CHAPTER XX

MUTATION

Concerning the origin of the germinal differences that give rise to mutant characters very little is known at present except, (1) that they appear infrequently, (2) that the change is definite from the beginning, (3) that some of the changes at least are recurrent, and (4) that the difference between the old character and the new one is small in some cases and greater in others. I do not think that any of the work purporting to produce specific mutational changes has succeeded in establishing its claims, at least in the sense that we can pretend at present to control the appearance of specific mutant changes, and until this is done we can not hope to find out very much as to the nature of these changes. Our study of the germ-plasm is largely confined, therefore, for the present, to a study of transmission of the genes, to the kinds of effects they produce on the organism, and to the special relations of the genes in the chromosomes where they are located.

Concerning the frequency of mutation there is a slowly increasing body of evidence showing in some animals and plants how often or how rarely changes of this kind take place. The impression prevails that mutation is less rare in some species than in others, and while I am inclined to think that this may be true, not much value can be ascribed to such impressions; for it is not improbable that the frequency with which mutations are found is often directly in proportion to the number of individuals examined and to familiarity with the type in question, so that the smaller changes are not overlooked. The discovery of new mutant types in almost every plant and animal that has been carefully examined indicates at least the very general occurrence of definite mutations, and the
great variety of types shown by nearly all of our domesticated animals and plants—varieties that follow Mendel's law—appears to give further support to the view that the process of mutation is widespread.

One of the most interesting phenomena connected with mutation is the recurrence of the same change. It has long been recognized that certain "sports" such as albinos and melanic forms are found again and again in nature. In insects there are many records of the sporadic appearance of the same type, such as the light form (lacti-color) of the moth Abraxas. It is true that not all such appearances are to be accepted offhand as the first appearance of the mutative change, since when these are recessive it is probable in most cases * that the actual mutation occurred several generations before the mutated genes came together to produce the mutant character. But granting this, it is at least probable that the same type has appeared in many cases independently. The only evidence that can be relied upon in such cases is from pedigreed cultures, followed up by evidence that the mutants that look alike are really due to mutations in the same locus. Fortunately there is actual evidence, both for plants and for animals, that can be appealed to to show that the same mutations recur.

The most extensive evidence is from Drosophila melanogaster. One of the first mutants that appeared, viz., white eyes, has appeared anew in our cultures about three times, in cultures known to be free from it before and not contaminated. The same mutant has been found by several other observers. The eye-color vermilion has appeared at least six times; the wing character called rudimentary, five times; cut wing has been found four times; truncate wing has frequently appeared, but has not necessarily been always produced by the same change. Certain characters such as notch wings, that have

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*Recessive mutations in the X-chromosomes of the XX-XY type may appear in the male in the next generation.*
appeared quite often, represent, it seems, a peculiar change whose relation to the changes that stand behind other mutant characters is not yet worked out.

In plants the best evidence is that reported by Emerson for Indian corn. Emerson has shown that when a race of corn (*Zea mais*) having red cobs and red seeds is crossed to a race having white cobs and white seeds only, the two original combinations appear in the second \( F_2 \) generation giving plants with red cobs and red seeds and plants with white cobs and white seeds. Either a single factor determines that both cob and seed are red in one case and white in the other, or if the color of each part is due to a separate factor these factors are completely linked. Now striped seeds with white cobs sometimes mutate to red seeds and red cobs. The new combination (red and red) acts as a unit toward the other known combinations. Therefore a single factor must have changed, for, if not, mutation must occur in two (or more) closely linked factors, *i.e.*, for seed and cob color at the same time, which is highly improbable.

In forms propagating by sexual methods it cannot be told whether mutation has occurred in one locus or in both homologous loci at the same time, because in the egg one of each pair of genes is lost in the polar body, and irrespective of whether one or two mutated genes were present only one member of the pair is left in the ripe egg; and in the sperm the chance of any one sperm reaching the egg is so small that it is unlikely that the difference between one sperm or two sperms having the mutated locus could be detected. It is true that of the twelve dominant mutants that have appeared in *Drosophila* each appeared at first in a single individual—never two—which might appear to favor the single locus view, but this evidence is too meagre to be significant. Mutants from recessive genes usually come to light in about a quarter of the offspring of a given pair. This means that both parents were heterozygous for the mutant gene, but this gene
must have arisen at least one generation earlier, and have been carried over into the two heterozygous individuals in question.

