which can bring immediate relief to cases of high adrenal insufficiency.

(11) The effect of hormones depends largely on the way of their administration. Newly introduced biological units allow exact quantitative comparison of the "output of activity" and the "efficiency coefficient". The application of hormones (peroral, perlingual, or subcutaneous as crystal suspensions) was successfully studied.

(12) The alkali fusion of estrogenes such as estrone and equilenine yielded doisynolic acid and bisdehydro-doisynolic acid of high estrogene activity, also when applied perorally. The elucidation of their structure led to the total synthesis of bisdehydro-doisynolic acid.

(13) The question of specificity of active substances leads to the problem of the specific reactivity of definite cell groups. The cortical hormones seem to play the role of promoters.

Position Effect and the Theory of the Corpuscular Gene

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Position Effect versus Classical Theory of the Gene

It is our considered opinion that a single explanation must embrace position effect and point-mutation, an explanation which must take care of all the basic facts of both phenomena, viz.:

(1) The fact that the production of chromosome rearrangements by radiation follows the same dosage law as the production of point-mutation.

(2) The fact that in such experiments with X-rays (not neutrons) the seriation is found: two hits (or more) give large rearrangements with at least two distant breaks; one hit may produce small rearrangements or point-mutations. Ultraviolet radiation produces almost exclusively point-mutation though it also produces breaks (only the former radiations are supposed to act via ionization).

(3) The fact that the phenotype of a position effect is the same or nearly the same (multiple allele) as that of one or more point-mutants in a nearby region of the chromosome.

(4) The fact that position effects and point-mutants of the same region act as alleles.

(5) The fact that all types of mutant action are known also as position effect, i.e., dominance, recessiveness, homozygous lethality, modifier action, dominance modification, multiple allelism and subjection to selection in the case of invisible effect.

(6) The fact that in certain regions position effect may be overlapping between two loci of point-mutation.

(7) The fact that, in properly studied cases, a point-mutant is located in a small chromosome segment within which rearrangement breaks give the position effect, though in some cases it is claimed that only one definite interval between two bands can produce the effect.

(8) The fact that sometimes breaks within a proper region do not produce position effects.

(9) The fact that sometimes the position effect is found with breaks very distant from the locus.

(10) The fact that the last feature seems characteristic for those rearrangements with a second break in the heterochromatin, and that other special effects of heterochromatic neighborhood (mottling) are known.

It is obvious that the simplest and most logical interpretation of points 1 to 5 is the assumption that point-mutants are also position effects, i.e., invisible rearrangements within a so-called locus, the smallest visible size of which is a single band in a salivary chromosome. Actually, MULLER and PROKOFIEVA (1935) had considered this interpretation but had rejected it because they thought that evolution needs the old concept of the gene (see below). The present author has since repeatedly tried to show that such an interpretation of mutation is unavoidable. The facts mentioned as points 6 to 10 require, in addition, the assumption that the properties attributed to a corpuscular gene or gene molecule are actually those of small chromosome segments which function differently when the order of their architecture is changed, i.e., visible change of order = position effect, invisible change of order = point-mutation. Furthermore, the existence of such an architectural mutant effect neither presupposes nor proves the existence of a not mutated gene in the same segment. (Most geneticists speak loosely of the demonstration of a gene, when only a mutant locus has been found.)

Let us discuss briefly these points. It might be stated first that there has been much misunderstanding of our conclusions. There is, of course, no doubt that the chromosome has a serial structure and that localized changes of this structure, the mutant loci, can be located by the cross-over method. There is no doubt either that these localized conditions of change can be handled descriptively as separate units, the mutant

locus or gene, and that for all descriptive purposes the extrapolation can be made that at the normal locus a normal gene exists. Further, there can be no doubt that almost all genetical facts can be described in terms of corpuscular genes, and that a geneticist who is not interested in the question of what a gene is may work successfully all his life long without questioning the theory of the corpuscular gene. In the same way (repeating a comparison used above), a chemist can describe and handle almost all the content of chemistry with valences represented as one or more dashes between atoms. But when he wants to know what valence is, he has to use the tool of quantum mechanics which the ordinary chemist does not need in his work. Similarly, the concept of the corpuscular gene comes under scrutiny only when the problem of the nature of the gene and the explanation of mutation and position effect is attacked.

