CHAPTER VI

ARE MUTANT RECESSIVE GENES PRODUCED BY LOSSES OF GENES?

MENDEL did not consider the question of the origin or the nature of the genes. He represented in his formula the dominant gene by a capital letter and the recessive gene by a small letter. The pure dominant was AA and the recessive was aa and the hybrid, or F_1, was Aa. The question as to origin did not arise, because the characters yellow and green, tall and short, round and wrinkled, were already present in the peas selected for the experiment. Only later, when the relation of the mutants to the wild species from which they were supposed to have come was considered, did their origin arouse interest. A specific case, that of rose comb and pea comb in domestic fowls, seems to have had something to do with the reasoning that led to an interpretation of recessive genes as losses or absences.

Certain breeds of domestic poultry have a comb called rose (Fig. 43c). They breed true to this type of comb. Other races have a comb called pea (Fig. 43b). They also breed true to their type. If these breeds are crossed, the F_1 has a new form of comb, called walnut (Fig. 43d). If two F_1 fowls with walnut combs are mated, the offspring show 9 walnut, 3 rose, 3 pea, to 1 single. The numerical result shows that two pairs of genes are involved, rose and not-rose, pea and not-pea. The single comb is not-rose, not-pea, which was then interpreted to mean the absence of pea and of rose genes. But the not-presence of pea and not-presence of rose genes does not prove

necessarily that the allelomorphs of these genes are absences. The allelomorphs may be only other genes that do not give rise either to pea or to rose comb.

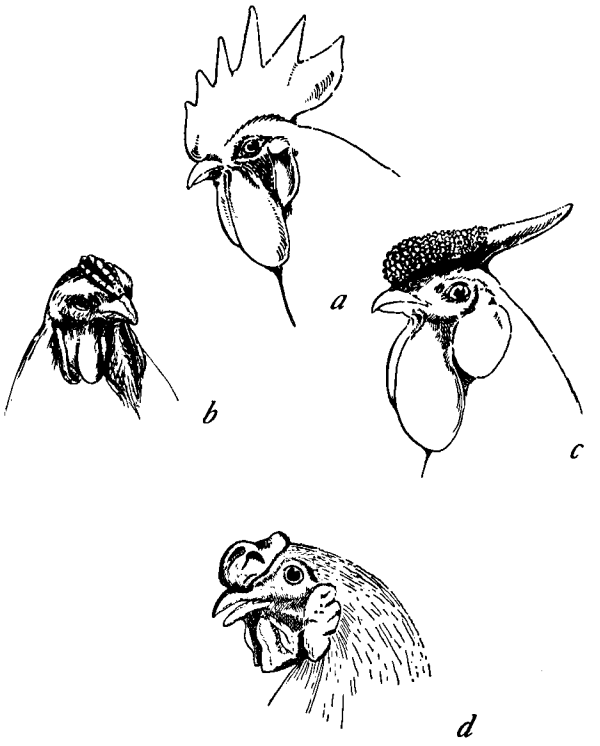

FIG. 43.

Combs of domesticated races of fowls. a, single comb; b, pea comb; c, rose comb; d, walnut comb (the hybrid or F_1 type when pea and rose are crossed).

The result may be stated in another way that may make the situation more obvious. If we assume that the wild jungle fowl, from which our domesticated races have come, had a single comb, and that at some time a dominant mutation occurred that gave a pea comb, and at

another time, in another bird, a dominant mutation occurred that gave a rose comb, it follows that in the cross described above, the F_2 single comb is due to the presence of the original wild type genes. Thus, a race with pea comb (PP) will contain the wild type genes (rr), from which the rose comb arose by mutation. Similarly the race with rose comb (RR) will contain the wild type genes (pp), from which the pea comb arose by mutation. The formula for the pea comb race is then PPrr and for the rose comb race RRpp. The germ cells of these two races will be Pr and Rp respectively, and the F_1 will be PpRr. The two dominants produce a new type, the walnut comb. Since two pairs of genes are present in F_1 there will be 16 combinations in F_2, and of these one will be pprr or single comb. The single comb is due then to the recombination of the wild type recessive genes that entered the cross.

Recessive Characters and Absences of Genes.

In the background of the presence and absence theory there lurks, beyond doubt, the idea that many recessive characters are actual losses of some character that was once present in the original type, hence by implication the gene of that character is also absent. This idea is a hangover of Weismann's theory of the relation of determinant to character.

It is instructive to look a little closer into the evidence that may have seemed at first to support such an interpretation.

An albino rabbit or rat or guinea pig may be interpreted to have lost the pigment characteristic of the original type. In a sense no one will deny that the relation of the two types may be expressed in this way, but, in passing, it may be noted that many albino guinea pigs have a few colored hairs on the feet or toes. If the pigment-pro-

ducing gene is absent and if color depends on the presence of this gene it is difficult to explain the presence of these colored hairs.

