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Position Effect and the Theory of the Corpuscular Gene

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Introduction

During the past decade many geneticists have realized that the classical theory of the corpuscular gene, i. e. the existence of actual separate bodies arranged along the chromosome in beadlike fashion, does not fit the facts any more. These facts are, first, that the number of chromosome breaks is proportional to the dosage of radiation, just as it is the case for so-called point-mutations (the latter are defined purely negatively as mutants for which, with present techniques, no changes in the architecture of the chromosomes can be discovered), secondly, the existence of position effect. Different geneticists have evaluated these facts differently. Some have closed their eyes and waved aside the facts concerning position effect by calling them rare and unimportant phenomena. Many have realized that no theory of the gene is possible which does not account for these facts, and have come to the conclusion that the classic conception of the gene must be widened to make it less rigid (e.g. MULLER). Only a few, like the present writer (see also PIZA[2], 1944, and SERRA[3], 1944), have decided that the whole classical concept of the corpuscular gene must be replaced by a different conception. It is not surprising that such a stand has been often criticized and that the mental difficulties of discarding a seemingly well-established conception are tremendous. But criticism is not helpful if the decisive body of facts is not explained simultaneously. Frequently the critical attitude is based upon a misunderstanding of the logical position of the newer conception. As a recent example of this I may mention BEADLE's[4] (1945) discussion of the subject which, though short and without going into the details of the case, will carry much weight with the biochemists to whom it is addressed. His contention is that the classical theory of the gene has worked so well and permitted such a successful description of the results of genetics that there is no reason to abandon it. May I point to the fallacy of this conclusion by using a comparison. All of the important facts of classical chemistry can be described in terms of the classical concept of valence. It is possible to be an excellent chemist and to teach the facts of chemistry without any allusion to the modern developments of the electronic and quantum mechanical theories of valence. Does this prove that the latter are unnecessary or false? Or does it not mean that, facts which can be described formally within the frame of the old concept are now being studied on a higher level, making the old notions appear superficial and primitive? I believe that the present situation in genetics is of the same type. Therefore, I propose to discuss the facts relevant to a critical study of the gene concept and to draw the conclusions which seem to me inevitable.

Occurrence and Frequency of Position Effect

The term position effect was introduced by STURTEVANT[1] (1925) for his discovery that two Bar "genes" in *Drosophila* (now known to be the effect of a tandem duplication after unequal crossing over, MULLER, BRIDGES) reduce the eye-facet number to a different degree if they are located in one chromosome compared with the reduction observed if they are located in two homologues. Since then the term has been applied to all cases of a phenotypic effect of a chromatin rearrangement looking like any mutation but produced entirely by the disturbance in the visible architecture of the chromosome. The early idea that a mutant arises at the point of a chromosomal break has been discarded by most investigators. Practically all cases of position effect (a better term would be rearrangement effect, because this term does not involve the theory of the corpuscular gene) have been found in *Drosophila*, the only exception being a few cases in maize. Some authors have contended that this must therefore be a special feature of *Drosophila*, without general significance. As there is no detail of heredity in *Drosophila* known which is not encountered generally (for the cytological feature of somatic pairing see below) such a conclusion has very little aprioristic probability. Actually there is no other organism known which is suitable for the reliable discovery of position effects. Small arrangements down to about $^1/_{1000}$ of the length of a chromosome can be seen only in the salivary gland chromosomes

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[2] S. DE T. PIZA, Rev. de Agric., São Paolo, *19*, 26–50 (1944).

[3] T. A. SERRA, Bol. da Soc. Broteriana *19*, 327–369 (1944).

[4] G. W. BEADLE, Chem. Reviews *37*, 1–96 (1945).