Let us first consider the facts in favor of the existence of the normal gene as a partner of the mutant locus. Experimental genetics informs us that the mutant loci represent the smallest sections of a chromosome which, if changed by mutation, can be recognized as located between two possible cross-over breaks. By deficiency tests the locus may be narrowed down to a single salivary-gland chromosome band. But only very few cases are known in which two adjacent bands contain different mutants and these are most probably interpreted correctly as repeats of the same band and locus (see SCHULTZ and CURRY[1], 1941, LEWIS[2], 1945). In chromosome regions which have been studied in detail such as the left end of the first chromosome, a number of bands are located between those bands which are assumed to contain the mutant loci. Together they constitute the sections in which breaks produce position effect. It is not known whether cross-over breaks can occur anywhere within such a section, as there is no method of discovering such breaks except by crossing-over between two loci. (Unequal crossing-over would furnish such a method.) Therefore the entire section of the chromosome which includes two known neighboring loci represents two "genes," because they can only be defined by cross-over breaks. We have seen such sections overlap in position effects, a fact which probably is responsible for the statement by DEMEREC[3] (1941) that the gene need not necessarily have definite boundaries.

As a normal section of the homologous chromosome can be inserted via double crossing-over between two mutated ones, the size of this section can give information about the minimum size possible for normal action. But whereas a double cross-over between three loci located in three adjacent bands, which would be needed to put one normal between two mutant loci in such a chain, could occur only with an infinitely small probability and therefore has not been found, we do not know in any case that the action of the normal allele is confined to a definite section which can be called a gene. Even the best duplication breaks known in the tip of the X-chromosome do not narrow down the size of a normal "gene" below that of the previously discussed sections in which breaks produce position effect. Actually, the overlapping sections of the position effect are in favor of the assumption that the normal action is not the function of a "gene" but of a segment of undefined length (possibly of tapering size). (Compare DEMEREC's conclusion that the gene need, not necessarily have definite limits, which says more or less the same thing but within the limits of the theory of the gene.)

Thus, the only apparent proof of the extrapolation that a mutant locus has as a corollary a normal gene is found in the existence of the covering effect of a duplication for homozygous recessive mutants present in the same section of a pair of homologues. As a rule this covering effect is a fact. But there are a number of loci known in which this covering does not occur. The usual interpretation in this case is that, occasionally, two recessives are dominant over the dominant allele. But if the first case is described as covering, then the second one is a failure of covering which might have many causes—among them also the nonexistence of the normal gene. We point here also to the facts reported above, that breaks in a duplicated piece near a definite locus change the covering action "by a position effect" (SIVERTZOFF-DOBZHANSKY and DOBZHANSKY, etc.). They expressly stated that this interference with the covering effect takes place only when the break of the duplication lies near the locus to be covered. The fact is described as a position effect, I suppose a kind of Dubinin effect. Is it not preferable to conclude that it is not the normal gene which is affected in the covering effect but that a chromosomal section of some length on both sides of the assumed locus (possibly tapering off in action) does not act or does not act completely as a dominant if curtailed by a rearrangement?

It may be added that a similar situation exists also in a somewhat different case. A deficiency opposite a recessive mutant gives the haploid effect, usually with exaggeration of the mutant phenotype. If a duplication is added, the phenotype is normal. But in one such case (GOLDSCHMIDT[1], 1945, p. 392) I found that the duplication covered some of the silver alleles but did not cover one of the silver alleles. Possibly comparable facts were found by DEMEREC and HOOVER (1936).

[1] J. SCHULTZ and V. CURRY, Carnegie Inst. Wash. Yearbook *40*, 282–287 (1941).

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

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

[1] R. GOLDSCHMIDT, Univ. Cal. Publ. Zool. *49*, 291–550 (1945).