A mutant race of Drosophila is called vestigial (Fig. 10) because only vestiges of the wings are present, but if the larvae are reared at a temperature of about 31°C. the rudiments are quite long and in extreme cases may be almost as long as the wings of the wild type. If the gene for producing long wings is absent, how can a high temperature bring it back again?

There is another highly selected race of Drosophila in which the eyes are absent in most individuals, but small eyes may be present in other individuals (Fig. 30). As the culture gets older more and more of the flies have eyes and the average size of the eyes is larger. It is not probable that the gene changes as the culture gets older and if it were absent in the eyeless flies that first hatch, it is not likely that the age of the culture could bring back the missing gene. Moreover, if this were the case, flies from the older culture should produce offspring more of which had eyes or larger eyes than the average of the race, but this does not happen.

In still other recessive mutant types the loss of the character itself is by no means obvious. A black rabbit is recessive to the gray wild type. The black rabbit has actually more pigment than has the gray rabbit.

There are dominant genes that produce pure white individuals. The white leghorn race of fowls is due to such a factor. Here the argument is reversed, and it is said that there is present in the wild type jungle fowl a gene that suppresses white plumage. When this suppressing gene is lost the bird is then able to develop white plumage. Logical as this argument may appear, the assumption of the presence of factors of this sort in the wild bird seems far fetched, and in the light of the occur-

rence of other dominant characters, the argument is not one that makes a favorable appeal but seems rather a forced attempt to save the theory at all costs.

It must be remembered, too, that the distinction between recessive and dominant genes is largely arbitrary. Experience has shown that characters are by no means always recessive or dominant. On the contrary, in a large majority of cases, a character is not completely dominant or completely recessive. In other words, the hybrid type, containing a dominant and a recessive gene, lies somewhere between the parent types—both genes have some effect on the character produced. When this relation is realized, the theory that a recessive gene is an absence does not appear in so favorable a light. It is true that it might be claimed in such cases, with some grounds for justification, perhaps, that the hybrid is intermediate because one dominant gene produces less effect than two dominant genes, but this introduces a new feature into the situation. It does not necessarily mean that the effect is really due to one absence. It can be brought into line with this assumption perhaps, but is not a necessary inference.

If the preceding arguments are admitted as cogent we might dismiss this interpretation of the meaning of the recessive gene taken in a literal sense. But in recent years another interpretation of the relation between the effect of all the genes and the character has appeared that makes the refutation of the presence and absence view much more difficult. For example, suppose a gene were actually lost from a chromosome and that when two such chromosomes are brought together, some character of the individual is modified or even absent. The modification or absence might be said to be the effect produced by all the rest of the genes. It is not the absence, as such, that determines the result, but the effect produced, when two

genes are absent, by the rest of the genes. Such an interpretation avoids the rather naïve assumption that each gene in itself represents a character of the individual.

Before discussing this view it should be pointed out that in certain aspects this interpretation is similar to, and in fact derived from, another more familiar interpretation of the relation between gene and character. For instance, if the mutation process is interpreted to mean a change in the constitution of a gene, the result that follows, when two recessive mutant genes are present, is not that the new character is due to the new gene alone, but that the new character is the end product of the activity of all the genes, including the new ones, in the same sense that the original character was also due to the original gene (that mutated) and to the rest of the genes.

These last two interpretations may be briefly stated as follows: The first one states that in the absence of a pair of genes all the rest of the genes are responsible for the mutant character. The second states that when a gene changes its constitution, the end-result, produced by the new genes, and the rest of the genes, is the mutant character.

There is a certain amount of recently obtained evidence that has some bearing on the question here at issue although it cannot be said to furnish a decisive answer in favor of either view. The evidence is, nevertheless, worth considering on its own merits, since it brings out certain possibilities relating to mutation that have not, so far, been discussed.

There are several mutant stocks called collectively notch that can be identified by one or more incisions at the end of the wings and by the thickening of the third vein of the wing (Fig. 44). Only females having these characteristics appear. Any male carrying the gene for

notch dies. The factor is carried in the X-chromosome. The notch female has one X carrying the factor for notch and another X with its normal allelomorph (Fig. 45). Half of her ripe eggs retain one X, half the other. If she

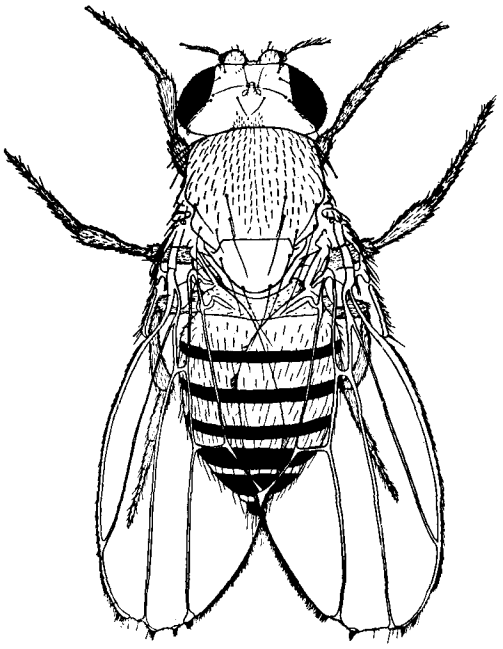

FIG. 44.

