

GENETIC REACTIONS IN NICOTIANA. III. DOMINANCE

E. M. EAST

Harvard University, Bussey Institution, Jamaica Plain, Massachusetts

Received March 10, 1935

The title of this paper is a slight misnomer. The views to be presented on the relation of dominance to gene activity are thought to have general validity. Naturally, therefore, they have not been formulated without due consideration of published genetic records. My own personal genetic experience necessarily has been influential in their development, however, and much of this experience has been gained by the use of material from the genus *Nicotiana*.

The accepted facts regarding the phenomenon of dominance may be outlined as follows, the statements departing only slightly from those set forth by WRIGHT (1934). 1. Dominance and recessiveness are one-word descriptions of the appearance of end-products in the physiology of development, and have nothing to do with the distribution of genes to the filial generation. 2. The contrast that these words describe is one in which the recessive is usually a restriction or a failure of a positive property found in the dominant. 3. An approach to dominance of a given allele *A* over allele *a* is the rule with the pairs of genes ordinarily used in genetic work. 4. Mutant genes that have been detected and their resultant activities described under controlled conditions are overwhelmingly recessive to the genes from which they have arisen when crosses are made with the stocks from which they have originated. 5. Recessive genes, when homozygous, are usually less advantageous to the possessor than their dominant alleles. It follows that recessive genes are ordinarily found less frequently than their dominant alleles in natural populations, since, as WRIGHT states, deleterious dominant genes tend to be eliminated rapidly (frequency in

population $q = \frac{u}{hs}$, where *u* is mutation frequency and *hs* is disadvantage

of heterozygote), and advantageous ones preserved. Disadvantageous recessive genes, however, are kept at relatively higher frequencies in a natural population than are disadvantageous dominant ones ($q = \sqrt{u/s}$, where *s* is disadvantage of the homozygote). WRIGHT calculated that when the selective disadvantage of a homozygous mutant is .01 and the mutation frequency is 1 per million per generation, a deleterious recessive gene will be kept at 100 times the frequency of an equally deleterious dominant.

The hypotheses in which endeavors have been made to account for dominance and recessiveness have not been very satisfactory.

The first to gain recognition was the "presence and absence" theory of

BATESON and PUNNETT. Here it was assumed that the commonest type of mutation was a loss of some kind. If this were the case, it was thought reasonable that the loss should entail recessiveness on the ground that one dose of a gene having constructive activity should produce an end product more like that of two doses than like none at all. The more ferocious critics of this conception have imputed to BATESON and PUNNETT the crude idea of an absolute physical loss, but I have always felt that this did not do the authors justice. What they really had in mind, I believe, was that the dominant gene can do something that the recessive gene can not do, and in this sense they approached the truth. Nevertheless, the presence and absence theory has been discarded by geneticists for various reasons. It was difficult to visualize evolution by losses, to account for reverse mutations, to explain certain multiple allelic series, or to see how certain apparent losses could result in dominant effects.

FISHER (1928 and later) has built up a theory of dominance which has only one physiological implication, namely, that the heterozygote is inherently more modifiable than either homozygote. FISHER simply accepts without question the postulate that nearly all mutations are recessive to wild-type. If one is to accept evolution, therefore, dominance must be evolved from recessiveness. This is done by assuming a continued selection of heterozygotes toward resemblance to wild-type by the collection of modifying genes.

It may be noted here that during the mathematical studies on evolution that FISHER has carried out, he found that the known mutation frequencies in various organisms are wholly insufficient to account for known results of the process. I believe that this observation is more important than the dominance theory, although the latter has received wide acclaim while the former has remained unnoticed.

WRIGHT has criticized FISHER's theory, on the ground that any conceivably sound selection pressure would be too small to do the work assigned to it. HALDANE (1930) has made a similar criticism. The essential point in these criticisms is that the modifiers may have selection pressures acting on them individually which will necessarily take precedence over effects on the so-called primary genes present in the rarer heterozygote. WRIGHT has "emphasized more the point that even in those cases in which the homozygote is not capable of being modified in the same respect as the heterozygote, the modifier is likely to have other effects subject to direct selection." HALDANE has stressed the point that the same reasoning which leads one to believe that a given gene will modify the heterozygote, also leads one to believe that it will modify the wild-type.