A powerful argument in favor of our point of view can be derived from the interesting most recent results of STERN[1] (1946), which I think to be closely related to the facts just mentioned. The mutant c. i. (cubitus interruptus) in the fourth chromosome produces a gap in a wing vein. If the normal locus is translocated to another place the heterozygote $+^{ci}$ transl→/ci appears in different cases either as an intermediate between c.i./c.i. and c.i./+ or even more extreme than c.i./c.i. As such exaggeration is characteristic of the deficiency (−/c.i.) the normal locus in the wrong position has, in my opinion, not acted at all. In other words the +locus fails to cover or only partly covers c.i. in the heterozygote, the degree of coverage depending on the different translocations. The phenotype of the combination c.i./c.i. plus the translocation which gave the exaggeration is more normal than $+^{ci}$ transl→/ci as would be expected in my interpretation.

There is one group of recently much discussed facts which might be considered by some geneticists as a proof of the existence of the normal allele as a distinct body, i.e., a corpuscular gene. It has been known for a long time that the action of genic material must be visualized—aside from its autocatalytic property (HAGEDOORN, 1901)—as catalyzing chains of reactions of definite velocity which finally lead to the production of the hormones of differentiation (which include genuine hormones, organizers, determining stuffs, specific enzymes, etc.). This conclusion had been derived (GOLDSCHMIDT 1916, 1917, 1920) by comparing genetic and embryological facts concerning pigmentation in caterpillars and concerning sex-determination by analysis of intersexuality. It is obvious that in all cases of determination of morphogenetic processes there is very little possibility of determining the chemical nature of the decisive products or of intermediate stages of the chains of reaction. Only in one case has such been claimed and, interestingly enough, one in which the genetical setting closely parallels that of the situation from which the generalization originally was derived (intersexuality in *Lymantria* based upon different valencies of the balanced female and male sex determiners). I refer to MOEWUS and KUHN'S work (see 1941[2]) on *Chlamydomonas* and its sex determiners of different valency (applied to conditions of protista, our general idea has also been termed by HARTMANN relative sexuality). If this much-discussed work is correct, these sex determiners control by their balance and valencies the ratio of the cis- and trans-isomeres of crocetin dimethyl ester which is responsible for sexuality (which includes its morphology and physiology).

Otherwise, as far as I am aware, chemically definable reactions controlled by mutant loci have been analyzed only for cases in which the end-product was obviously a chemical change (as opposed to morphological change) e. g., abnormalities of metabolism (alcaptonuria, GARROD), changes in oxydizing enzymes and chromogens (rodents' pigment ONSLOW, DANNEEL, school of WRIGHT) changes in anthocyanin, and other plant pigments (WHELDALE, school of HALDANE and others), in precursors of eye pigments of insects (schools of KÜHN, BEADLE-EPHRUSSI and KIKKAWA), and in failures of synthesis of necessary vitamins and amino acids in fungi, especially *Neurospora* (BEADLE; see last review by BEADLE[1], 1945). As the results of this important work show that in most cases a mutant blocks one definite step, and different mutants different steps, in a chain of synthesis or hydrolysis, BEADLE has concluded that the normal gene is responsible for the specific catalyzer of the respective step and that thus a one-one relation exists for each catalyzer to one gene. If this conclusion were valid it could be classed as a proof of the existence of the normal gene.

With due admiration for the work under discussion, I cannot consider the conclusion as established. The reasons are the following:

(1) The fact that a mutant has a definite effect does not give us any information about the normal chromosome except that a local change interferes with the normal action. The assumption that the latter is based upon a definite unit, a gene with that normal function, is a possible but not necessary extrapolation. If I stop the A string of a violin about an inch from the base, the tone C is produced by the string. This does not mean that the string has a $+^{C}$ body at the point which, when stopped, becomes C.

(2) It remains to be seen whether different loci will be found affecting one and the same step in a reaction, as might be expected from genetical facts. Such an occurrence has been claimed by KIKKAWA[2] (1938) for insect eye colors. I realize that, in the case of only a few such loci, an interpretation in terms of BEADLE'S theory would still be possible. (Genetically controlled serological specificity has specific aspects not typical for other loci. The facts seem to be compatible with the classic as well as with my interpretation; see STURTEVANT[3], 1944, and EMERSON[4], 1945.)

(3) Mutants have been found which block a definite step of synthesis in the usual way, but only at one temperature; at another temperature the synthesis takes place (school of BEADLE). This cannot be fitted simply into the one-one relation idea.

(4) Many facts of physiological genetics, though relating to unknown reactions controlling morpho-

[1] C. STERN, Rec. Genet. Soc. Amer. *14*, 62 (1946).
[2] F. MOEWUS, see Ergebn. Biol. *18*, 287 (1941).