Notch-wing, a dominant sex-linked, recessive lethal of Drosophila melanogaster.

is fertilized by a normal male, an X-sperm uniting with an egg carrying the normal X produces a normal daughter; an X-sperm uniting with an egg carrying the notch-bearing X produces a notch daughter. A Y-sperm uniting with an egg carrying a normal X produces a normal son; a Y-sperm uniting with an egg carrying a notch-bearing X forms a combination that dies. The output is two daughters to one son.

As far as this evidence goes, notch might be interpreted as a recessive lethal gene that acts as a dominant wing modifier in the hybrid. It was later shown by Metz and Bridges (1917) and by Mohr (1923) that more of the X-chromosome is involved in the notch mutation than in

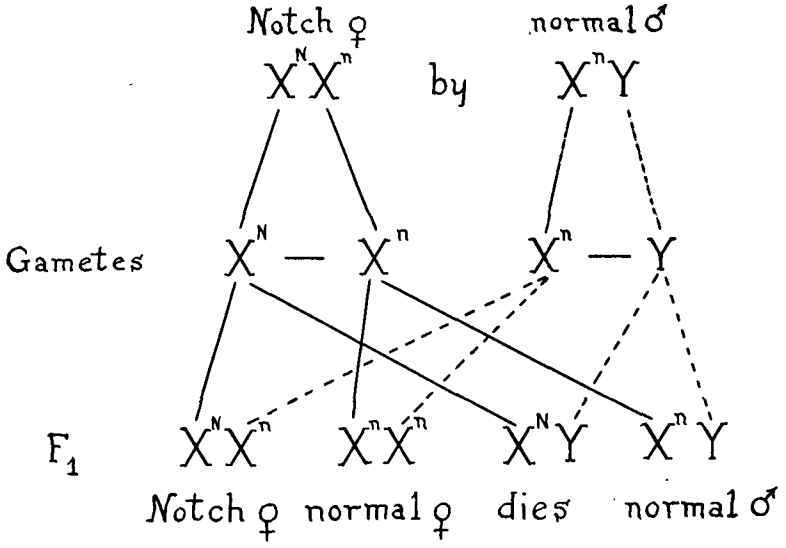

FIG. 45.

Diagram to illustrate a cross of a Notch female, $X^N X^n$ by a normal male, $X^n Y$. The X-chromosome with Notch is X^N; the other X, carries the normal allelomorph, X^n.

an ordinary "point mutation"; for when *recessive* genes are present in the region of notch in one X-chromosome, and notch in the other X-chromosome, the recessive characters appear in such an individual as though a certain region of the notch chromosome were absent or at any rate inactive (Fig. 46a). The result is practically the same as though an absence had actually arisen. In some of the notch mutants the "lost" region extends over about 3.8 units (from the left of white to the right of

abnormal) (see chart, Fig. 19); but in other notches the lost region extends over fewer units. In each case the test seems to mean that a small piece (more or less) of the chromosome has, in some sense, dropped out.

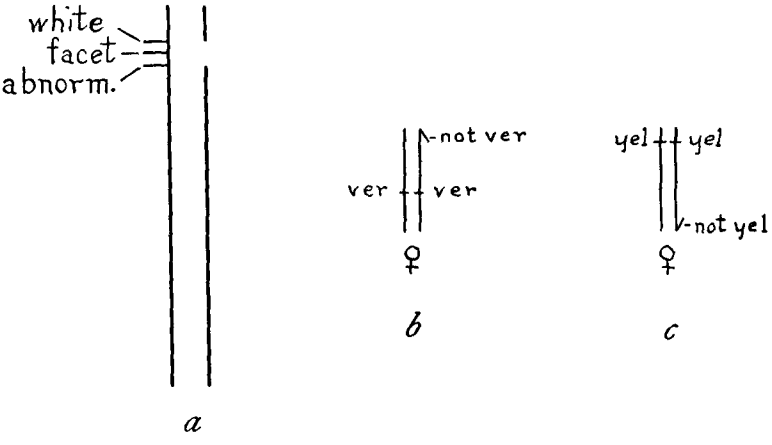

FIG. 46.