It would be a point of capital importance if it could be determined beyond doubt that at times recessive mutant genes change back to the original (wild type) gene, or even if a recessive gene could mutate to a dominant one. The appearance of the wild type in a pure culture of a mutant race can be accepted as good evidence of such a change only when every possibility of contamination by the wild type is excluded, and this is difficult to regulate. In our cultures we have come across such cases, but have not ventured to exploit them, since wild-type flies are always present in the laboratory, and hence the discovered form may have arisen through accidental contamination. Thus even when a red-eyed yellow fly appeared in the white-eyed yellow stock there is the barest chance that a yellow red-eyed fly, or an egg of such a fly, had somehow gotten into the stock. Certainty can be attained only when a stock, pure for several mutant characters, reverts to the normal in one of these characters, and not in the others. Only one case of this kind that is above suspicion has been as yet recorded. This is a mutant stock in which, as May has recorded, reversion to the wild type occurs with such frequency that there can be no chance of error. The stock in question, bar eye, is a dominant mutant and the reversion therefore is to the recessive wild type of eye (round eye). The change back to normal is complete, since such individuals give only normal offspring. When such a mutant chromosome comes from the mother and goes into a son he has normal (wild type) eyes; when it comes from the father, and goes to a daughter, she is heterozygous for bar eye. Baur has recently recorded the appearance of recessive (?) mutants from self-fertilized plants (snapdragon) that bred true at once. Punnett has described a similar case (1919). The result can be accounted for, if a mutation occurred in only a single chromosome far enough
back in the germ-tract to give rise, after reduction, both to pollen and to ovules, each one carrying the mutated genes. Such an interpretation is supported by the evidence from *Drosophila*, where, although mutations are much more numerous, no such cases have been observed, and none such would be expected if mutation occurs in a single chromosome at a time, since here the germ-cells come from separate individuals.

Probably the most important evidence bearing on the nature of the genes is that derived from multiple allelomorphs. Now that the proof has been furnished that the phenomena connected with these cases are not due to nests of closely linked genes, we can properly appeal to these as crucial cases. As already explained, in ever-increasing numbers of animals and plants, series of genes have been found in each of which mutant characters with the same normal allelomorph have been found. These mutant characters of each series are also allelomorphs of one another—only two ever existing in the same individual. Obviously, not all such mutants can be due to the absence of a factor present in the germ-plasm of the wild type, since only one kind of absence is thinkable. If to save the situation for the theory of presence and absence it be assumed that only a part of the original gene is absent, and a different part in each case, then nothing is gained by the admission; and while this may be true it is equally possible that the genes change in other ways. It is not essential that we should specify the nature of the change, but simpler to look upon the mutant gene as due to some kind of change or changes that have taken place in the original germ-plasm at a specific locus—there is nothing known at present to furnish even a clue as to the nature of this change.

The demonstration that multiple allelomorphs are modifications of the same locus in the chromosome, rather than cases of closely linked genes, can come only where their origin is known, and at present this holds only in
the case (just stated) for Indian corn and for the fruit fly. If each member of such a series of allelomorphs has arisen historically from the preceding one in the series, by a mutation in a locus closely associated with the locus responsible for the first, they would be expected to give the wild type when crossed; and as the proof of their allelomorphism turns on the failure of members of the

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Fig. 108.—Diagram illustrating mutation in a nest of genes so closely linked that no crossing over takes place.

series to show the atavistic behavior on crossing, it is necessary, as stated, to know how they arose. This may be made clear by the following illustration:

Let the five circles of Fig. 108, A represent a nest of closely linked genes. If a recessive mutation occurs in the first one (line B, a) and another in the second gene (line B, b), the two mutants a and b if crossed should give the atavistic type, since a brings in the normal allelomorph (B) of b, and b that (A) of a. If a third mutation should occur in the third gene it, too, will give the atavistic
type if crossed to a or to b. Similarly for a mutation in the fourth and in the fifth normal gene. Now this is exactly what does not take place when members of an allelomorphic series are crossed—they do not give the wild type, but one of the other mutant types or an intermediate character. Evidently independent mutation in a nest of linked normal genes will not explain the results if the new genes arise directly each from a different normal allelomorph.