[1] References found in the author's book "Physiological Genetics", New York, McGRAW-HILL, 1931, are not repeated in this paper.

of Diptera. Actually, in *Drosophila* each year some other long-known standard mutant turns out to be a position effect of a very small rearrangement. But the large rearrangements, the only ones which can also be seen in the chromosomes of many plants (large, of course, by *Drosophila* standards), could as a rule reveal position effect only when the effect is of a visible phenotype. This again requires a genetically and cytologically well-known organism. The only plant which thus far fulfills the requirement is maize. But what is a small visible rearrangement in maize would be a very large one in a salivary chromosome. With the relatively small number of loci known in maize, the probability of breaks near a known locus is a small one (Most position effects in *Drosophila* have the phenotype of a nearby point-mutant. A break near a known locus in maize does not refer to visible maize chromosomes but is meant in terms of a comparison with salivary chromosomes!). To this must be added that position effects of a physiological nature or of a modifier type are usually not observed. We shall further see that also in *Drosophila* not every rearrangement has a position effect. There must be a reason for this (see below), and it is quite possible that in maize the chromosomal constitution is such that breaks without position effect can occur more easily. Thus much more important than the negative evidence is the positive one that in the only organism except *Drosophila* which lends itself to a certain extent to detailed cytogenetic analysis, maize, position effects have been claimed in thus far three or four instances.

In *Drosophila*, the frequency of the position effect is much greater than generally suspected. A rough survey which I made (GOLDSCHMIDT[1], 1944) showed that approximately half of all *bona fide* mutants are based on position effects, while many of the remaining ones have never been checked sufficiently to be certain.

Types of Position Effect

The position effects thus far described may be grouped in different types.

(1) The original type of the Bar duplication. In this case it is irrelevant whether or not the Bar effect is itself a position effect (see below). Assuming that it is not, this type of position effect means, as already stated, that the presence of two Bar loci in one chromosome has an effect on the phenotype which is different from that of one Bar locus each in one homologous chromosome. According to STURTEVANT B/B = 68·12 $\pm$1·09 facets, and BB/+ = 45·42$\pm$·24 facets. The only comparable case has been described by LEWIS[2] (1945) but it seems much more complicated. Here two mutants are involved which lie side by side, Star (S) and asteroid (ast), both of which have approximately the same effect on the eyes. These effects are different in the combinations S/ast versus S ast/+. In addition, these mutants have been arranged in a tandem duplication i. e. (S ast) (S ast) or (S +) (+ ast), etc., in one chromosome. In this case the visible effect is different among pairs of arrangements of the following type: (+ ast) (S ast) versus (S ast) (+ ast). This is interpreted as a position effect acting between the two parts of the tandem duplication. We shall discuss the duplication effect as a possible position effect below.

(2) The most frequent and most important position effect is one in which a chromosome break by Inversions or Translocations (deficiency and duplication, see below) located near the known location of a point-mutant produces a phenotypic effect which is identical with or closely resembles the mutant phenotype. These position effects behave genetically as multiple alleles of the respective point-mutants. The number of these cases known and their distribution over the chromosomes is such that one may safely state that breaks near any known locus will, in the majority of cases, produce this position effect. Let me mention only a fraction of the cases in *Drosophila melanogaster* involving well known loci: in the first chromosome position effects for yellow (y), scute (sc), white (w), cut (ct), Bar (B), forked (f); in the second chromosome for brown (bw), aristaless (al), Star (S), held out (ho); in the third chromosome for Stubble (Sb), ebony (e); in the fourth chromosome for eyeless (ey). In some of these cases a number of alleles, even large multiple allelic series, based upon different rearrangements, all with one break near the point-mutant locus have been found e.g. for y, sc, w, B, bw.

(3) This group is probably identical with the preceding one. Here no neighboring point-mutants, with the same phenotypical effect as the rearrangement, are known and therefore the position effect is described as an individual mutant or as "inseparable from Inversion X, etc." Examples are the Curly (Cy) inversion, Moiré (Mé) inversion, Translocation Xasta (Xa). (The claim that Cy was separated from the inversion seems to be based on a misinterpretation; unpublished data.)

The few position effects that have been found in maize belong to the group under discussion. ROBERTS[1] (1942) studied a large number of translocations in maize in detail. No clear position effect with a large phenotypic effect was found, but a statistical study of quantitative characters revealed that quite a number of significant deviations from the controls existed. These can be explained as position effects upon growth. This interpretation is made still more

[1] R. GOLDSCHMIDT, *in:* Science in the University, Univ. Calif. Press, pp. 183–210 (1944).

[2] E. B. LEWIS, Genetics *30*, 137–166 (1945).