Diagram a, showing the location of the genes in the Notch-bearing chromosome. In the right-hand rod the break in the chromosome stands for Notch. In the left-hand rod the location of three recessive genes (white, facet, abnormal), that stand opposite Notch, are indicated. In b the translocation of a piece of an X-chromosome to another X is shown. There are two vermilion-bearing X-chromosomes to one of which the piece is attached carrying the normal allelomorph of vermilion, *i.e.*, not-vermilion. In c there are two yellow-bearing X-chromosomes to one of which is attached a piece carrying the normal allelomorph of yellow, *i.e.*, not-yellow.

As has been stated, recessive genes, when opposite to notch, produce their recessive characters. This is consistent either with the view that these recessives are absences and the effect is produced by all the rest of the genes, or with the view that the recessive genes are present and produce their effect in combination with all the rest of the genes. The result does not permit a decision between the two views.

There is, nevertheless, a slight difference between the character produced by two recessive genes in this region and one recessive and the notch "absence." This difference might seem to be due to one real absence (notch) and one recessive not being equivalent to two recessive genes, but further consideration shows that the two situations are not quite comparable owing to the absence of other genes in the lost notch piece. These genes are present in the double recessive type, and the slight differences in the result in the two cases may be referable to the presence or absence of these other genes.

In the preceding case it has not been possible to show by cytological evidence that a piece of the X-chromosome is absent in the notch mutant—its absence is deduced from the genetic evidence alone. In the next case, however, an actual absence has been demonstrated.

Occasionally one of the small fourth chromosomes is lost (haplo-IV, Fig. 29). This chromosome carries, in certain mutant stocks, recessive genes. It is possible to make up an individual that has a recessive gene—eyeless for example—in its single IV-chromosome. Such individuals show the characteristics of the eyeless stock but are, as a class, more extreme than when two eyeless genes are present. This difference may be due to the absence of the other genes in the absent chromosome.

A different relation arises in the case of translocation, so called by Bridges and Morgan (1923) which means that a piece of a chromosome has become detached and reattached to some other chromosome. It perpetuates itself, and, owing to the genes that it carries, introduces a complication into the genetic results. For example, a piece of the normal X-chromosome in the region of the vermilion locus became attached to another X-chromosome (Fig. 46b). A female with vermilion genes in each of its X-chromosomes and the transposed piece attached to one

of them (Fig. 46b) is vermilion despite the fact that one normal allelomorph of vermilion is present in the piece. At first sight it may seem, if the vermilion genes are interpreted as absences, that two absences cannot possibly dominate one presence. On second thought, however, another explanation is possible, for, if the vermilion eye color is due to the action of all the other genes when vermilion is absent, the same result might happen even though one dominant normal allelomorph is present. The situation is not identical with one in which a vermilion gene is present in one chromosome and its normal allelomorph in the other.

The relation shown here between two recessive genes and a dominant gene in the translocated piece does not always lead to the development of the recessive character. For example, there is another case of translocation reported by L. V. Morgan. A piece of an X-chromosome of the region of the mutant genes yellow and scute became stuck to the right end of an X-chromosome. A female that has the recessive genes for yellow or for scute in each of her X-chromosomes (Fig. 46c) and a piece attached to one of these X's shows the wild type character. Here the effects of the recessive genes are counterbalanced by the dominant allelomorphs of the attached piece. This is interpreted to mean that all the other genes, plus those in the attached piece, combine to turn the scale toward the dominant type and this is expected on either of the contrasted interpretations as to the nature of the gene.

The relation of two recessive genes to one dominant has also been studied in the triploid endosperm of corn and in one triploid animal. The nuclei of the endosperm cells of the seed of corn arise from the union of one pollen grain (haploid in chromosome number) and two nuclei of the embryo sac (each haploid). A triploid or threefold

nucleus results (Fig. 47), which by division gives rise to the triploid nuclei of the endosperm cells. In floury corn the endosperm is composed of soft starch, while flint corn has a large amount of corneous starch in the endosperm. If a floury corn be used as the female parent (ovule) and

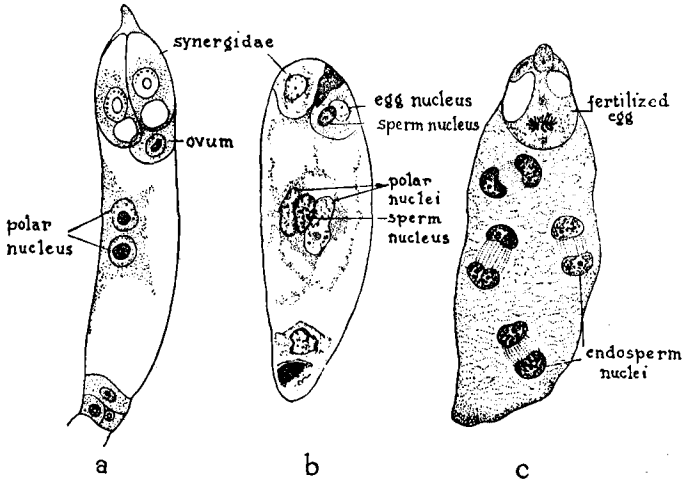

FIG. 47.