But suppose, as shown in Fig. 4 (line C) after a mutation had occurred in the first gene a new mutant, b, arose from a new gene, and from b a mutation arose in a third gene c, and c similarly gave rise to d; then a crossed to b will give a (or something intermediate if the heterozygote is an intermediate type). Likewise c crossed to b will give b, or c crossed to a will give a, etc. If mutant allelomorphic genes in a series such as C, a, b, c, d, e, arise as successive steps, i.e., Ca to Cb and Cb to Cc, etc., then the hypothesis of closely linked genes would seem to be a possible interpretation of the data, but if they do not arise in this way, but by independent mutations from the wild type (or even from each other, but not seriatim), then they must be due to mutations in the same gene: for, to assume that they are not, requires that, when the second mutation took place both gene a and gene b mutated at the same time, and that when c appeared three genes mutated, when gene d appeared four; when gene e five genes mutated at once, four of them being mutant genes that have already arisen independently. Such an interpretation is excluded, since it is inconceivable, even in a readily mutating form like Drosophila, that five mutations could have occurred at the same time in distinct but neighboring loci. As has been stated, the evidence from Drosophila shows positively that multiple allelomorphs arise at random.

Only two members of a series of multiple allelomorphs can be present in any one individual, and in the case of
genes carried by the sex-chromosome only one can exist at a time in the sex that has only one of these chromosomes. In the individual with two mutant allelomorphs one of them replaces the normal allelomorph of the ordinary Mendelian pair. The two mutant allelomorphs behave towards each other in the same way as does the normal towards its mutant allelomorphs. It is doubtful whether we can conclude anything more from this relation of Mendelian pairs than we knew before, although there is at least a sentimental satisfaction in knowing that both normal allelomorphs can be replaced by mutant ones without altering the working of the machinery.

The linkage relation of each member of a series of multiple allelomorphs to all other genes of its chromosome is, of course, the same. While the theory of identical loci requires this as a primary condition it is not legitimate to use this evidence as a proof of the identity of the loci, because it is not possible to work with sufficient precision in locating genes by their relation to other linked genes to distinguish between identical loci and close-linked genes.

The question of lethal genes has attracted in recent years increasing attention, both on account of their frequency and because of a curious complication they may produce in hiding the effects of other genes also present. In Drosophila we have records of more than 20 sex-linked lethals, and about 15 not sex-linked, and scattering records of many others. Gametic lethal genes are those that destroy eggs or pollen cells that contain such genes. Zygotic lethal genes affect the embryo, the larva, or the adult, so that it dies. In the case of the garden plant known as double "stocks," the genetic evidence obtained by Miss Saunders indicates that certain kinds of pollen are not produced, and presumably die because of a contained factor. The same factor does not kill the ovules.

1 The substitution by crossing over really furnishes as good a demonstration of this point.
which may therefore transmit the recessive lethal gene to half the progeny. How far the frequent occurrence of imperfect pollen grains in many species of plants is due to such factors is still uncertain.

Belling found that while the Florida velvet bean produces normal pollen grains and ovules, and the Lyon bean, another bean of the same genus, also produces normal gametes, the $F_1$ hybrid contains 50 per cent. abortive pollen grains, and possibly about 50 per cent. of the ovules are abortive. In the second generation ($F_2$) half of the pollen grains of half of the plants are abortive. The other half of the plants have normal pollen grains. This is the result expected if there are present in one of the species the factors $AAbb$, and in the other species the factors $aaBB$, the viable gametes in the $F_1$ generation being those containing $Ab$, $Ba$, and the two gametes that die being $AB$, $ab$.

Other observers have made records of abortive pollen in hybrids, but without knowing the condition of the pollen in the parents the interpretation of the results is doubtful, for, as Jeffrey has emphasized, abortive pollen is a characteristic of many wild species. There is one fact of capital importance recorded by several botanists, viz., that the degeneration of the germ-cells only takes place after the tetrad has been produced, and only in some of the cells of each tetrad. In other words, the lethal effect is not observed until the chromosomes have undergone reduction. It is obvious that if there is present a recessive lethal for the germ-cells (or for any cells, in fact), it causes no injury in the presence of its normal allelomorph, but kills when the counter-effect of its partner is removed.

Tischler found in a hybrid currant that tetrad formation was normal, and that the shrinking of the pollen grains occurred afterwards. Geerts found that one-half of the pollen grains of *Enothera Lamarckiana* degenerate, and that half of the embryo sacs abort in the tetrad
stage. Other related (wild) species and genera of the evening primrose have also been found to have some abortive pollen and ovules.

Complete or nearly complete abortion has been seen in other hybrids; *viz.*., by Rosenberg in the sundew, by Osawa in the Satsuma orange, by Goodspeed and others in the hybrid tobacco (*N. tabacum* by *N. sylvestris*), by Jesenko in the wheat-rye hybrid, and by Sutton in the hybrid between the Palestine pea (*Pisum humile*) and the edible pea. These cases may be in part the same phenomenon and in part a different one connected with failure of the chromosome to conjugate or to be properly distributed during the maturation divisions.