[1] L. M. ROBERTS, Genetics *27*, 584–603 (1942).

probable by the work of JONES[1] (1944), who found an abnormal growth in maize endosperm associated with a chromosome rearrangement and considers this a position effect. JONES[2] (1939) had already interpreted as a probable position effect the behavior of twin-spots in the endosperm of maize, where a rearrangement near the locus C changes the action of C, as well as that of its allele, toward the type of action of another allele. There is, however, one case in *Œnothera*, described by CATCHESIDE[3] (1939), which parallels some of the cases in *Drosophila* (see below DUBININ effect). A translocation with a break near the locus P^s, which controls pigment on the flower-buds, reduces the pigmentation. The normal action is restored if the locus is separated from the translocation by crossing over.

(4) The rearrangements have no effect by themselves, but if combined with other mutants they exercise a modifying effect upon the phenotype. The position effect thus emulates a genetic modifier effect. Such effects have been described for different Inversions and Translocations and different modified mutants (see GARDNER[4], 1942, and GREEN and OLIVER[5], 1940, for modification of vestigial, GOLDSCHMIDT and GARDNER[6], 1942, for modification of Beaded). One might safely assume that such effects could be detected for all rearrangements without direct position effect if extensive tests were made.

It should be added at this point that the absence of a visible position effect of many rearrangements (including most inversions and translocations in plants) does not exclude an undetected position effect of a physiological type. This is best illustrated by the recent work of DOBZHANSKY[7] (e.g. 1943) and DUBININ and TINIAKOV[8] (1946), who found that inversions present in *Drosophila* populations were subject to the action of selection. This cannot mean anything but a physiological position effect which is subject to selection just as is any visible mutant.

(5) A specific position effect of the modifier type is dominance modification. DUBININ discovered that the fourth chromosome recessive, cubitus interruptus (c. i.) becomes more or less dominant in the presence of a translocation between the fourth and another chromosome, which involves a break near the c. i. locus. Also as in the cases reported under (4), dominance modification was involved, but in those cases without a break near the locus of the modified recessive. The Dubinin effect has also been reported for other loci, e.g., hairy in the third chromosome.

A variant of this group is found when the inversion or translocation brings a heterochromatic section into the neighborhood of the mutant locus. In this case the phenotype shows frequently a mosaic, e. g., mottled if a color is involved. In many of these cases there is no doubt that heterochromatin from the chromocentral region is involved. In many other cases heterochromatic nature of the neighborhood of the break has been claimed without real proof, and in some cases mottling is said to occur without heterochromatic neighborhood (KANE and GRIFFEN, 1940). The mottling effect is very typical if eye-colors are involved, and acts as a dominant. Thus, breaks near the brown locus (second chromosome) produce the dominant character Plum, which is a mottled brown. One might say that heterozygous brown has become dominant, but that the dominance does not work in all of the cells. For a recent discussion of explanations, see BELGOVSKY[1] (1946). Similar mosaicism has also been described for other characters resulting from heterochromatic neighborhood by rearrangement. But not all of the cases are reliable, as sometimes ordinary discrete variation has been called mosaicism.

The whole case of mottling is not completely clear, except for the fact of a position effect. Thus KAUFMAN[2] (1942) has found that rst^3, a typical case of position effect, changes into normal phenotype if further breaks are produced in the heterochromatin, which would mean a superimposed position effect acting in the opposite direction. Such a counteracting position effect has also been reported for other position effects: Curly (Cy), Glazed (Gla) and Bar^S (T 1, 4 B^S) by SUCHE, PARKER, BISHOP, and GRIFFEN[3] (1939), GRIFFEN and STONE[4] (1940), GRIFFEN[5] (1941). This means that the position effect of an inversion or translocation disappears if a new rearrangement is superimposed.

