherto considered, in the grouse locusts and the fishes, belonging to different phyla of the animal kingdom, should resemble each other in three such striking and distinct peculiarities as polymorphism, close genetic linkage, and the contrast among the forms occurring in nature between a single recessive form and a large number of dominant variants. That we are here dealing with a causal connection is shown by the genetic behaviour of the polymorphic land snails Helix hortensis and nemoralis. Little has so far been published on the genetic work which has been done in these species, though I understand that a memoir by Captain Diver is shortly to be expected. It is, however, known that the greater number of the commoner variants affecting the ground colour of the shell, the suppression of one or more bands, the confluence of

the bands, or their discontinuity, are produced by factors dominant to the standard or typical form, which, on a yellow background, has five distinct and continuous bands. Further, it is known that these factors are either allelomorphic or so closely linked in inheritance that recombinations have seldom if ever been observed in culture. The parallelism with the grouse locusts is thus extraordinarily complete, although there are among these snails some variants, such as partial albinism and dilute coloration of the bands, which behave as recessives. In the case of the snails too we have what is lacking in most other animals, fossil evidence that polymorphism of the same kind, and with approximately the same frequency ratios, has been present from a very early period (Diver, 1929). A stability mechanism controlling the gene ratios may therefore be postulated with some confidence, and, on the analogy of the grouse locusts, we should expect to find that these dominant variants produce colour patterns which are in some respects more advantageous in wild conditions than the typical pattern, but that this advantage is counterbalanced by an inferior viability or fertility of the homozygous dominants. The fact that Mendelian theory provides the numbers to be expected in broods of mixed composition, on the assumption that viability is equal, should make it possible, as with the grouse locusts, to compare their viability under very closely controlled conditions; and with the assistance of the Oxford Evolution Fund I hope to breed sufficient numbers to ascertain whether, in viability also, the snails will parallel the facts observed in the grouse locusts.

It is obvious that in the case of these polymorphic species, occurring in widely separated branches of the animal kingdom, the phenomenon of dominance has only provided the first clue towards unravelling the complexities of their genetic and evolutionary situation. In the case of *Lebistes* there are, as we have seen, some grounds for regarding the close sex linkage as either the consequence, or the condition, of the balance of selective forces acting in different directions in the male and the female. On the other hand, the colour patterns in the grouse locusts are not sex limited, nor sex-linked in inheritance, and the snails, being hermaphrodite, could not show either effect. What, then, is the meaning of the extremely close linkage within or perhaps between chromosomes observed in these two cases ?

It is, strictly speaking, beyond our immediate subject to speculate on this question. Yet a consideration of the obstacles which extremely close genetic linkage must oppose to the normal evolutionary development of a species, does seem to supply a rational explanation of the method of obtaining improved colour patterns, by means of partially inviable mutants, which seems to have been adopted in the grouse locusts, and possibly in the polymorphic snails. Any considerable change in the evolution of a species from its ancestral form at a remote geological period must have involved numerous genetic substitutions. The genetic novelties ultimately adopted must, as far as we know, have originated in mutations, and have won their way gradually from extreme rarity to an ultimate predominance or universal prevalence in the loci in which these genes are situated. Where free recombination is possible, hundreds of such improvements may be in progress simultaneously, the greater improvements gaining ground more rapidly, but in no way impeding the progress of such slighter improvements as may at the same time be taking place. If,

on the contrary, recombination were entirely suppressed, then all the possible genotypes in the species will compete with one another like a system of multiple allelomorphs, and any mutation providing only a slight advantage to the species, in survival and reproduction, will be threatened throughout the long period which it requires to spread through the species, by the danger of a more advantageous mutation occurring elsewhere, which will inevitably thrust it aside. The smaller the advantage conferred by a mutation the greater is this danger, both because more advantageous mutations are more frequent, and because the time will be longer during which they must fail to occur, if our mutation is to be successful. In such a species therefore genetic improvements must take place in succession, one at a time, the weaker always making way for the stronger.