Three stages in the fertilization of the egg-nucleus in the embryo sac of plants. In b the two maternal haploid nuclei and the single paternal haploid sperm nucleus are shown. By their union the triploid endosperm is produced as shown in c. (After Strasburger and Guinard from Wilson.)

flinty corn as the male parent (pollen) the seeds produced by the F_1 plant have floury endosperm. The result shows that two floury genes are dominant over one flinty gene (Fig. 48a). If the reciprocal combination is made, flinty female parent and floury pollen, the F_1 seeds are flinty (Fig. 48b). Here two flinty genes dominate one floury. It is a matter of choice which gene is chosen to represent the absence of the other. If the absence is floury, then two absences would be said to dominate one presence

in the first case, and two presences to dominate one absence in the second case.

The interpretation of two absences dominating a presence would have no meaning if taken literally, but as has been pointed out it is possible to explain such a statement, if, in the absence of a gene, the floury character is determined by the rest of the genes, and, of course, the same

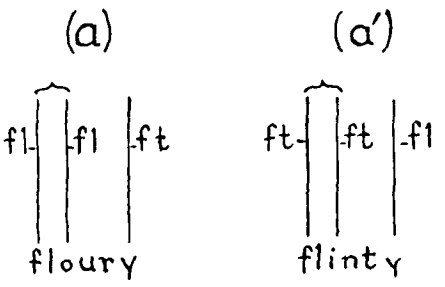

FIG. 48.

Diagrams of triploid condition of endosperm of corn when, as in a, two floury genes and one flinty are present giving floury endosperm; and when, as in a', two flinty genes and one floury gene are present giving flinty endosperm.

explanation applies if there is present a gene for floury (a mutated gene from flinty) whose effect is produced by itself plus the rest of the genes. This evidence from triploid endosperm is no more decisive than when a translocated piece of a chromosome introduces a third element into the situation.

There are several other cases in corn where two recessive elements do *not* dominate a single dominant, but these have no further bearing on the present question.

If a triploid female Drosophila has a vermilion gene in each of two of its X-chromosomes and a red gene in the third, the resulting eye color is red. One dominant gene here dominates two recessives. This result is the opposite

of that where the wild type (dominant) gene present in the duplicated piece was opposed to two vermilion genes. The two situations are, however, not identical in all respects, for the triploid differs from duplication by the occurrence of nearly an entire X-chromosome instead of only a short piece of this chromosome. The excess of genes in the extra X-chromosome may account for the difference in the two cases and this holds equally whether the recessive genes be interpreted as real absences or as mutated genes.

The Bearing of Reverse Mutation (Atavism) on the Interpretation of the Mutation Process.

If recessive genes arise by losses, then there is little expectation that a pure recessive stock would ever produce again the original gene, since this would mean apparently the production of something highly specific from nothing. On the other hand, if mutation is due to a change in the constitution of the gene, it seems less difficult to imagine that the mutated gene might sometimes return to the original condition. It may be that we know too little about the gene to give much weight to such arguments; nevertheless, the occurrence of return mutants would appear more plausibly explained on the latter view. Unfortunately the evidence bearing on the question is not entirely satisfactory. There are, it is true, a number of instances in Drosophila where a mutant recessive stock has given rise to an individual with the original or wild type character; but an occurrence of this sort, unless controlled, cannot be accepted as sufficient evidence, since the chance of contamination of the stock by a wild type individual is not to be ignored. If, however, a mutant stock is marked by several mutant characters, one only of which reverts, the occurrence furnishes the desired evidence, provided no other combinations of these mu-

tants are present in the vicinity at the time. There are a few recorded cases in our stocks that fulfill these conditions, and the evidence, as far as it goes, shows that reversal may take place. There is also another possibility that has to be guarded against. Some of the mutant stocks have, after a time, seemed to lose more or less the characteristics of that stock, yet when outbred it has been found that the mutant character can be recovered in its original strength. The fourth chromosome character, bent wings (Fig. 30), that is itself variable, and subject to environmental influence, has shown, when not selected, a tendency to return to the wild type in appearance. If a fly of this kind is outcrossed to wild stock and the F_1's inbred, the bent character reappears in many of the individuals of the expected bent class. A similar result has been found in another mutant stock called scute, characterized by the *absence* of certain bristles on the thorax. Individuals appeared in certain pure cultures in which the "missing" bristles were present. Apparently the mutant had reverted to wild type. But that this had not occurred was shown by breeding such flies to wild type stock. In the second generation, scute flies reappeared. A study of this case has shown that the return to normal was due to the appearance of a recessive factor which, when present in homozygous condition in scute stock, brings about the development there of the missing bristles. Aside from the bearing of this result on the question under discussion, the fact of a new recessive mutation occurring, that brings back the mutant character to the original type, is in itself an interesting and important fact.