[1] G. W. BEADLE, Chem. Reviews *37*, 1–96 (1945).
[2] H. KIKKAWA, Genetics *20*, 458–516 (1938).
[3] A. H. STURTEVANT, Proc. nat. Acad. Sci. *30*, 176–178 (1944).
[4] S. EMERSON, Ann. Missouri Bot. Gard. *32*, 243–249 (1945).

genesis, point out that such results as those mentioned in point 3 are very frequent, e.g., the mutant vg (vestigial) produces vestigial wings but, at high temperatures the wings are normal; in other cases, low temperature or moisture may be the controlling agency. Whatever the reaction involved in all these cases might be, it certainly is impossible that a one-one relation between a locus and the production or not production of a specific catalyzer is involved. Actually, the known facts point out that it is not the production or non-production of a specific catalyzer but a series of concomitant and necessary conditions which are controlled in such cases, e.g., concentration or quantity of substance, threshold of action on morphogenesis, time of action in relation to other morphogenetic processes, conditions of the substrate, etc., as frequently stressed by the present author.

(5) Exactly the same conclusion must be derived from the phenomenon of phenocopy (GOLDSCHMIDT, 1929, 1935[1], and many followers) which I consider to be the basic fact of physiological genetics in regard to morphogenesis. It is proven that in *Drosophila* the phenotype of probably any known morphological mutant, even the most aberrant ones, can be produced as a modification by action of heat, cold, poison or radiations during sensitive periods in development. It is easily conceivable how this can be accomplished by changing rates and timing of developmental processes. From this it might be concluded that the mutant locus, the visible effect of which is copied, acts in a similar way. (See the discussion concerning the absence of phenocopies of qualitative chemical properties in GOLDSCHMIDT, 1945, and HENKE[2] *et al.* (1941) and MA's work (1941, 1943[3]) on the time relations between the sensitive periods for production of phenocopies and the embryological determination of mutants.)

Thus, whereas the one-one relation between the mutant locus and an enzyme for a definite step in a reaction is proven for certain cases, but does not seem to apply to the most important genetical feature, determination of morphogenesis, I am loath to accept the extrapolation upon the normal gene and, therefore, do not consider this body of facts to constitute a proof for the existence of the corpuscular gene. Thus, we conclude that there is no real obstacle to the abandoning of the theory of the corpuscular gene if a theory of the position effect requires it.

Deliberations of the type just presented have led me to develop on different occasions the idea that in spite of the serial differentiation of the chromosome and the existence of mutant loci a corpuscular gene, so useful for descriptive purposes, does not actually exist. The general tenor of my ideas is that point-mutants are the result of rearrangements, just as are position effects, and that therefore the mutant action of a segment of a chromosome is in all cases the result of a structural change along the chromosome, an architectural change as opposed to a chemical change in a side-chain or a change of stereoisomeric type within a gene molecule. If this is true, there must be possible changes of activity as the result of structural changes involving segments of different size in the chromosome, which again leads to the idea that in the normal chromosome it is not a string of individual sections, genes, which individually produce the genic reactions, but that sections of any size, from the smallest parts up to a whole chromosome, may be the active units at one or another time (hierarchy).

It is very unfortunate that the chemistry of the chromosome is, thus far, of no help in solving these problems. Actually in this field the geneticist and cytologist are more advanced than the chemist. The serial structure of no single chain molecule of protein is completely known and no generally accepted theory of how such a chain is synthesized exists. But both in serial structure and in regard to synthesis the chromosome, a giant in comparison with the longest known chain molecules, copies the features of a single molecule. We know that the chromosome has an orderly serial structure, and that it reproduces itself as a unit, i.e., that it somehow synthesizes its like in a way which cannot be conceived otherwise than as building up a copy from point to point. Actually the chemists (e.g., BERGMANN) hat to use a similar model to visualize the synthesis of a protein chain molecule, and the problem has been repeatedly discussed with reference to the chromosome and the gene (e.g., DELBRÜCK[1], 1941, GULICK[2], 1944). Recent developments in the ideas concerning antigen-antibody relations as surface copies and templates have also been discussed as probable solutions for biological syntheses as well as for the reproduction of the genic material (see PAULING and DELBRÜCK[3], 1940, EMERSON[4], 1945). As these more recent ideas can be applied to any conception of the architecture of the genic material, with or without genes, we do not need to discuss them further.