The "yellow mouse case" is an example of a *zygotic lethal* effect. The gene that produces the dominant yellow color is lethal in double dose, so that all homozygous yellow mice die, as Cuénot first discovered, and as has been more positively demonstrated by the work of Castle and Little. There is some evidence indicating that these homozygotes die as young embryos. Little has also shown that black-eyed white mice carry a lethal, that acts in the same way. In *Drosophila* there is a sex-linked recessive lethal factor that causes the development of tumors in the larvae, destroying every male larva that contains the sex-chromosome carrying this gene. This effect, discovered by Bridges, has been the basis for an extensive series of experiments by Miss Stark. The gene is present in the X-chromosomes; it follows the rules for all sex-linked genes in its inheritance. The females of the stock are of two kinds: One has the lethal in one sex-chromosome, and its normal, dominant allelomorph in the other. Such a female has survived because the effect of the lethal gene is counteracted by the effect of its normal allelomorph. Half of her sons get the affected chromosome. All such sons develop the tumor—one or more melanotic growths that appear in the imaginal discs or in other parts of the larva. The other sons get the other chromosome with the
normal allelomorph. They never produce a tumor and never transmit the disease. The same mother that gave these two kinds of sons—having been fertilized by a normal male, since no affected males exist—produces also two kinds of daughters, one containing the gene for the tumor (and its normal allelomorph), the other having two normal genes. The former transmit the disease as just explained, the latter daughters are perfectly normal and do not transmit the disease.

Other lethal genes kill the pupae, a few of them even allow the fly occasionally to come through, but such flies rarely propagate. Certain races of Drosophila have sterile or nearly sterile females, other races sterile males. The sterility is here lethal in so far as it affects the germ-cells. Some effects on other characters are also generally to be seen.

The presence of a lethal gene near to, i.e., linked to, another mutant gene may affect the kinds of individuals that appear because owing to the linkage the other mutant character fails to appear, except when crossing over takes place. Some examples of this relation may be given. There is a mutant race called beaded (Fig. 109) in which the margin of the wing is irregularly broken, giving the appearance of a beaded edge. The gene for beaded is dominant, and lethal when homozygous.

As in the case of the yellow mouse, only the hybrid (heterozygous) combination exists, and consequently when two beaded flies mate they produce two beaded to one normal fly, as shown in Fig. 110. Here the first pair of vertical lines stand for the pair of third chromosomes present in the egg before its reduction. The two genes here involved, that for beaded and its allelomorph for normal, are indicated at the lower end of the vertical lines. The two corresponding chromosomes in the male are represented to the right of the last. After the ripening of the germ-cells each egg and each sperm carries one or the other of these chromosomes. Chance meetings of egg
and sperm are indicated in the figure by the arrow-scheme below, which gives the combinations (classes) included in the four squares. The double dominant $BB$ is the class that does not come through. The result is two beaded (heterozygous) to one normal fly.

The beaded stock remained in this condition for a long time; although selected in every generation for beaded, it did not improve, but continued to throw 33 per cent. of normal flies. Then it changed and bred nearly true.

![Diagram showing the relation of the chromosomes (represented by the vertical rods) in a cross of “beaded” by “beaded.” Flies homozygous for beaded die as indicated by the cross-hatched square.](image)

The change must have been due to the appearance of another lethal factor (now called lethal three, here $L_3$) in Fig. 111). Such a gene was found in the race when studied later by Muller.

The lethal gene that appeared in the beaded stock was also in the third chromosome, and in the chromosome that is the mate of the one carrying the gene for beaded, i.e., in the normal third chromosome of the beaded stock. The lethal gene lies so near to the level of the beaded-normal
Fig. 109.—Two flies (Drosophila) with beaded wings.
pair of genes that almost no crossing over takes place between the levels occupied by the two pairs. These relations are illustrated in the next diagram, Fig. 111. Here again the two pairs of vertical lines to the left represent the two third-chromosome pairs in the female and to the right in the male. The location of the two pairs of genes involved, \( N-l_1 \) and \( B-N \), are indicated. These combinations give the four classes in the squares of which two classes die, viz., \( NNBB \) (pure for beaded) and \( l_1l_1NN \) (pure for lethal three). The result is that only beaded flies come through, and since all these are heterozygous both for \( B \) and \( l_1 \), the process is self-perpetuating.