Finally, there is the peculiar reversion to normal of the dominant or semi-dominant character, bar-eye (Fig. 49, 1 and 2). For some years it has been known from the observations of May and Zeleny that bar-eye reverts

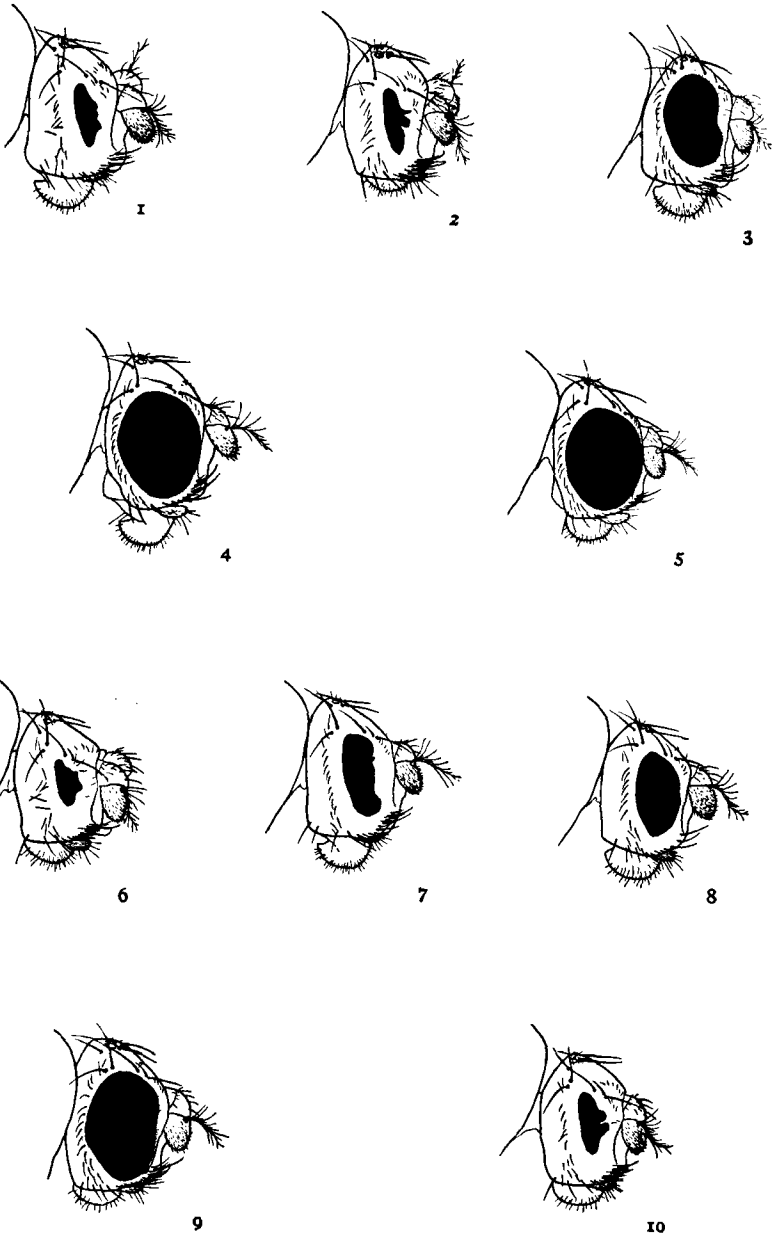

FIG. 49.

Different types of bar eyes; 1, homozygous bar female; 2, bar male; 3, bar-over-round eye female; 4, female homozygous for round that was obtained by reversion; 5, male that carries the gene for round eye obtained by reversion; 6, double-bar male; 7, homozygous infra-bar female; 8, infra-bar male; 9, infra-bar-over-round female; 10, double-infra-bar male.

to normal eye, and this instance has been cited as evidence that reverse mutation may take place. The frequency of the return mutation varies in different stocks. It has been estimated to occur about once in 1600 times. It was later discovered by Sturtevant and Morgan that when the reversion occurs, crossing-over takes place in the vicinity of the bar gene, and Sturtevant has obtained crucial evidence in regard to the nature of the changes that there take place.

FIG. 50.

Diagram of a cross between a female bar-eyed fly, heterozygous in forked and fused, and a forked bar fused male.