Returning to the protein molecule, it is of course very small in comparison with a stretched chromosome, and chemical information on the super-molecular level refers only to fibres involving one single protein. A chromosome certainly behaves like a fibre (leaving out of consideration the relation to nucleic acid), but it must be a type of fibre which is composed of numerous dif-

[1] See R. GOLDSCHMIDT, J. exp. Zool. *100*, 193–201 (1945).

[2] K. E. HENKE, VON FINK and S.-Y. MA, Ztschr. Ind. Abstl. *79*, 267–316 (1941).

[3] S.-Y. MA, Roux Arch. *142*, 508–618 (1943).

[1] T. DELBRÜCK, Cold Spring Harbor Symposia *9*, 122–126 (1941).

[2] A. GULICK, Adv. Enzymol. *4*, 1–39 (1944).

[3] C. D. H. PAULING and M. DELBRÜCK, Science *92*, 77–79 (1940).

[4] S. EMERSON, Ann. Missouri Bot. Gard. *32*, 243–249 (1945).

ferent protein chains associated end to end in a definite and orderly pattern, imitating, as it were, the longitudinal pattern of amino acids and prosthetic groups within a protein molecule. The chemists inform us that it is impossible to divide a protein molecule into two or more indentical pieces. The same is true for a chromosome. Other comparisons might be made, e.g., the constant distance of residues in a molecular chain and, on the chromosomal level, the rather constant distance between two chromomeres, i.e., thymonucleic acid aggregation to protein. As far as I am aware, no such types of macromolecular aggregates have been studied (SZENT-GYÖRGYI's[1], 1941) association of macromolecules might belong here) and therefore the geneticist must form his ideas in the hope of future chemical information which might give a positive meaning to what I have called the hierarchy of action. (LONDON's work on chemical differences based upon the distributions of active groups might one day come into play.)

At this point a word should be said about another problem which thus far has not been solved, though its solution is required for a full understanding of the problems under discussion. I mean the respective roles of the thymonucleic acid and the protein fibre in the genic action of the chromosome. It has been generally assumed that this action resides in the proteinic component of the chromosome (see, e.g., DARLINGTON[2] 1942). But a number of facts seem to indicate that the genic action requires some interaction of both components, e.g., the maximum mutation frequency caused by ultraviolet radiation is found at the wave length absorbed by nucleic acid (KNAPP; STADLER); the virus molecule of tobacco mosaic is a nucleoprotein (STANLEY); work on bacteria (AVERY, MCLEOD, and MCCARTY[3], 1944) showing that it is the specificity of thymonucleic acid, which produces "mutation" of pneumococcus strains to its own type. It is probably also significant that the polymerized molecule of thymonucleic acid is split into smaller units by the action of X-rays (WEGMÜLLER[4], 1942). The same is claimed for ultraviolet rays. (The claim of SCHULTZ[5] (1941) to have shown a change in the quantity of nucleic acid at the mutated white locus has thus far not been confirmed.) It seems hardly possible that final ideas can be formed before a decision has been reached on the genic properties of the protein and the attached nucleinic acid as well severally as in interaction.

One of the great difficulties of the theory of the gene is the fact that the mutant locus again reproduces its kind faithfully and that therefore the assumed chemical change within the gene does not change the ability of the molecule to synthesize or model its own copy. This ability practically restricts the possibility of mutation to stereoisomeric changes, or surface changes according to the new viewpoints. GULICK[1] (1944) actually demanded that all active groups of a gene must occupy its surface. There is, of course, no difficulty of any kind if only changes of order at a supermolecular level are involved in mutation. Thus we realize that much factual knowledge is still missing. Any theory of the chromosome and its genic action is therefore provisional.