If the preceding account represented all of the facts in the case, the stock of beaded should have bred perfectly true, but it has been shown in \( Drosophila \) that crossing over between the members of the pairs of genes takes place in the female. Hence we should expect a complication due to crossing over here unless the level of the two pairs of genes was so nearly the same as to preclude this possibility. In fact, in addition to the beaded flies the
stock in this condition alone should give 10 per cent. of crossing over, i.e., it should still produce a small percentage of normal flies. It so happened, however, that there was present in the stock a third gene that lowers the amount of crossing over in the female to such an extent that, for the two "distances" here involved, practically none takes place. When it does, a normal fly appears, but this is so seldom that such an occurrence, if it happened in a domesticated form of which the wild type was unknown, would be set down as a mutation like that shown by the evening primrose.

The third factor that entered into the result is not unique, for Sturtevant has shown that crossover factors are not uncommon in *Drosophila*. The analysis that Muller has given for beaded, while theoretical, is backed up by the same kind of genetic evidence that is accepted in all Mendelian work. It makes an assumption but one that can be demonstrated by any one who will make the necessary tests. It is also possible to produce at will other balanced lethal stocks that will "mutate" in the sense that
they will throw off a small predictable number of a "mutant" type—a type that we can introduce into the stock for the express purpose of recovering it by such an apparent mutation process.

For example, dichete is a third chromosome dominant wing-and-bristle character and, like beaded, a recessive lethal. Sturtevant bred flies with the gene for dichete in one of the third chromosomes and with a gene for the recessive eye-color, peach, in the other for several genera-

![Diagram](image)

Fig. 113.—Diagram illustrating how in the presence of a dominant factor, dichete, and a lethal in its homologous chromosome at about the same level, together with another factor, peach-colored eyes (p), gives the result shown in the squares. No peach appears in the offspring except where crossing over takes place as shown in the next diagram.

tions. A lethal appeared by mutation in the peach-bearing chromosome very near the level of the dichete gene in the opposite chromosome.

The order of these genes is shown in Fig. 113. This is then a balanced lethal stock that throws only dichete flies,\(^2\) except for a small percentage of dichete peach flies due to crossing over. The result for the non-crossover classes is shown in the square to the right. Only two of the four classes come through: the two that die are the

\(^2\)Very rarely a crossover not-dichete fly will appear.
one pure for dichete and the one pure for lethal. The surviving classes continue to produce the same kind of offspring since they are, like the parents, heterozygous for the two lethal factors. But the factors are not near enough together to prevent crossing over, which occurs in about 5 per cent. of cases between the lethal and peach genes. The next diagram, Fig. 114, shows how when crossing over takes place in the female, there result four classes (see squares), of which two die (as before), and of the two that survive one is dichete peach. Taking both non-crossover and crossover results together, the expectation is 95 + 95 + 5 dichete to 5 dichete peach or 97 1/2 to 2 1/2. This stock then breeds true for dichete without showing the gene it carries for peach eye-color except in a small percentage of cases, and if the peach-eyed fly should be unable to establish itself in nature, like some of the *Enothera* mutants, the stock would not be changed by it, but continue to throw off a few “mutants” with peach-colored eyes.

Fig. 114.—Diagram illustrating crossing over of factors shown in Fig. 113.
Now this process is not what is ordinarily meant by mutation, for we mean by the latter that a new type has suddenly arisen in the sense that some change has taken place in the germ-plasm—a new gene has been formed. The process here described is one of recombination of genes shown by Mendelian hybrids, the only unusual feature being that all the phenomena involved do not come to the surface because many classes are destroyed by lethals.

The results are interesting also in another way. It has been assumed by those who think that *O. Lamarckiana* is a hybrid that the mutant types are only the segregation products of the types or combinations that went in to produce the hybrid. But the *Drosophila* cases show that balanced lethal stocks may arise within stocks themselves by the appearance in them of lethal factors closely linked to other factors—new or old ones. When new genes arise in such lethal stocks the process may be one of true mutation, but the revelation of the presence of the gene is hindered by the lethal factors, so that when the character appears, it appears as a "new" mutant, but is in reality due to recombination of mutant genes that had arisen in an earlier generation. As a matter of fact, the first
appearance of even ordinary mutants, unless they be dominant, must come two or more generations after the mutation has taken place; for, the evidence indicates that mutation appears in only one chromosome at a time. In the case of sex-linked genes, however, any mutation that takes place in one of the X-chromosomes of the mother is revealed if the egg containing it gives rise to a son, because he has but one X-chromosome and that comes from his mother.