PLUNKETT (1932) has drawn attention to the fact that if there is direct

selection of a type, this would tend to build up a factor of safety insuring an organism against variation in general.

GOLDSCHMIDT (numerous papers) and WRIGHT (1934) have endeavored to build up an idea of dominance based largely on what they conceive to be the physiology of developmental processes. GOLDSCHMIDT stresses quantitative action of catalyzers entering into action at specific times as development proceeds. WRIGHT also uses the catalysis idea, but brings it to bear specifically on the dominance question rather than on general development. He postulates that the most active phase of a gene is dominant over less active phases. Partial dominance, he feels, implies that "variations of the gene and its successive products leading to the observed character *all* affect the limiting components in the reactions into which they enter." "If there is still incomplete dominance at a stage in the reaction chain at which an all-or-none reaction intervenes, dominance of a gene comes to depend on the effects of independent modifiers and in this case is without relation to its primary activity."

I feel that each of these writers is reaching toward the truth. There is something worth-while in the presence and absence theory when stated in a manner in keeping with modern genetic knowledge. Modification of a given effect A can be changed by the action of accessory genes (see "Genetic reactions in *Nicotiana*. II," for reactions on petioled and sessile leaves), though I do not feel that this process is important in evolution. Chain reactions are the rule in development; and naturally, mass action, all-or-none reaction, and reactions of numerous other types must enter. One can get a very fair theoretical idea of the situation, provided one does not try to explain everything on a single mechanism or process.

Several years ago, I became convinced that certain modifications of our ideas on the nature and frequency of mutations are necessary before we can obtain a clearer view of these matters than now prevails. I believe that sufficient evidence exists to support these changes of view. If this is granted, a number of puzzling problems no longer present difficulties. These theses will follow. They are stated categorically, though exceptions must be recognized.

1. *The great bulk of the mutations detected in the genetic laboratory and used in genetic research are recessive to the normal, the wild-type, or the survival type, as it may well be called, because they cause restrictions in the physiological processes in which they are involved.*

It may be assumed that a high degree of efficiency in carrying out essential life-processes is called for in types of organisms that have survived the sieve of natural selection. The basis for these developmental processes lies in the bundle of genes that the individual inherits from its

parents. Each gene has an indispensable function to perform, if one may judge from the fact that deficiencies for single genes always appear to be lethal when in the homozygous condition; but it is not necessary to assume that the efficiency rating of each and every process must be similar. Now, if we look upon the gene as a chemical entity, or a chemical factory—if need be—it is clear that on chemical analogy a limited number of changes is to be expected. It is convenient to denote these changes, or mutations, by the term “genetic isomers,” without wishing to stretch the chemical simile to the breaking point. These changes we may expect to be quite limited on any imaginable biochemical view and because of the facts as we have them in the genetically well-known organisms such as *Drosophila melanogaster* and *Zea Mays*. It must be remembered, however, that the facts, as they are usually listed, may give a distorted view of the truth. When the wild-type eye of *Drosophila* mutates to eosin in various stocks, they are recorded together to make up an eosin mutation frequency; but there is no way by which to be certain that two or more eosins (that is, different genetic isomers) giving similar results are not included. TIMOFÉEFF-RESSOVSKY (1932) has recognized this problem and has tried to throw some light on it through studying mutations and inversion frequencies in material from various sources.

It is probably to be expected that the great bulk of the possible genetic isomers result in physiological restrictions of the normal (selected) processes, though this is not necessarily so. At all events, the mutations producing physiological restrictions are the ones easily detected, just as the faults of a car which cause missing cylinders, et cetera, are easier to detect than the vague matters which make it run a little better than it did yesterday. If the process needing the gene's activity comes to a complete stop, the condition is lethal. If, on the other hand, it limps along inefficiently, the organism will live, though the principal end product by which genes are named will not be the same as in the normal.