Let us now look at a possible model of a chromosome and the relation of mutation to position effect as we see it. The smallest visible chromosome segment, i.e. a single band in a salivary chromosome, must be a chain of different protein molecules arranged in a definite order, say $\alpha, \beta, \gamma, \delta, \varepsilon, \zeta$. It has been shown (KODANI[2], 1942, GOLDSCHMIDT and KODANI, 1942[3]) that after treatment of salivary chromosomes with urea the single band appears as a coil to which are attached nucleoproteinic bulb-like bodies which we called perultimate chromomeres. A point-mutant would be a change in the order of the perultimate chromomeres including deletions of members of the series. Thus it is a position effect on the smallest scale. The next larger segment is the type of chromosome section discussed above, within which rearrangements give the typical position effects. If we call the supermolecular group α—ζ just mentioned *a*, the chromosome section under discussion would be *abcdef*. Changes or interruptions of this order would result in the typical position effect, the phenotype of which is identical with the phenotype of one or the other of its constituents if rearranged on the next lower level. In most cases the position effect is not produced by a rearrangement within the section, as would happen in the case of very small rearrangements, but by breaks which change the series *abcde* to *abxyz* etc. It can be visualized that some such new seriations may be of such a nature as to resemble the original composition *abcde*, and therefore the rearrangement would have no position effect. It is further possible that *b* or *c* as well as *a* might be composed of $\alpha\beta\gamma\delta\varepsilon$ or a similar series, $\alpha'\beta'\gamma'\delta'\varepsilon'$. In this case two different localization experiments, using deficiencies etc., might result in locating the locus of the point-mutant within the section once in band *a*, once in *c*. Such findings in the scute section have been discussed in GOLDSCHMIDT[4], 1944.

[1] M. SZENT-GYÖRGYI, Science *93*, 609 (1941).

[2] C. D. DARLINGTON, Nature *149*, 66–69 (1942).

[3] O. T. AVERY, C. M. MCLEOD and M. MCCARTY, J. exper. Med. *79*, 137–157.

[4] F. WEGMÜLLER, 1942, quoted from W. MINDER and A. LIECHTI, Exper. *1*, 300 (1945).

[5] J. SCHULTZ, Cold Spring Harbor Symposia Quant. Biol. *9*, 55–65 (1941).

[1] A. GULICK, Adv. Enzymol. *4*, 1–39 (1944).

[2] M. KODANI, J. Hered. *33*, 114–133 (1942).

[3] R. GOLDSCHMIDT and M. KODANI, Amer. Nat. *76*, 529–551 (1942).

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

Cytologically such a section probably corresponds to a chromomere in the leptotene chromosome, as the numbers are of the same order of magnitude (see GOLDSCHMIDT[1], 1944). I call these BELLING'S chromomeres. The next larger section is probably determined cytologically by the alternation of heterochromatic and euchromatic blocks. HEITZ had shown these in mitotic chromosomes, PROKOFIEVA[2], 1939) had localized them by the method of intrachromosomal synapsis of heterochromatic sections, and KODANI[3] (1941) localized them and showed their different chemical composition in salivary chromosomes by treatment with alkali. The number of these sections corresponds to the number of large diplotene chromomeres studied first by WENRICH and therefore this third section may be called the WENRICH chromomere. These segments could be called *A*, *B*, etc., arranged in the order *A* → heterochromatin → *B*-heterochromatin → and *A* is composed of the position effect sections *abcd* etc. Thus far no absolute proof exists that this *A* section may act genetically as a unit. But some facts agree best with such an idea. Here belong probably the position effects stretching over long distance mentioned above and their obvious relation to heterochromatin is very suggestive. Another suggestive fact is that chromosome sections are known in which many mutants have a similar effect, e.g., the group of homœotic mutants in the third chromosome of *Drosophila*.