(6) Another type of position effect is a combination effect. An example is the following (GOLDSCHMIDT[6], 1945). The recessive mutant bran, at or near the arc locus, produces broad wings. The mutant pointed (svr^{poi}) near the tip of the X-chromosome produces pointed wings. The combination bran/bran svr^{poi}/ svr^{poi} has short soft and blistered wings. A small inversion, In (1) $y^{px\ bl}$, in the X-chromosome has one break near the yellow locus and therefore a yellow phenotype (position effect). The other break is in

[1] D. F. JONES, Genetics *29*, 420–428 (1944).
[2] D. F. JONES, Genetics *24*, 100 (1939).
[3] D. G. CATCHESIDE, J. Genetics *38*, 345–352 (1939).
[4] E. J. GARDNER, Univ. Calif. Publ. Zool. *49*, 85–112 (1942).
[5] M. GREEN and C. P. OLIVER, Genetics *25*, 584–597 (1940).
[6] R. GOLDSCHMIDT and E. F. GARDNER, Univ. Calif. Publ. Zool. *49*, 103–124 (1942).
[7] TH. DOBZHANSKY, Genetics *28*, 162–186 (1943).
[8] N. P. DUBININ and G.G. TINIAKOV, J. Hered. *37*, 39–44 (1946).

[1] M. L. BELGOVSKY, Amer. Natur. *80*, 180–185 (1946).
[2] B. P. KAUFMAN, Genetics *27*, 537–549 (1942).
[3] M. L. SUCHE, D. R. PARKER, M. BISHOP and A. B. GRIFFEN, Genetics *24*, 88 (1939).
[4] A. B. GRIFFEN and W. S. STONE, Univ. Texas Publ. *3932*, 190–200 (1940).
[5] A. B. GRIFFEN, Genetics *26*, 154–155 (1941).
[6] R. GOLDSCHMIDT, Univ. Cal. Publ. Zool. *49*, 291–550 (1945).

the silver region but no second position effect is visible. But in the homozygous combination of yellow inversion and bran the wings are soft blistered, i.e., a position effect of the break in the silver region becomes visible in the combination. I may add at this point that position effects are known to take part in combination effects just as if they were the proper recessive mutant. If the mutants brown (second chromosome) and vermilion (first chromosome) are present simultaneously, the eyes of the fly are white. Plum is a position effect with a break in the brown region. The combination vermilion and Plum is also white (KIKKAWA[1], 1938).

Duplications and Position Effect

A visible effect of a duplication was formerly ascribed to a disturbance in the genic balance brought about by the presence of one gene in triplicate. Actually, many difficulties arise when one tries to explain why the presence of three normal loci in the Bar region should shift development toward a Bar eye. Facts have become known more recently which suggest that it is not the presence of two or three sections in tandem within the chromosome that causes the Bar or double Bar effect, but that a position effect of the rearrangement is involved. One of the reasons is that rearrangements in this region which have their breaks at the same point as in the Bar duplication, but are not duplications, produce a Bar effect (SUTTON[2], 1943). Another reason is that the duplication can be made to lose the Bar effect (GRIFFEN[3], 1941) by separating the tandem sections via translocation. We have already mentioned the comparable position effects studied by LEWIS at the Star-asteroid loci, where the facts seemed to indicate that the duplication break produces a position effect which changes the action of the asteroid locus toward normal. If the interpretation of the Bar duplication effect as a position effect is correct, the original position effect hypothesis of STURTEVANT (B/B contra BB/+) would find its explanation in the presence of the extra break with a modifying position effect in only one chromosome in the BB/+ genotype. (The type of phenotypical effect in these cases is not under discussion here.)

As an appendix to this group of facts, a strange phenomenon should be mentioned. If a homozygous recessive locus is "covered" by an additional duplicated piece of chromosome containing what is assumed to be the normal allele, the normal is usually dominant over the two recessives. But if the duplicated fragment has its break near the locus in question, dominance is shifted toward the recessive, which can be explained as an inverse Dubinin position effect (DOBZHANSKY and DOBZHANSKY, 1932, DOBZHANSKY and STURTEVANT, 1931). See the discussion of "covering," below.

Deficiency and Position Effect

The fact that a normal locus opposite a deficiency frequently produces the phenotype of a mutant of that locus (example $+ \; {}^{vg}/\mathrm{Df} =$ scalloped wings) has been explained by the assumption that such a locus is too weak to act in one dose sufficiently to produce the normal type. Recently a number of cases have been interpreted differently, namely as a position effect of the deficiency break near the locus in question. Thus SUTTON[1,2] (1940) found a small terminal deficiency at the tip of the X-chromosome, not including the so-called yellow locus. If the other chromosome contained y, i.e., not opposite the deficiency, the phenotype was yellow. This was regarded as a Dubinin type position effect making y dominant, when the other chromosome is broken near the $+^{y}$ locus.