It is easy to see that, on the view that numerous mutations are in the nature of physiological defectives, several conclusions follow that are borne out by experience. Physiological defective *a*, unless disturbing to the activity of the normal *A*, will be recessive to a degree proportional to the defectiveness; for, on any reasonable biochemical view of the gene as a working laboratory, the activity of one normal gene should give an approach to a normal product. This type of mutation should often be lethal or deleterious in the homozygous condition; but if the main activity of the gene is the production of non-essential products (as flower colors), it need not be so. Such genes should be readily detectable because commonly the activity of defective genes should result in end-products that are qualitatively different from those produced by the normal.

2. "*Defective*" *genic isomers are not the mutations that serve as material in evolution.*

FISHER found it necessary to formulate a theory of the evolution of dominance because he assumed that the mutations described for *Drosophila* gave a true picture of the mutations available for the differentiation of forms. If the assumption is false, the theory is unnecessary. I feel convinced that it is false.

It is unnecessary to labor the defense of this point. The place to seek the kind of material useful in the origin of species is in Nature rather than in the genetic laboratory. Let the taxonomist be the judge. And taxonomists, whether they deal with animals or plants, whether they consider the so-called lower or the higher forms, are unanimous in maintaining that the type of alternative characteristic ordinarily utilized in the genetic laboratory for the study of heredity is useless in discriminating between species. Species commonly differ in a lot of quantitative relations, in patterns. The beginning of species differentiation may be visualized as change in a few of these quantitative relations.

These quantitative changes (there may also be occasional qualitative changes) in the end results that we know as characters, require the accumulation of numerous "gene change" effects in order to be recognizable. The mutation in a single gene, therefore, is not readily detectable. Even many such changes resulting in describable end results, are difficult to deal with genetically. This is the reason why investigators familiar with wild forms that will cross together and produce fertile hybrids have found difficulty in interpreting their results. As competent an investigator as SUMNER, for example, worked for years with *Peromyscus* before he became convinced that inheritance in this genus is Mendelian. The reason for his hesitation is understandable. He was dealing with the kind of situation that we are discussing.

These mutations, as I have said, commonly produce results that may be said to be quantitative. Such a description is not wholly satisfactory, however, for there may be many exceptions. What I feel to be a truer conception, though one that is difficult to prove conclusively, is that the gene changes which give these results are physiologically non-defective. Perhaps an example will serve to show the distinction. The ligule is characteristic of the entire group known as the Gramineae. Liguleless stocks are known in maize, rye, and oats. And the two conditions behave as if controlled by a single pair of genes. Now, although a liguled type may give rise to a liguleless type by one mutation, it is not reasonable to assume that liguled forms arose from liguleless stocks in a similar way. It is more in keeping with our general knowledge to assume that the ligule is an organ having a long evolutionary history, for it exists in numerous forms. It pre-

sumably is the result of a very large number of non-defective mutations in various genes, and, physiologically speaking, is the end product of a long chain of reactions. But a single defective change breaks this chain and gives a liguleless plant. The building up of the normal mind, contrasted with the single defective mutation that entails feeble-mindedness, is an even better example.

3. *Non-defective gene mutations are frequent in Nature, but are difficult to detect.*

I believe that every experienced plant breeder will agree with this statement. It will accord with his experience. I will relate some of the experiences that have led me to the conclusion.