The demonstration that crossing-over takes place whenever reversion occurs, was as follows: To the left and very close to bar (⅕ unit) there is a gene called forked; to the right and very near bar (2½ units) a gene called fused. A female is made up with bar lying between these two genes in one X-chromosome, and bar with the wild type allelomorphs of forked and fused in the other (Fig. 50). Such a female is bred to a forked bar fused male. The ordinary sons will be either forked bar fused or bar, since each has received either the forked bar fused or the not-forked bar not-fused X-chromosome of the mother. When, as happens rarely, a reversion takes place, *i.e.*, a male appears that has round eyes, it is observed that crossing-over has taken place between forked and fused. For example, the reverted male is either fused or else forked; it is never forked and fused, nor is it ever both not-forked and not-fused. Crossing-over must have

taken place in the mother of the male between forked and fused. The total cross-overs between forked and fused are less than 3 per cent and yet they include all the reversions to full eye.

Only the reverted sons have been spoken of above in order to simplify the situation, but of course the reverted chromosome might have passed into an egg that develops into a female. The experiment can be so planned that evidence of crossing-over will also be detected in the reverted daughter. The ordinary daughters will be homozygous bar (see Fig. 49, 1). The reverted daughters will be heterozygous for bar eyes, and either forked or fused. None of them are both forked and fused and none of them are not-forked not-fused.

The crossing-over, that brings about reversion to round eye, must not only have left one X-chromosome without a bar gene, but must have put the other bar gene into the bar chromosome (Fig. 51a). In appearance a male with two bar genes (double bar) is similar to a male with one bar gene, but its eyes are smaller and the number of its facets is reduced. It has been named double bar (Fig. 49,6). The presence of two allelomorphic genes in the same linear series is an exceptional occurrence that has as yet not been observed in any other mutation. It can be pictured only by supposing that the bar genes lying opposite to each other before crossing-over are shifted a little when the crossing-over occurs. The result is that the double bar chromosome is lengthened by one bar gene at least, and conversely that the other chromosome has been shortened by the "loss" of the bar gene.

Sturtevant has put the theory of reversion of bar to a number of critical tests. There is an allelomorph of bar (that arose as a mutation of bar) called infra-bar (Fig. 49, 7 and 8), whose eyes are somewhat different in size

and in the number of facets. In infra-bar stock, reversion also takes place (Fig. 51b), producing a full round eye closely similar to wild type, and a new type called double-infra-bar (Fig. 49, 10).

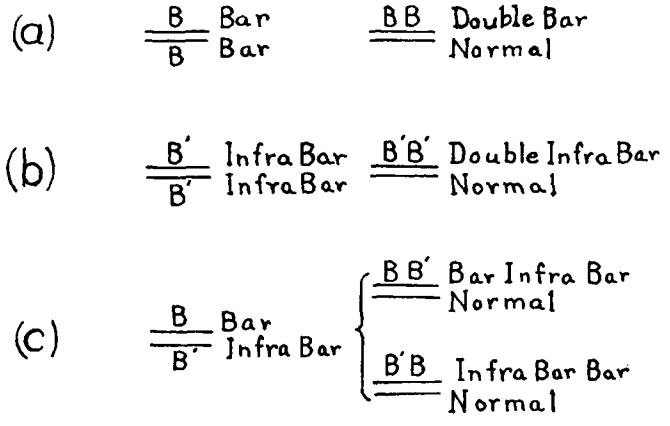

FIG. 51.

Diagram of mutation in bar and infra-bar and bar-infra-bar.

A female with bar in one chromosome and infra-bar in the other (Fig. 51c) produces, when reversion takes place, a full round eye (wild type) and bar-infra-bar or infra-bar-bar types (Fig. 51c).

Sturtevant has also utilized these two types, the bar-infra-bar type and the infra-bar-bar, in order to prove that when crossing-over takes place in bar-infra-bar over normal (Fig. 52a), the result gives either forked bar or else infra-bar fused, and when crossing-over takes place in infra-bar-bar over normal (Fig. 52b) the result is either forked infra-bar or bar fused, provided the mutant genes all lie in the same chromosome, as shown in the diagram (Fig. 52a, b).

It follows that in both types the genes not only keep their identity but also their sequence. From the way in which the two types, fBB′fu and fB′Bfu, were made up, the sequence of the genes is known, and in all cases the breaking apart of B and B′ agrees with the sequence previously determined.

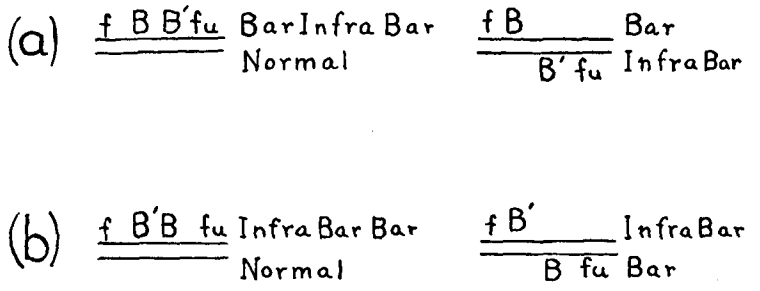

FIG. 52.