The delayed occurrence then of mutants in balanced stocks is not different from the delay in other stocks—

![Diagram illustrating balanced lethals and twin hybrids.](image)

Fig. 116.—Diagram illustrating balanced lethals and twin hybrids.

only when the recombinations occur in balanced lethal stocks they must have been preceded by crossing over, which diminishes the number of mutants that appears. The number of mutants that appears is determined by the distance of the genes for the character from the nearest lethal gene.

One of the most interesting features of Lamarck’s primrose arises when it is bred to certain other species or varieties. It gives rise to two kinds of offspring called Twin Hybrids, to which De Vries gives the names *lacta* and *velutina* (Fig. 115). Now it is a feature

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If in self-fertilizing forms a mutation takes place so early in the germ-plasm that it gets into both eggs and sperm the new character may appear at once (see ante).
of balanced lethal stocks like beaded that they repeat precisely this phenomenon. For instance, if a beaded male is crossed to wild female, two kinds of offspring are produced, viz., beaded and normal. A similar process would account for twin hybrids in *Oenothera* crosses. There is another peculiar phenomenon that has been described for crosses in the evening primroses, viz., the occurrence in $F_1$ of four types. This phenomenon, too, can be imitated in *Drosophila* by crossing balanced lethal dichete to balanced lethal beaded (Fig. 117).

![Diagram illustrating lethals and four types in F1](image)

**Fig. 117.—Diagram illustrating lethals and four types in F1.**

Other parallels might be cited, but these, I think, will suffice to indicate that the discovery of balanced lethal stocks may solve some at least of the outstanding difficulties of mutation and inheritance in *Oenothera*, and bring it into line with other groups. There are, of course, other peculiarities of the evening primrose that such zygotic lethals will not explain; such, for instance, as the 15-chromosome type, and *O. gigas*. But these cases are already on the road to solution.

The occurrence of other lethals, called *gametic* lethals,
that kill the germ-cells—gametes—before they are ready for fertilization, has already been invoked by De Vries and others to explain the peculiarity of "double reciprocal hybrids."

Is the Direction of Mutation Given in the Constitution of the Genes?

When writers have brought forward evidence of continuous and progressive change in a character, they have not concerned themselves with the analysis of the change in the germ-plasm that has brought it about—in fact, in most of these cases the possibility of advance in a principal gene or of advance through modifying genes has not been appreciated or even understood. Paleontologists who have in the main been the strong advocates of orthogenesis have based their conclusions on the observed advances in a character in the same series and in "parallel" series. They overlook the fact that to-day there is experimental evidence demonstrating that variations as small even as those they record have been shown to rest on mutational stages. If the progress has been in the direction of adaptation, natural selection of small mutant differences will completely cover their findings. If it is claimed that in some of these cases the orthogenetic series is not in the line of adaptive advance, the burden of proof lies heavily on their shoulders. Moreover, the fact, that recent work has made clear, that genes generally have more than a single effect on the organization, opens wide the door of suspicion, for the observed morphological progress might be a by-product of influences that have other and important, though unseen or unknown, effects. In a word, an orthogenetic series of changes does not in itself without a closer analysis than has as yet been furnished, establish that an innate principle, urge, vis-a-tergo, "kick," or vital "force" is causing the successive moves. The genetic evidence concerning multiple factors must create at least a strong suspicion against the "will to
believe' in the mystic sentiments for which these terms always stand. That a progressive series of advances in a gene might take place with a consequent advance in the many characters involved is thinkable, especially if it could be shown that environmental changes cause parallel progress in the gene, and this in turn on the character. How probable this is the reader must decide for himself in the light of the very clear evidence that each character is affected by changes in many genes differently located in the germ-plasm, and that it is not a progressive change in one gene that makes selection possible, but changes in any one of many genes.