Another group of facts which may best be explained as position effects concerns the phenotypic effect of homozygous deficiencies. A considerable number of cases have become known in *Drosophila* in which a homozygous deficiency has the phenotypic effect of a mutant located within the limits of the deficiency. Thus the homozygous mutant y in *Drosophila* is yellow (y/y). The mutant opposite a deficiency (y/−) is yellow and the homozygous deficiency −/− is also yellow (EPHRUSSI, 1934, STERN, 1935, etc.). Similar results have been obtained for the mutants scute, sc (STURTEVANT and BEADLE[3], 1936), roughest, rst^2 (EMMENS[4], 1937, PROKOFYEVA-BELGOVSKAYA[5], 1939, PANSHIN[6], 1941). Other mutants with homozygous deficiency effects are white, w (PANSHIN[7], 1938, 1941), and facet, fa (?) (OLIVER, 1937[8], 1938[9]). The rst^2 deficiency is especially interesting because no point-mutant is known at this point, whereas inversions with a break in this region produce the phenotype as a position effect (In rst^3, GRÜNEBERG, 1935, 1937). Quite a number of such cases are known also in maize (MCCLINTOCK[10], 1944) where they actually seem to be typical. Let us consider the following series of genotypes for yellow with more or less similar phenotypes:

[1] H. KIKKAWA, Genetics *20*, 458–516 (1938).
[2] E. SUTTON, Genetics *28*, 97–107 (1943).
[3] A. B. GRIFFEN, Genetics *26*, 154–155 (1941).

[1] In a previous paper (1944) I had misinterpreted SUTTON's views, for which I apologize.
[2] E. SUTTON, Genetics *25*, 628–635 (1940).
[3] A. H. STURTEVANT and G. W. BEADLE, Genetics *21*, 554–604 (1936).
[4] C. W. EMMENS, J. Genetics *33*, 191–202 (1937).
[5] A. PROKOFIEVA-BELGOVSKAYA, Bull. Acad. Sci. U.S.S.R., Ser. biol., *2*, 215–227 (1939).
[6] T. B. PANSHIN, C. r. Acad. Sci. U.S.S.R. *30*, 51–60 (1941).
[7] T. P. PANSHIN, Nature *142*, 837 (1938).
[8] C. P. OLIVER, Amer. Natur. *71*, 560–566 (1937).
[9] C. P. OLIVER, Genetics *23*, 162 (1938).
[10] B. MCCLINTOCK, Genetics *29*, 478–502 (1944).

1. y/y = homozygous point-mutant; 2. y/− = opposite deficiency; 3. −/− = homozygous deficiency; 4. $+^{y}/+^{y}R$ = homozygous normal plus a rearrangement nearby; 5. $+^{y}/+^{y}D$ = homozygous normal plus a deficiency nearby; 6. r^{y}/r^{y} = homozygous recessive rearrangement. It seems most probable that the −/− effect is a position effect based upon an abnormal sequence of the chromosomal material in the yellow region. This conclusion is possible only if the so-called yellow gene, which is absent here, has nothing to do with the position effect.

Important Features of the Position Effect

If we want to find an explanation of the position effect, we must realize the decisive general features as well as a number of additional details. The basic fact is that the position effect of chromatin rearrangements parallels in every respect the behavior of so-called point-mutations:

(1) In the case of mutations induced by radiations, point-mutations and small rearrangements (small ones only because large ones require two hits in the case of X-rays; for neutrons see below) follow the same law that effects are proportional to dosage.

(2) Position effects are allelic to point-mutations of the same region and large series of multiple alleles are known which consist of both types intermingled.

(3) There is no type of mutational effect known which is not also represented as position effect, e.g., dominant, recessive, semidominant, and lethal mutants; recombination effects of different mutants; modifier actions of different kinds including dominance modification. To the latter belong the invisibles, i.e., mutants or position effects without visible action by themselves, but with visible effect in combination with other genotypes.