During the early years of my *Nicotiana* investigations, over 100 varieties of *Tabacum* and *rustica* were studied. Some were discarded after one population had been grown; others were observed in selfed lines over long periods (maximum 28 years). Numerous crosses were made between commercial types of *Tabacum* and, to a less extent, between commercial types of *rustica*. Several studies, involving hereditary differences in height, number of leaves, and size, shape, and texture of leaves, were published by HAYES, JONES and EAST. It is not necessary to discuss these reports beyond saying that the selection experiments on these quantitative characteristics, such as those published by EAST and HAYES (1914), were carried on to the F_{13} generation and were evaluated statistically, though not published. They are mentioned for one purpose only. This very considerable experience with continuously self-pollinated lines of supposedly pure types and with successively selected self-fertilized lines from varietal crosses indicated very strongly that though there is a rapid approach to homozygosis of gross characters, there still remains a large amount of apparently irreducible variability in all parts of the plant, some of which can be proved, by appropriate tests, to be heritable. For example, the tobacco leaf varies in characteristic items of shape from the tip to the base, in color, in size, in veination, in fullness between the veins, in thickness, and in various other factors that go to make up commercial quality after what is ordinarily thought to be a pure type is obtained. In selected descending self-fertilized lines, one may obtain a still more uniform progeny temporarily, as regards almost any peculiarity, thus showing a residuum of heterozygous genes affecting these characteristics. But there must be a high mutation frequency since, after 10 or 12 generations of closest inbreeding, one can not reduce, in an appreciable degree, the variability of any indices for the leaf as a whole.

In spite of the effect of environmental differences on the plants of such populations, and in spite of the limited validity of such observations due to errors of sampling, the uniform nature of such experiences leads me to

believe that in organisms currently undergoing a fairly rapid evolution (and most Angiosperms probably belong in this group), gene mutations are constantly occurring with many times the frequency that is generally assumed. The reason for this discrepancy lies in the ease with which one can detect the physiologically defective mutations, the changes which throw sand in the life machinery—as one may designate 99 percent of the *Drosophila* mutations—and the difficulty of detecting slight genic isomers where the results must usually be expressed by ideas of plus and minus.

This conclusion was strengthened some years later by another series of experiments, though I did not appreciate their significance at the time, and therefore can not support them quantitatively. While I was endeavoring to produce certain specific hybrids, numerous combinations were observed which yielded only maternals. Nearly all the plants were ordinary fertile diploids, though occasionally (perhaps 1 per 1000) smaller sterile plants occurred that must have been haploids. Afterwards it was proved, first on *Fragaria* (EAST, 1930) and later on *Nicotiana*, that these maternals came from mature gametes in which parthenogenetic development had been induced. There were several reasons for supposing that diploidy came about at a very early embryonic division, and therefore that each plant was a complete homozygote. Since the immediate populations in such cases are simply random samples of the gametes of a given mother plant made diploid by mitosis (the capsules often being full), there was nothing noticeably peculiar about them. But several species were continued from such plants self-fertilized, *N. rustica* furnishing the most extensive series of observations. Over a dozen different progeny rows of *rustica*, for example, gave a somewhat astonishing result. The plants of each progeny test were as much alike as if they had been cut with a die. The condition was so noteworthy that I tried, without very great success, to make photographs showing the uniformity. A few measurements of various characteristics were taken, but they gave too much of a partial picture of the situation to be of value. One may rest assured, however, that the individuals in each of these populations were more strikingly similar than those of *any* ordinary inbred populations that I had ever examined. And now comes the feature to which I wish to draw particular attention. Several of these lines were continued from self-fertilized seed, and within 3 or 4 years they were showing approximately the same amount of variability as ordinary selfed populations, a result which could only have come about from frequent small mutations.

Attention should also be called to the minuteness of the parental influence on the hybrid patterns of any plant organ, as shown in the analyses made in "Genetic Reactions in *Nicotiana*. II." It is difficult to explain these influences unless one assumes that during the differentiation of the

Nicotiana species a large number of non-defective mutations have occurred at various loci. It is clear, however, that individually they would be difficult to detect.

If the truth of theorem No. 3 is granted, FISHER'S requirement of a higher degree of mutation frequency than is shown by calculations made from the defective gene mutations of *Drosophila* is satisfied.