**Chance Mutation and Natural Selection**

The mutation process rests its argument for evolution on the view that among the possible changes in the genes, some combinations may happen to produce characters that are better suited to some place in the external world than were the original characters. Apparently this appeal to chance, like Darwin's appeal, has offended some of the adherents of the doctrine of organic evolution, because it has seemed to them inconceivable that chance could ever bring about the assembling of such an intricate piece of machinery as a highly complex organism. The attempt to mitigate the rude shock of the appeal to chance was made by Darwin by pointing out that evolution had been gradual and that the assemblage has not taken place out of chaos, but each stage has been built up on one a little less complex than the preceding one. Nevertheless the fact remains that persistent efforts continue to be made from time to time to introduce into the theory of evolution some sort of directive mystical agency. The Lamarckian theory has tried to bring about a more immediate relation between the organism and its environment of such a kind that the adaptive change that appears in the body as a result of a reaction between the environment and the animal or plant, is reflected into the germ-plasm. Bergson
has cut the knot by postulating an innate adaptive responsiveness of the animal to every critical situation that calls out a response. The adherents of orthogenesis appeal, apparently—in so far as they commit themselves—to some sort of innate principle that causes advance in complexity along one line, and they seem to hint at times even along directed lines of adaptation. Still more elusive are vague appeals made to some unknown principle—some sort of mysterious element, some "Bion," resident in living material and peculiar to it that is responsible for evolution.

We are not concerned with any of these so-called agents, but there is a relation between chance and evolution shown by living things that has been largely neglected, or at least vaguely referred to, even by natural selectionists, that is of fundamental importance when evolution is treated as a phenomenon of chance.

This relation may be stated in a general way as follows: Starting at any stage, the degree of development of any character increases the probability of further stages in the same direction. The relation can better be illustrated by specific cases. The familiar example of tossing pennies will serve. If I have thrown heads five times in succession, the chance that at the next toss of a penny I may make a run to six heads is greater than if I tossed six pennies at once. Not, of course, because five separate tosses of heads will increase the likelihood that at the next toss a head rather than a tail will turn up, but only that the chances are equal for a head or a tail, so that I have equal chances of increasing the run to six by that throw, while if I tossed six pennies at once the chances of getting six heads in one throw are only once in 64 times.

Similar illustrations in the case of animals and plants bring out the same point. If a race of men average 5 feet, 10 inches, and on the average mutations are not more than two inches above or below the racial average, the chance of a mutant individual appearing that is 6 feet tall is greater than in a race of 5-foot men. If increase in height
is an advantage, the taller race has a better chance than the smaller one. This statement does not exclude the possibility that a short race might happen to beat out in height a taller race, for it might more often mutate; but chance favors the tall. In this sense evolution is more likely to take place along lines already followed, if further advantage is to be found in that direction.

A rolling snowball that already weighs 10 pounds is more likely to reach 15 pounds than is another that has just begun to roll. The chance that a monkey could change into a man is far greater than that an amœba could make the transition. The monkey has accumulated, so to speak, so many of the things that go to make up a man that his chance of reaching that goal is vastly greater than the amœba’s.

There is also a peculiarity of animals and plants that assists greatly towards progress along lines already started. The individual multiplies itself, and a new mutant character that is advantageous becomes established in a large number of individuals, or even in all individuals of the race. The number of individuals increases the chance of a new random mutation along the path already taken. It is true that the chance of a random variation in the opposite direction is equally great, but as this, by hypothesis, is the less advantageous direction it will fail to establish itself in numbers.

Darwin built up his evidence for natural selection and even for evolution, on the artificial selection of variations of animals and plants under domestication. It is in this field that the student of Mendelism revels. Almost without exception he finds that the domestic races of animals and plants are built up by mutational differences. It is this evidence that to-day is a hundredfold stronger for the theory of evolution than it was in Darwin’s time.

The slightest familiarity with wild species will suffice to convince any one that they differ from each other generally, not by a single Mendelian difference, but by
a number of small differences. The student of Mendelian heredity at least is not likely to fall into the error of identifying single Mendelian differences with the sum total of differences by which wild types and often even wild varieties differ from each other, but whenever he has had an opportunity to study these single differences in wild varieties he has found that they seem to originate and to be inherited in the same way as other Mendelian characters.

Species as Groups of Genes

If related species have many genes in common they may be expected to produce at times the same mutants. In fact, it is not at all uncommon to find even in Mendelian literature such forms as albinos spoken of as though they represent the same mutation wherever it arises. Attractive as such a view appears, experience has shown that it is very unsafe to judge as to the nature of the mutation from the appearance of the character alone. Two different white-flowered races of sweet peas are known which give the wild purple-flowering pea when crossed, showing that they represent different mutations. Similarly, at least two recessive white races of fowls are known, as well as a third dominant white race. Three independent mutations have produced white birds. Whether albino mice, rats, rabbits, squirrels and guinea pigs have arisen through a mutation in a common gene cannot be determined because they cannot be crossed to each other. When we consider that many factors may combine to produce a given pigmented animal, and that a change in any one of them may affect the end result, it will be evident that the expectation would be against rather than for the conclusion that the same gene had changed in all cases. Only when it could be shown that a particular gene of the complex is more likely to change in a given direction than other genes of the complex would this interpretation become plausible.
There is evidence in *Drosophila melanogaster* showing that the same mutation to white eyes has occurred several times, and the additional and all-important proof has been obtained that it is the same locus that has produced the white-eyed mutant. This may appear to give some slight support to the view that albino mutants appearing in other related species may be due to the same mutative changes, but without additional evidence this conclusion is problematical.