(4) Mutants can be modified by position effects and position effects can be modified by position effects. Position effects may also be modified by mutants (suppressors, enhancers).

(5) Position effects may be accumulated in one chromosomal section as markers just as in ordinary mutants, e.g., no one could distinguish the difference between the phenotype or genetic behavior of a standard stock yw and one In (1) y; In (1) w.

The following detailed facts are relevant:

(1) If a position effect can occur by changing the order within a chromosome by breakage and rearrangement, it should be possible to observe effects at both breaks if both are located in regions near which visible mutants can occur. Actually a few such cases are known, as the one for yellow and silver reported above.

(2) It is to be expected that it is not irrelevant for the position effect whether one or another distant section is brought near the region which produces the position effect, with the result of different sequences beyond the break. RAFFEL and MULLER[1] (1940) have tested this by comparing different scute alleles based upon position effect with differently located second breaks. Actually the phenotype was somewhat different, but more uniform if the second breaks were in the same region.

(3) There is no case known in which a position effect near the locus of a known point-mutant does not resemble the mutant or its multiple alleles. In all known cases the position effect opposite its proper mutant acts as an allele of this mutant. In case that the homozygous effects of small deficiencies represent position effects, more complicated conditions of allelism should be expected. As the interpretation of position effect is not certain in these cases, I point only to the analyses of these features by MCCLINTOCK[2] (1944) and SCHULTZ and CURRY[3] (1941).

(4) As a rule a position effect occurs only when the rearrangement break is one to three salivary chromosome bands distant from the band which is supposed, on the basis of deficiency tests (also duplication, etc.), to contain that locus of which the mutant phenotype appears as position effect. This is frequently expressed in terms of the classical theory of the gene by saying that the position effect of the gene reaches over so many bands. We shall discuss the meaning of this below. In some cases it has been claimed that only breaks between two definite bands produce the position effect (e.g., for Bar, see GRIFFEN and STONE[4], 1940, and SUTTON[5], 1940). In other cases it is however certain that different breaks within a section produce allelic position effects. This is true, for example, of the scute (sc) locus, where all different breaks within a section of five bands produce a scute effect (see DEMEREC[6], 1941, GOLDSCHMIDT[7], 1944).

(5) A number of cases are known in which a break in the region of two neighboring loci produces the effect of both loci. Such is the case, for example, of the $y^{px\ bl}$ Inversion (GOLDSCHMIDT[7], 1944, 1945[8]) which produces both yellow and achete effect. DEMEREC[6] (1941) mentions many more such cases, but without giving details.

(6) In some cases position effects have been described with breaks a considerable distance away from

[1] D. RAFFEL and H. J. MULLER, Genetics *25*, 541–583 (1940).
[2] B. MCCLINTOCK, Genetics *29*, 478–502 (1944).
[3] J. SCHULTZ and V. CURRY, Carnegie Inst. Wash. Yearbook *40*, 282–287 (1941).
[4] A. B. GRIFFEN and W. S. STONE, Univ. Texas Publ. *8032*, 190–200 (1940).
[5] E. SUTTON, Genetics *25*, 628–635 (1940).
[6] M. DEMEREC, Univ. Pennsylvania Bicent. Conference, 1–11 (1941).
[7] R. GOLDSCHMIDT, *in:* Science in the University, Univ. Calif. Press, p. 183–210 (1944).
[8] R. GOLDSCHMIDT, Univ. Cal. Publ. Zool. *49*, 291–550 (1945).

the locus to which the phenotype of the position effect is attributed. Such effects have been described by VOLOTOV[1] (1937) for the Bar locus. It seems as if this behavior is characteristic for the mosaic position effects caused by inversions with one break in the heterochromatin. DUBININ (1936) found this when he studied the position effect Plum (brown region) by a complicated method which resulted in both breaks to be adjacent to heterochromatin. In this case rather long sections of the chromosome showed the position effect when broken anywhere. DEMEREC[2] (1941) found the same for a number of heterochromatic breaks affecting different loci in the X-chromosome, with a position effect up to a distance of 35 bands.