Such a situation would be normal in organisms without sexual reproduction. It is a more extreme condition, probably, than is found in any sexually reproducing form. Nevertheless, in a lower degree it must be approached by any organism whose germplasm is tied up into one or a few closely linked complexes; and in such organisms we may reasonably infer that the normal evolutionary process is not available for relatively slight or unessential improvements, being wholly occupied with matters of greater importance. Now the system of obtaining improved colour patterns, such as appears to fit the facts with the grouse locusts, by dominant mutations, possibly duplications, which are deleterious in the homozygous phase, raises the problem of why the recessive cannot itself be modified to a more advantageous pattern, and so supersede the dominants, with which it appears to be now in equilibrium. The possibility at once suggests itself that the colour pattern is not among the more important matters with which its evolution is urgently occupied. Possibly its sense organs, or its digestive system, or its reproductive instincts, are of more real importance to the insect; at all events we have no reason to suppose that a species with such close linkage as the grouse locusts is in a position to seize upon such a trifling advantage as an improved colour pattern might confer.

It is this point of view which brings out one of the most attractive features of Haldane's theory that the dominants are due to the duplication of a chromosome, or fragment of chromosome; for such a fragment supplies a tract of the germplasm, mutations in which are judged solely by their success in the particular dominant in which they occur. Such a tract may be regarded as set apart especially for the improvement of a particular heterozygote, or in less degree of the corresponding homozygote. Consequently, though they may compete among themselves, mutations in this tract are shielded from the competition of the mutations of higher selective value, occurring in that part of the germplasm, which is common to the dominants and the recessive alike. The modification of dominance would on this view take place by a process closely analogous to the selection of multiple allelomorphs suggested in another connection by Haldane. The exceptional conditions induced by close linkage, by the obstacle which it opposes to normal evolution by gene substitution, makes it possible for abnormalities, such as duplications, occasionally to possess a selective advantage. If, as is extremely probable, they are injurious when homozygous, they will set up the stability of the gene ratio needed for polymorphism.

When the advantage lies in the external appearance, the polymorphism will be manifest, and the variant form will tend to become dominant.

XI. SUMMARY AND CONCLUSION.

We can now attempt to draw together the several groups of observational facts upon which the theory of the evolutionary modification of dominance is based, and upon which it finds a simple and coherent explanation. The theory itself is the simple outcome of the view which, with increasing knowledge, has impressed itself more and more upon geneticists, that the effects of Mendelian factors are largely susceptible of modification through interaction with other factors in the germinal complex; it applies this generalisation particularly to the modification of the heterozygote, which, since it contains both of two alternative genes, might be expected to be particularly susceptible of modification, in those respects in which these genes produce different reactions. By its aid we can appreciate why the deleterious mutations commonly occurring in wild species, and the fancy novelties favoured by man in his domesticated animals and plants, should generally be recessive, while at the same time the variant forms of species polymorphic in nature should generally be dominant. We have seen that the special group of dominants found in domestic poultry may be interpreted without assuming for *Gallus* a special and progressive evolutionary tendency, unknown in other birds. In more detail, we can see why the observed absence or incompleteness of dominance is to be expected in the case of different mutants of the same wild gene, or again in the case of minute internal effects produced by mutations, whose principal visible effects are quite recessive. The theory is strongly corroborated by the numerous cases of mutants which normally are completely recessive, but which, in special genetic combinations, or under special treatments, unknown in nature, give heterozygotes distinguishable from the non-mutant homozygotes.

In many cases in which the facts so far known are extremely suggestive, further investigation should produce more decisive evidence. This is true of the poultry, in which the inference that the dominant characters of our domestic breeds will be found in the wild *Gallus* to be incompletely dominant awaits the experimental test. It is true also of the very important case in cotton, where it has been possible to introduce a recessive mutant found in one species into other related species, in which it does not naturally occur, and in which the evidence so far available shows it to be incompletely recessive. The theory has been verified by the imperfect viability of the homozygous dominants in the grouse locusts, but still remains to be verified in the case of the polymorphic land snails. In both these cases, however, more extensive observations, in conjunction with the enumeration of the forms found in nature, are needed to put upon a quantitative basis the inference of a bionomic advantage of the dominant phenotypes. Even in the case of *Lebistes*, where, owing to the sexual differentiation, the consequences of the theory have been verified in the greatest detail, genetic tests on a sample of the wild population, on a scale sufficient to ascertain the frequency of colour genes in the *X*-chromosome, are needed to put the selective situation beyond a doubt. It is obviously also of great importance that other