In the mammal's melanin individuals have been frequently described, but there is no direct evidence to show that they are due all to the same change. In the roof rat there is a black type that is dominant to the gray of this race, while the black type of the Norway rat is recessive to the gray of that race. It seems probable that they are different mutations, but not necessarily so.

Yellow in the mouse is dominant and lethal; two races of yellow rats are known, both recessive forms. The relation of yellow to black in mice is different from the relation of either of the yellows to black in the Norway rat. If the blacks are the same mutant the yellows are different; if either yellow of the rat is the same as the yellow of the mouse, the blacks must be different, etc.

The uncertainty of reaching any conclusion in regard to the nature of the mutation from the appearance of the character of the mutant is excellently illustrated in such a group of mutants as that of the fruit fly, where a considerable number of cases are known in which mutants that are almost indistinguishable externally have been shown to be due to mutations in different parts of the germ-plasm. There are five kinds of black mutants, three or more yellows and several eye colors that are practically indistinguishable. The evidence showing their difference is obtained from the results of crossing, where, as a rule (except, for example, cases of complete or incomplete dominants), reversion to the wild type occurs. In addi-
tion, the localization of the gene causing the modification shows them to be different.

The method of localizing genes offers an opportunity for obtaining evidence in regard to like-mutants in related species that cannot be crossed, and a step forward in this direction has been taken by C. W. Metz for other species of the genus *Drosophila*. In one species, *D. virilis*, he has found 12 mutants, and these fall into three groups of linked genes. Three of them, yellow, forked and confluent, resemble externally characters of *D. melanogaster*. Yellow and forked are sex-linked and look like the same characters in *melanogaster*. Confluent is like a second chromosome character of the same name in *melanogaster* in three respects: first, in that the structures are similar; second, in that the character is dominant in both forms; and, third, in that it is lethal in the homozygous state. The terminal position of yellow and the large amount of crossing over with forked are, roughly speaking, the same in both.

Even in this case further work is needed, first, because within the same species the occurrence of similar-looking characters due to different factors is known, e.g., there are two genes for yellow color (yellow and lemon) in the first chromosome of *D. melanogaster* and in the same part of that chromosome, and second, because it is not to be expected that the number of crossovers would be identically the same between the same loci in different species, since marked variations are known within a single species. Unless such species can be crossed, the only convincing evidence that we can hope to get will be to establish the same linear order in the chromosome for several genes whose characters appear to be the same or similar.

Other evidence of a different kind also helps to make probable that the same mutations occur in different species. For example, in cases where a mutant gene produces a number of changes in different parts of the body, the probability that it is the same as one in a different species that causes the same modifications, is in propor-
tion to the number of the same kinds of change that they produce. The two following cases recorded by Sturtevant illustrate this relation:

Two species, *viz.*, *Drosophila melanogaster* and *D. funebris*, have each produced a mutation called notch. This character, notch, involves not only a notching at the end of the wings but also the thickening of the second and fifth veins of the wings, frequent reduction and roughening of the eyes, inequalities of the rows of hairs on the thorax, frequent doubling of the anterior scutellar bristles, and a recessive lethal effect. The character is also dominant and sex-linked. It is one of the commonest mutations in *melanogaster* and was the first to be picked out in *funebris*. So many peculiarities in common make it hard to believe that they do not represent the same genetic change. Another mutant also found in *D. funebris* that parallels one in *D. melanogaster* is called hairless, producing several similar effects in both. In both the factor is an autosomal dominant; it affects the hairs, certain bristles, and the second, fourth and fifth veins of the wings, and has a recessive lethal effect.

One of the most interesting ideas that De Vries brought forward in his mutation theory is that groups of "small species" or of varieties are made up of many common genes and differ in a relatively small number of genes. The genetic analysis of a group of smaller species would consist in finding out how the different genes are distributed amongst the members of this group. Phylogenetic relationship comes to have a different significance from the traditional relationship expressed in the descent theory; but this point of view is so novel that it has not yet received the recognition which we may expect that it will obtain in the future when relationship by common descent will be recognized as of minor importance as compared with relationship due to a community of genes.