4. *Non-defective gene mutations, though distributed in the ordinary manner, operate in such a way that the result of their activities is not ordinarily recessive to wild-type.*

There is no reason to believe that non-defective gene mutations may not sometimes show an approach to dominance and sometimes an approach to recessiveness to wild-type, but the characteristic of a non-defective gene is its physiological constructiveness. The characteristic of the genes with recessive tendencies is physiological destructiveness. The allelic red eye-white eye series in *Drosophila*, for example, I should regard as a physiologically destructive series in which recessiveness is directly proportional to amount of defectiveness. The agouti series in rabbits, on the other hand, may possibly be a non-defective series, though I do not so regard it. It is mentioned only because similar series appear to be found in the wild and therefore could be considered as a hypothetical example of a non-defective series where there is partial dominance of higher degrees of pigmentation over lower degrees. I also wish to point out that the recognized agouti series is such only because of detectable differences between the members. There may be numerous other grades that are not detectable. Mammalian geneticists have suspected that they exist.

The experiences from my own work leading to the formulation of theorem No. 4, however, come largely from a consideration of the species hybrids in *Nicotiana*. Naturally one must admit that here the situation is complicated because of the existence of numerous genic differences. Nevertheless, when one considers the minuteness of detail in which one can trace the influence of both parents in forming an intermediate pattern in habit of growth, type and form of leaf, hairiness, chlorophyll production, and size and shape of all flower parts, it would seem that the theorem is valid.

5. *The deviations forming the fundamental material of evolution are the small variations of DARWIN.*

This conclusion follows as a matter of course. We return to the Darwinian idea, modified by the demonstration of alternative inheritance.

SUMMARY

In this paper there has been an attempt to show: (a) that most recessive genes are genic isomers that are defective physiologically and are easy

to detect on this account; (b) that such mutations are not the material that is useful in evolutionary processes; and (c) that non-destructive mutations occur with a high degree of frequency, that are not ordinarily recessive or dominant to wild-type but are active pattern formers just as are wild-type genes, and are difficult to detect on this account.

It is thought that the recognition of this class of mutations gives geneticists a new orientation to the problem of evolution. If such mutations occur with the frequency which certain evidence obtained from species hybridization experiments and from selections experiments suggests, the mathematical requirements for evolution under alternative inheritance may be satisfied, and theories as to the evolution of dominance made unnecessary.

LITERATURE CITED

- EAST, E. M., 1930 The origin of plants of maternal type which occur in connection with interspecific hybridizations. *Proc. Nat. Acad. Sci. Washington* **16**: 377-380.
- EAST, E. M. and HAYES, H. K., 1914 A genetic analysis of the changes produced by selection in experiments with tobacco. *Amer. Nat.* **48**: 5-48.
- FISHER, R. A., 1928a The possible modification of the response of the wild-type to recurrent mutations. *Amer. Nat.* **62**: 115-126.
- 1928b Two further notes on the origin of dominance. *Amer. Nat.* **62**: 571-574.
- 1929 The evolution of dominance; reply to Professor Sewall Wright. *Amer. Nat.* **63**: 553-556.
- 1930 The genetical theory of natural selection. Oxford, Clarendon Press. 272 pp.
- HALDANE, J. B. S., 1930 A note on Fisher's theory of the origin of dominance, and on a correlation between dominance and linkage. *Amer. Nat.* **64**: 87-90.
- PLUNKETT, C. R., 1932 Temperature as a tool of research in phenogenetics; methods and results. *Proc. Sixth Int. Congress Genetics* **2**: 158-160.
- TIMOFÉEFF-RESSOVSKY, N. W., 1932 Mutations of the gene in different directions. *Proc. Sixth Int. Congress Genetics* **1**: 308-330.
- WRIGHT, SEWALL, 1929a Fisher's theory of dominance. *Amer. Nat.* **63**: 274-279.
- 1929b The evolution of dominance. *Amer. Nat.* **63**: 556-561.
- 1931 Evolution in Mendelian populations. *Genetics* **16**: 97-159.
- 1934 Physiological and evolutionary theories of dominance. *Amer. Nat.* **68**: 24-53.