(7) Just as the position effect of one break may affect more than one locus, position effects may also be overlapping, i.e., a break at, say, band 10 may give a position effect with the phenotype of a locus at band 7, while another break near the band 8 might give an effect with the phenotype of a locus near band 12. Examples are found in DEMEREC[2] (1941) and GOLDSCHMIDT[3] (1944).

(8) An important observation of DEMEREC[2] (1941) is that a number of rearrangements without phenotypic expression are known with breaks in an interval that usually gives position effects (see also DOBZHANSKY, 1936, for the Dubinin effect).

(9) These data show that well-studied parts of the chromosome consist of sections of $\pm 5-10$ bands, within which the locus of a point mutant can be located and within which a rearrangement break almost always produces the position effect with the phenotype of that mutant. But these sections may overlap, furthermore, some rearrangements have no position effect, and, finally, the same effect may under certain circumstances be produced by a break in the following or even a distant segment. All of these facts must be taken into account in any explanation of position effect.

Explanations of Position Effect within the Classical Theory of the Gene

A number of explanations of position effect within the classical theory of the gene have been presented, some of them specific, some more vague. As an example of the latter I mention DOBZHANSKY's (1936) statement that position effects affect the coordinates, on which the reactions between the primary gene products take place. The hereditary material, though made up of discontinuous genes, is a continuum of a higher order; since the independence of the units is incomplete, they are changed if their position in the system is altered. In other words, it is realized that a loosening up of the classical gene concept is needed in order to account for position effect. MULLER (1935) and OFFERMAN (1935) are more specific. An interaction between the genes themselves is not excluded, but the decisive point appears to be an interaction between gene products. The idea is the following: In the production of phenotypic effects the gene begins by interacting with the cellular substances to produce specific products, which diffuse from the locus of origin and cause or affect further physico-chemical changes. When such interactions involve the immediate products of neighboring genes, distance may count. It is to be assumed that the highest concentration of the gradient of gene-controlled primary products will be near the gene, whereas with increasing distance these substances will be altered by undergoing new reactions. MULLER and STURTEVANT (1925) think that the somatic pairing of chromosomes in Diptera might contribute to making such interactions possible. (In WADDINGTON's[1] book (1939) an improved variant of MULLER's conception is used, namely, a competition of two genes for the same substrate. Thus the change in the distribution of the substrate is responsible for position effect.)

There are many serious objections to such a view, even assuming its possibility from a point of view of chemical kinetics (see below). The chromosomes of the resting nucleus are probably in completely stretched condition and are floating in a liquid medium. It is hardly possible that in the case of a one- or two-band inversion the actual change in order of "genes" could influence primary reactions in their neighborhood, except by diffusion along the chromosomal surface. In such a set-up, further, any point of a chromosome has a chance of meeting any other point of the same or other chromosomes, and this meeting should produce a position effect each time. In addition, the decisive fact remains unaccounted for—namely, that whatever the new neighboring locus, the effect of this disturbance in the primary reactions is always the same as that of a mutant at the locus in question. Such difficulties arising in any attempt to go into the details of such a conception have probably influenced many geneticists interested in these problems to prefer a rather vague and equivocal idea, namely, that the change of neighborhood at the point of the break radiates a kind of action, a position effect, toward a neighboring gene which is thereby caused to function differently. A corollary of this would be that a mutant effect is always a disfunction of the gene, whatever this may mean.

[1] M. VOLOTOV, Biol. Zhurn *6*, 970–922 (1937).

[2] M. DEMEREC, Univ. Pennsylvania Bicent. Conference pp. 1–11 (1941).

[3] R. GOLDSCHMIDT, *in:* Science in the University, Univ. Calif. Press, pp. 183–210 (1944).

[1] C. H. WADDINGTON, An Introduction to Modern Genetics, Macmillan, New York 1939.

Such a viewpoint would, of course, have to take into account the facts reported above concerning the segments within which position effects occur, their overlapping and the occasional occurrence of effects with long distances between breaks and loci. These difficulties are either ignored or they are removed by expanding the strict classical conception of the gene, by assuming that a gene may consist of smaller units of similar action, or that the gene has not a definite limit (see MULLER[1], 1941, DEMEREC[2], 1941). This shows that even the adherents of the classical theory of the gene realize that the facts of position effect require at least a less formal conception of the gene and its relation to the chromosome.

