GENETIC BASIS FOR TWO TYPES OF RECESSIVE LETHALITY AT THE NOTCH LOCUS OF DROSOPHILA[1]

W. J. WELSHONS

Department of Genetics, Iowa State University, Ames, Iowa 50010

Received November 12, 1970

NOTCHES, symbolized as *N*, are inherited as sex-linked dominant mutations that are lethal in the homozygous and hemizygous condition. In heterozygotes *N*/+, typical females have notched wings, thickened wing veins and an irregular distribution of thoracic hairs. Since many Notch mutants are associated with a visible cytological deficiency for salivary band 3C7, it has been concluded that the Notch gene is contained within this single band (MOHR 1919, 1923; SLIZYNSKA 1938; DEMEREC 1939). In addition to these deficiency types of Notches, many *N*'s are cytologically normal and phenotypically similar to or, in some instances, indistinguishable from the deficiency type; they have been used to demonstrate the linear arrangement of mutant sites in the Notch gene within salivary band 3C7 (WELSHONS 1958, 1965; WELSHONS and VON HALLE 1962).

Interspersed in the linear array of *N*'s, are mutant sites inherited as recessive visibles. The phenotypes of these recessives fall into two catagories: Those that roughen the eye are facet (*fa*), facet-glossy (fa^g) and split (*spl*). Those that produce wing notching or alterations in wing venation are facet-notchoid (fa^{no}), notchoid (*nd*), and notchoid-2 (nd^2). Additional details relevant to these mutants will be found in LINDSLEY and GRELL (1968).

In heterozygotes of a *N* (deficiency or nondeficiency type) with *fa*, fa^g, *spl*, *nd*, and nd^2, there is a phenotypic expression of the recessive in addition to that of the dominant Notch. In the case of N/fa^{no}, depending upon the *N* mutant used, heterozygotes are very inviable or completely lethal, although the recessive in homozygous or hemizygous condition has good viability and fertility. Excepting fa^{no} for the moment, the pseudodominant manifestation of recessive visibles when combined with Notch suggests that these recessive mutant sites permit the synthesis of a gene product that is functional but slightly aberrant, whereas the *N*'s totally lack a product or fashion one that is largely or completely impaired at the functional level. The mutant fa^{no}, like some of the other recessives, seems to be a hypomorph (WELSHONS 1965), and the lethality of N/fa^{no} evidently results from the hypomorphism of fa^{no} combined with the amorphism of Notch, yielding a heterozygous hypomorphic condition more extreme than in fa^{no} homozygotes.

There is in Drosophila stocks an *X* chromosome tandemly duplicated for a series of salivary bands, one of which is 3C7; the chromosome is symbolized as *Dp(1;1)Co*. When heterozygous with a normal *X*, the flies express a Confluens

[1] Journal Paper No. J-6767 of the Iowa Agriculture and Home Economics Experiment Station, Ames, Iowa, Project No. 1659. Work supported in part by National Science Foundation grants GB-5014, GB-7631, and GB-8651.

phenotype recognized as a thickening of one or more wing veins; the homozygous condition is more extreme. In his investigation of this tandem duplication, SCHULTZ (in MORGAN, SCHULTZ and CURRY 1941) provided a convincing demonstration that the extra 3C7 alone was responsible for the Confluens expression. Combining the Notch and Confluens information, one sees that individuals with no functional 3C7 bands are lethal, with one less than normal they are Notch, and when an extra band is present, the phenotype in Confluens. Females of the genotype *N/Dp(1;1)Co* are wild type rather than Notch or Confluens since they have the normal complement of two functional 3C7 bands, although both are carried on the same chromosome.

An autosome, especially useful in this research, contains an insertion of band 3C7 plus some adjacent material; it is identified as *Dp(1;2)51b7* (LEFEVRE, 1952; LINDSLEY and GRELL 1968). Even though the extra element is inserted into an autosome in this case, while carried as a tandem duplication on the *X* in *Dp(1;1)Co*, the generalities relevant to the number of 3C7's and associated phenotypes remain unchanged. The genotype *N*/+; *Dp(1;2)51b7* equals *N/Dp(1;1)Co*, phenotypically wild type, since both genomes have only two functional 3C7 bands.

Another dominant called Abruptex (Ax^{28a}) was investigated by SCHULTZ. Homozygous females have shortened wing veins, generally lack some prominent bristles, and the hairs on head and thorax are fewer. In heterozygotes, Ax^{28a}/+, the phenotype is less extreme. Cytological investigation revealed the presence of a duplication for a single band presumed to be 3C7 since Ax^{28a}/N^{8} females had a phenotype that approached wild type in all characteristics (MORGAN, SCHULTZ and CURRY 1941). However, the convincing demonstration that a duplication for 3C7 is Confluens suggested that the extra cytological element might not represent the locus of Notch. Alternatively, if two 3C7's are present, the contiguity has evoked a position effect recognized phenotypically as Abruptex.