Another group of facts which I expect to play a considerable role in the problem under discussion is the following: Notch deficiencies in the X-chromosome of *Drosophila* may cover a number of known mutant loci, all of which show the typical hemizygous Notch effect opposite the deficiency. GOTTSCHEWSKY[4] (1937) found such a deficiency effect, including the Notch phenotype, with completely normal chromosomes. DEMEREC[5] (1941) found other cases and recently BARIGOZZI[6] (1942) has assembled a whole series including one of considerable length containing the known mutants W, co, spl, fa, dm, ec. GOTTSCHEWSKY'S interpretation is that the normal genes were somehow paralyzed. To me this looks as if a sectional change had occurred on the *A* etc. level, producing a position effect upon many or all loci and sections within the region of the standard position effect type, i.e., of the type of the mutant allele. What this sectional effect is we do not know, but this problem might be attacked experimentally. Finally, there is a possibility that such sectional effects may be found within the sphere of sex determination. There are cases known in which sex determination is probably bound to a single locus in the X-chromosome (*Chlamydomonas*, MOEWUS, if correct). In other cases no single locus could be found (*Drosophila*) and also no definite section of the X-chromosome. We shall return to this point below. Recently WARMKE[1] (1945) and independently WESTERGAARD[2] (1946) have shown that the Y-chromosome of *Melandrium* (which is known to be the seat of male determiners) contains sections, one of which is needed for male determination, one for finishing male differentiation, and one for female suppression. It cannot be stated with certainty that here actions of whole sections are involved but the possibility must be kept in mind.

If the idea of the seriated or polarized hierarchy of architectural units and their proper order within the chromosome is correct, one should expect finally also genetic actions of the chromosome as a whole, which certainly are difficult to prove, for obvious reasons. I am inclined to consider such an action possible in the case of the X-chromosome of *Drosophila*. All points have been tested and no single sex "gene" has been found. When triplication tests in triploid intersexes showed some shifts in the degree of intersexuality, DOBZHANSKY and SCHULTZ[3] (1934) interpreted this as a proof for multiple sex genes. Very elaborate work of a similar type performed by PIPKIN[4] (1940) has failed to substantiate this claim (which, as I had already shown was not basically sound—GOLDSCHMIDT[5], 1935), so that neither single nor multiple sex genes could be demonstrated thus far. The possibility that more or less the whole chromosome produces the stuffs of the male sex determination as a unit appeals strongly to me.

SERRA[6] (1944) has tried to compromise between the classic theory of the gene, the difficulties of which he realizes, and the views of the present author by modifying the latter so as to allow for the gene as a unit. His idea is that a chromomere (comparable to the chromomere of BELLING, above) consists of a number of genes separated by linking zones which, like the interchromomeric and intergenic zones, have an irregular arrangement of molecules. Position effect and mutation would both be the results of rearrangements with breaks in the interzones. Clearly, the difference from my point of view is the retention of the gene concept for one of the members of what I called the hierarchy of the chromosome structure.

When MULLER first discussed the possibility of explaining mutation as a rearrangement effect, he re-

[1] R. GOLDSCHMIDT, *in:* Science in the University, Univ. Calif. Press, p. 183–210 (1944).
[2] A. PROKOFIEVA-BELGOVSKAYA, Bull. Acad. Sci. U.S.S.R., Ser. biol., *2*, 363–370 (1939).
[3] M. KODANI, J. Hered. *32*, 146–156 (1941).
[4] G. GOTTSCHEWSKI, Ztschr. Ind. Abstl. *73*, 131–142 (1937).
[5] M. DEMEREC, Univ. Pennsylvania Bicent. Conference, 1–11 (1941).
[6] C. BARIGOZZI, Riv. di Biol. *34*, 3–16 (1942).

[1] H. E. WARMKE, Rec. Genet. Soc. Amer. *14*, 64 (1946).
[2] M. WESTERGARD, Hereditas *32*, 60–64 (1946).
[3] TH. DOBZHANSKY and J. SCHULTZ, J. Genet. *28*, 349–386 (1934).
[4] S. B. PIPKIN, Univ. Texas Public. *4032*, 126–156 (1940).
[5] R. GOLDSCHMIDT, J. Genetics *31*, 145–153 (1935).
[6] T. A. SERRA, Bol. da Soc. Broteriana *19*, 327–369 (1944).

fused to draw such a conclusion because he thought that evolution needed the classical concept of the gene. I do not propose to speculate here on this subject, but I want to point out some of the consequences of the conclusions reached now and previously. If standard mutations are position effects, there is a possibility that chemical changes (as opposed to structural ones above the molecular level) within a chain molecule produce a different and much more decisive effect (equivalent to the origin of a new gene in the classic theory). LAMPRECHT[1] (1945, and other papers) has recently emphasized the existence of complex mutations as different from ordinary ones. It will be good to keep this subject in mind. (LAMPRECHT has actually drawn conclusions on evolution which this is not the place to discuss.) A second point is that the conception of the chromosome and its action as presented here permits purely architectural changes within a chromosome which change completely the action of the higher members of the hierarchy. At a certain level or threshold this might mean a profound change in chromosomal activity and therefore a profound change of the organism, if viable. I have called this possibility a systemic mutation (GOLDSCHMIDT[2], 1941) (not yet demonstrated just as the Neodarwinian concept based upon the classical gene has never been demonstrated). There is no doubt most geneticists disagree with such ideas and try to go to the limit in applying the classic theory of the gene. Majorities have not always turned out to be right.