Returning to the chemical difficulties encountered when a type of explanation is used involving gene products, EPHRUSSI and SUTTON[3] (1944) (who call this general type of theory a kinetic one) have calculated the possibilities of such reactions on the basis of DELBRÜCK's suggestions. They came to the conclusion that the distances for position effect actually found are many times larger than the maximum distance possible on the basis of calculation. They add that actually, if an action over such long distances were possible, it should also occur between normal loci if they happen to come near each other in the nucleus. From this they conclude that not a kinetic but a structural hypothesis must account for the position effect. This means that something is involved which spreads along the chromosome, i.e., a change in the physical state of the chromosome itself. MULLER (1935) had already discussed such a possibility, pointing to the forces of attraction between different chromosomes. If a similar force should act between different loci, a kind of stress could be produced by abnormal neighborhoods which would result in distortions and therefore change of chemical action of the gene (see also MULLER[1], 1941). In a completely different way GOLDSCHMIDT (1938, 1940[4]) had arrived at the conclusion that both position effect and mutation must be explained on a structural basis, which would require the abandonment of the classical theory of the gene (see below). EPHRUSSI and SUTTON, following MULLER's lead, developed the following structural theory: Recent chemical work on the myosine molecule is taken as an analogy, which has shown that a fibrous protein exercises an enzymatic property when in a stretched condition. It is now assumed that the synaptic association of chromosomes in Diptera leads to a stretching of chromosome structure. The presence of a rearrangement may lead, through changes in the pairing condition, to modifications of the state of stress in the immediate vicinity of breakage points. EPHRUSSI and SUTTON try to interpret a few actual details on the basis of this assumption, e.g., STERN and HEIDENTHAL's[1] (1944) comparison of dosage relations in mutant combinations with those involving a position effect at the same locus (DUBININ's c. i. effect). The results had shown that a kinetic interpretation found for the dosage effects did not work with the position effects. For this case and a few others, an interpretation in terms of stretching is proposed. In my opinion the hypothesis does not work, for many reasons, e.g.: 1) We do not know anything about the condition of chromosomes in the resting nucleus. 2) The hypothesis demands a heterozygous position effect. Actually, many recessive homozygous or hemizygous position effects are known; an exact study of the salivaries made by A. HANNAH (GOLDSCHMIDT[2] *et al.*, 1945) for homozygous inversions in the yellow and white region do not show any abnormality of synapsis in the female and certainly nothing, either, in the hemizygous male. 3) An acceptance of the stretch theory would require either that point mutants be also products of stretch or that a gene produces invariably the same mutant type of reaction, whatever happens to it, e.g., stretching, or disappearance altogether, or chemical change. However, I think EPHRUSSI and SUTTON's discussion of great importance, because it disposes of the kinetic theory of position effect and stresses the necessity of a structural interpretation, as I had emphasized repeatedly, though upon a completely different basis. Thus, I should agree with BEADLE's[3] statement in a recent review (1945) that no explanation of position effect has been found thus far, if he had added "within the classic theory of the gene." As a matter of fact, I have repeatedly emphasized (1937, ff.) that an explanation of position effect requires an abolition of the oversimplified classic theory of the gene. *(Continued)*

[1] H. J. MULLER, Cold Spring Harbor Symposia *9*, 151–165 (1941).
[2] M. DEMEREC, Univ. Pennsylvania Bicent. Conference, 1–11 (1941).
[3] B. EPHRUSSI and E. SUTTON, Proc. nat. Acad. Sci. *30*, 183–197 (1944).
[4] R. GOLDSCHMIDT, Publ. Amer. Assoc. Adv. Sci. *14*, 56–66 (1940).

[1] C. STERN and HEIDENTHAL, Proc. nat. Acad. *30*, 197–205 (1944).
[2] R. GOLDSCHMIDT, Univ. Cal. Publ. Zool. *49*, 291–550 (1945).
[3] G. W. BEADLE, Chem. Reviews *37*, 1–96 (1945).