cases, where polymorphism is less pronounced, should be investigated, with particular attention to such physiological factors as may affect the fertility or viability of the different genotypes. These have hitherto appeared rather as an obstacle to genetical research, than as a primary object of study; although, in respect of juvenile inviability, the genetic method offers particularly favourable conditions for its measurement. An interesting feature of the whole subject is that in nearly every case we are concerned with a minor or secondary by-product of selective action. Anyone who accepts the view, which was propounded by some of the earlier geneticists, that selective agencies have been ineffective or unimportant in the morphological evolution of living forms, must of necessity, irrespective of the evidence, reject the view that it has been influential in the present group of cases. When, however, the matter is viewed, not with dogmatic partisanship, but in relation to the calculable magnitudes of the selective agencies at work, and to the known effects of selection in artificial cultures, it is clear, as we have seen, even with the extremely minute selections favouring recessiveness in the mutants of *Drosophila*, that they are quantitatively of a magnitude sufficient to have produced the effects ascribed to them, provided their action has not been obstructed or opposed by some unknown and hypothetical cause. It is certainly astonishing to consider that the heterozygotes of, perhaps, some thousands of lethal mutations in *Drosophila* have each been modified back to normality, yet this is scarcely more astonishing than the admitted fact, that each of these genotypes does, on a different biochemical foundation, succeed in building something so nearly resembling the normal fly as to be indistinguishable from it; and a theory, which exhibits so remarkable a fact as this as a natural consequence of the action of known causes, cannot properly be debited with the astonishment which such a fact admittedly produces.

REFERENCES.

DEMEREC, M. (1928). " A possible explanation for Winge's findings in *Lebistes reticulatus." Am. Nat.* 62, 90.

DIVER, C. (1929). "Fossil records of Mendelian mutants." *Nature*, 124, 183. DOBZHANSKY, TH. ---- (1927). "Studies on the manifold effects of certain genes in *Drosophila melanogaster." Zeit. f. ind. Abst. u. Ver.* 43, 330. FISHER, R. A. (1927). " On some objections to mimicry theory; statistical and genetic." *Trans. Ent. Soc. Lond.* 75, 269.

---- (1928 *a*). " The possible modification of the response of the wild type to recurrent mutations." *Am. Nat.* 62, 115.

-----(1928 *b*). " Two further notes on the origin of dominance." *Am. Nat.* 62, 571.

-----(1929). "The evolution of dominance; reply to Professor Sewall Wright." *Am. Nat.* 63, 553.

-----(1930). "The evolution of dominance in certain polymorphic species." *Am. Nat.* 64, 385.

FORD, E. B. (1930). "The theory of dominance," *Am. Nat.* 64, 560.

FRYER, J. C. F. (1913). "An investigation by pedigree breeding into the polymorphism of *Papilio polytes." Phil. Trans.* B, 204, 227. GEROULD, J. H. (1923). " Inheritance of white wing colour, a sex-limited (sex-controlled) variation in yellow Pierid butterflies." *Genetics*, 8, 495.

HALDANE, J. B. S. (1920). "Note on a case of linkage in *Paratettix." Journ. Genetics*, 10, 47.

-----(1930). "A note on Fisher's theory of the origin of dominance and on a correlation between dominance and linkage." *Am. Nat.* 64, 87.

LANCEFIELD, D. E. (1918). "An autosomal bristle modifier affecting a sex-linked character." *Amer. Nat.* 52, 462.

MORGAN, T. H., BRIDGES, C. B. and STURTEVANT, A. H. (1925). "The genetics of *Drosophila." Bibliographica Genetica,* 2, I.
NABOURS, R. K. (1925), " Studies of inheritance and evolution in *Orthoptera.* V." *Kansas Agr. Exp. Sta. Tech. Bull.* No. 17.
PATTERSON, J. T. and MULLER, H. J. (1930). "Are progressive mutations produced by X-rays?" *Genetics,* 15, 495.
SNELL, G. D. (1931). " Inheritance in the house mouse." *Genetics,* 16, 42.
STERN, C. (1929). "Über die additive Wirkung multipler Allele." *Biol. Zentr.* 49, 261.
WINGE, Ö. (1927). "The location of eighteen genes in *Lebistes reticulatus." jfourn. Genetics,* 18, I.
WRIGHT, S, (1925). "The factors of the albino series of guinea-pigs and their effects on black and yellow pigmentation." *Genetics,* 10, 223.
---- (1929). " Fisher's theory of dominance." *Am. Nat.* 63, 374.