A mention might be expected of SCHRÖDINGER's[3] book (1945) on the gene from the standpoint of quantum mechanics, in which it is claimed that a definite view of gene mutation is required by quantum mechanics in conformity with DELBRÜCK's former derivations. As no other point of view is discussed or mentioned, the question remains whether an architectural theory which requires after all also breakage of bonds does not also fit the requirements of wave mechanics. The answer is up to the physicist but I anticipate a positive answer from former statements by DELBRÜCK which I quoted repeatedly in former papers.

[1] H. A. K. LAMPRECHT, Agri hortique genetica, III, 45–60 (1945).
[2] R. GOLDSCHMIDT, The Material Basis of Evolution, Yale Univ. Press (1941).
[3] E. SCHRÖDINGER, What is Life?, Macmillan, New York 1945.

Finally a brief mention of newer work on mutation is in order which, in my opinion (GOLDSCHMIDT[1] *et al.*, 1945), shows that mechanical conditions between and within the chromosomes are the causes of spontaneous mutation. But it would lead too far to include a discussion of the literature on this subject as well as on other facts in favor of our views, e.g., increase of rearrangements and mutations in the presence of sticky chromosomes (BEADLE); increase of mutation after crossing *Drosophila* species with chromosomes of different architecture (STURTEVANT); production of mutants by aging of seed or by chemical means (mustard gas!). *(Concluded)*

Zusammenfassung

Der sogenannte Lageeffekt wird in dieser Arbeit in allen Richtungen diskutiert. Es handelt sich darum, daß ein Bruch im Chromosom einen phänotypischen Effekt hervorruft, der mit dem einer Mutante identisch ist, welche nahe der Bruchstelle lokalisiert ist. Es wird gezeigt, daß dies ein sehr häufiges Phänomen ist, ja, wahrscheinlich bei *Drosophila* häufiger als Punktmutationen. Der einzige andere Organismus, für den die zytogenetische Technik so weit fortgeschritten ist, daß ein Lageeffekt entdeckt werden könnte, Mais, zeigt ihn tatsächlich in vier Fällen. Die verschiedenen Arten von Lageeffekt werden im einzelnen beschrieben und fünf verschiedene Arten unterschieden. Dazu kommen noch als wahrscheinliche Fälle die Effekte von Verdoppelungen und Ausfällen. Eine genaue Analyse dieser Fälle zeigt, daß im ganzen Lageeffekte sich in nichts von Mutanten unterscheiden, und ferner, daß sie zeigen, daß in der Umgebung eines jeden Lokus ein Chromosomensegment existiert, in dem kein anderer Lokus sich findet, in dem aber ein Bruch den Lageeffekt hervorruft. Es werden dann die Erklärungen beschrieben und kritisiert, die versuchen, den Effekt im Rahmen der klassischen Theorie des Gens zu erklären. Da dies unmöglich erscheint, wird des Verfassers Ansicht wiederholt, daß alle Mutanten Lageeffekte sind und daß kein korpuskulares Gen nötig ist, um Mutationen zu verstehen. Diese Idee wird im einzelnen ausgeführt und gezeigt, daß keiner der Beweise für die Existenz des korpuskularen Gens stichhaltig ist. Es wird schließlich zu zeigen versucht, daß eine Hierarchie der Funktion des Chromosoms, basiert auf seiner seriierten Struktur, besteht, die es ermöglicht, daß irgendein Segment vom kleinsten Lageeffektsegment bis hinauf zum ganzen Chromosom als Einheit funktionieren kann und nicht als Summe hypothetischer Einzelgene.

[1] R. GOLDSCHMIDT and collaborators, Univ. Calif. Publ. Zool. *49*, 291–550 (1945).