Diagram, in a, of a mutation of forked bar, infra-bar fused and in b, a mutation of forked infra-bar, bar fused.

These results furnish crucial evidence in favor of the correctness of the theory that reversion in bar is due to crossing-over. This is, at present, a unique case. There would seem to be some peculiarity in the X-chromosome at the bar locus that allows crossing-over between allelomorphic factors to occur. Sturtevant speaks of this as unequal crossing-over.[1]

This result raises the question as to whether all mutations may not be due to crossing-over. There is explicit evidence in Drosophila that this is not the general expla-

[1] Several curious problems concerning the bar locus are involved in these relations. For instance, when bar crosses over what is left in the bar locus? Is it an absence of bar? Did the original bar arise by mutation in a wild type gene, or was a new gene created? These questions are still under investigation.

nation of mutations, because, for one reason, it is well known that mutation may occur in the male of Drosophila as well as in the female. In the male of Drosophila there is no crossing-over.

The Evidence from Multiple Allelomorphs.

It has been shown in Drosophila, as well as in a few other types (in corn, for example), that more than a single mutation may occur at the same locus. The series of allelomorphs at the locus for white eye in Drosophila is the clearest case of the sort. No less than eleven eye colors, in addition to the red eye of the wild fly, have been recorded. They form a graded series from white to red as follows: white, écru, tinged, buff, ivory, eosin, apricot, cherry, blood, coral, wine. They have not, however, appeared in this sequence, although white was the first mutation observed at this locus. That they have not arisen by the mutation of a series of adjacent genes is clearly shown by their origin and their relation to each other. For example, if the white were due to a mutation from the wild type at one locus and cherry by mutation at an adjacent locus, then when white is crossed to cherry the female offspring should have red eyes, because white would, on this assumption, carry the wild type allelomorph of cherry and cherry would carry that of white. When white and cherry are crossed they do not give this result, but the daughters have an intermediate eye color. The F_1 female gives again white and cherry sons in equal numbers. The same relation holds for all the other allelomorphs, any two of which can exist simultaneously in any one female.

If the presence and absence theory is taken literally there cannot be more than one absence for each gene. The theory in this form is disproven in all cases where the occurrence of multiple allelomorphs is known to have

taken place independently from the wild type;[2] but it is possible to interpret absence in such a way that it is not in contradiction with the occurrence of multiple allelomorphs. Suppose, for instance, that different quantities of materials are lost at the locus in question for each mutant type. The loss of one quantity might stand for white, another quantity for cherry, and so on. The result might then not appear to be inconsistent with the facts, although it should be noted that the assumption calls for a somewhat different interpretation of the gene as a unit. The "compound" formed by the presence of two of these allelomorphs might then not be expected to give the wild type but something else. To admit this, however, changes the idea of presence and absence in such a way as to make it essentially the same as the view that is here maintained, namely, that mutation is due to a change of some sort in a gene. There is no advantage, that I can see, in urging that the change must be a loss of part of the gene (gene meaning a quantity of something at a given locus). This is a gratuitous assumption in regard to the nature of the change—one that is not necessary to explain the results. It may be, of course, that a gene may be lost or a part of a gene may be lost and a new mutant result, but it is theoretically possible that the constitution of the gene may change in some other way. So long as we do not know anything definite concerning the kind of change that takes place there is nothing to be gained by limiting it to only one kind of process.

[2] If the multiple allelomorphs had arisen seriatim, *i.e.*, one from another, then of course it might be possible that each one carried the preceding mutant gene. If so the two when crossed would not give the wild type. But when, as in Drosophila, each has arisen independently from the wild type the situation is different, as explained in the text.

Conclusions.

An analysis of the evidence at hand does not justify the view that the actual loss of some character present in the original type must be interpreted to mean that a corresponding loss has taken place in the germinal material.

Even by extending the literal interpretation of the presence and absence idea so that the postulated connection between the loss of the character and the loss of the gene means the effect produced by other genes, the assumption of a loss still has no advantage over the alternative view that a mutation is due to a change of some sort in the gene. Furthermore, the occurrence of mutation in the reverse direction (omitting the special case of bar reversion), while not sufficiently established as yet, is in better accord with the view that genes may mutate by a change in their constitution without that change being necessarily a loss of the whole gene. And finally, the evidence from multiple allelomorphs seems more consistent with the view that each is due to a change in the same gene.

The theory of the gene as here formulated, regards the wild type genes as specific elements in the chromosomes, that are relatively stable over long periods. There is at present no evidence that new genes arise except by changes in the constitution of the old genes. The total number of the genes remains on the whole constant over long periods. Their number may be changed, however, by a process of doubling the full set of chromosomes and perhaps in other similar ways. The effect of changes of this sort will be considered in later chapters.