We have investigated two newly originated *Ax* mutants that were isolated after the irradiation of mature sperm (GREEN, personal communication). Noting the origin of the two mutants, one would not expect them to carry duplications, and cytologically they appear completely normal, possessing only one salivary band 3C7. Interestingly, these two mutants, unlike the original *Ax*, are distinctly semilethal at 22°C, and lethality at 25°C very closely approximates 100%. Furthermore, *N/Ax* heterozygotes are lethal, suggesting the interruption of a common function. The data to be presented indicate that these recessive lethal *Ax*'s represent mutant sites in the Notch gene and lead to a plausible explanation for their Abruptex phenotype, although the lethality of *N/Ax* would logically suggest that they should be phenotypically Notch. Additional observations and comparisons are in harmony with the view that the original Abruptex does in fact carry an extra 3C7 band and suggest a plausible alternative for the appearance of the Abruptex phenotype in $Dp(1;1)Ax^{28a}$.

MATERIALS AND METHODS

The Abruptex mutants Ax^{59b} and Ax^{59d}, lethal in the combination Ax^{59b}/Ax^{59d}, express both

wing and bristle abnormalities as $Ax/+$ heterozygotes. The wing effects recognized primarily as a shortening of longitudinal veins 4 and 5 are the most obvious phenotypic manifestations, although some specific bristle abnormalities seem somewhat more reliable. (A more complete description of the two mutants will appear in a future issue of Drosophila Information Service.) Since these *Ax*'s have quite good viability and fertility in combination with recessive visibles at the Notch locus, recombination values and the linear order of mutant sites could be directly obtained from appropriately marked heterozygotes. When the recessives fa^g and *spl* were used, both wild-type and double mutant recombinants were detected. With nd^2, only the wild-type recombinant could be isolated from heterozygotes with an *Ax*.

The detection of recombination and linear order of mutant sites in Ax/N heterozygotes required the introduction of *Dp(1;2)51b7* into the genome to cover the recessive lethality. Recombinants cannot be detected in progeny when the autosomally inherited duplication also is present; hence, the resolving power is diminished. Fortunately, some compensation can be achieved by eliminating significant numbers of nonrecombinant flies by mating Ax/N; *Dp(1;2)51b7* heterozygotes to males carrying fa^{no}, thereby killing a large proportion of the nonrecombinant N/fa^{no} progeny that are free of the duplication. Only wild-type recombinants with respect to *Ax* and *N* were recovered in these experiments.

A direct test for recombination between Ax^{59b} and Ax^{59d} was not attempted since we discovered early in the investigation that Ax^{59b}/Ax^{59d}; *Dp(1;2)51b7* females were quite inviable and infertile. It is possible to obtain some progeny from the heterozygotes, but they are so infrequent as to make the experiment impracticable.

The autosomal mutant Enhancer of split *E(spl)* was used to make comparisons between the coupled mutant combinations *N spl* and *spl Ax*. In homozygous or heterozygous condition, *E(spl)* enhances the split phenotype to such a degree that $spl/+$ females are indistinguishable from homozygotes *spl/spl* (see LINDSLEY and GRELL 1968).

RESULTS AND CONCLUSIONS

Heterozygotes of Ax^{59b} and Ax^{59d} with point mutation *N*'s are lethal, suggesting the interruption of a function common to both Notch and Abruptex. When *Ax*'s are combined heterozygously with recessive visibles at Notch, unlike *N*'s in the same combinations, the pseudodominant expression of the recessives is observed only with the eye mutant facet-glossy. Heterozygotes Ax/fa^g are phenotypically Abruptex; the eyes are rough, but not glossy or only very slightly so. No eye effect was noticeable in heterozygotes of *Ax* with *fa* or *spl*, nor were the notched phenotypes of wing mutants fa^{no} or nd^2 expressed in heterozygotes, although the expression of *Ax* was moderately enhanced when heterozygous with a recessive wing mutant.

The relationship between Notch and Abruptex can be understood if *Ax*'s are represented as mutant sites within the Notch gene; however, the *N* mutants represent a complete or virtually complete loss of function, and the lethality of N/Ax suggests the loss is shared by Ax^{59b} and Ax^{59d}. Why then are the phenotypes of $N/+$ and $Ax/+$ so different and the pseudodominant expression of an *N* and an *Ax* with recessive visibles at Notch so variant? Alternatively, one might suppose that recessive lethal Notches represent the loss of function in one gene and that the *Ax's* represent a loss in an adjacent cistron functionally related to Notch as in an operon. Discrimination between alternative interpretations should be provided by genetic tests. If *N*'s and *Ax*'s represent mutant sites in the same cistron, Abruptex mutants will localize within the Notch gene; otherwise, they will be found outside the presently defined limits of Notch.

To determine the position of the Abruptex mutants relative to mutant sites at the Notch locus, recombinants were sought among the progeny of appropriately marked heterozygotes. The mutant sites defining the left and right limits of the Notch gene, plus the intervening ones used in these experiments, exist in a linear order as indicated:

$$N^{55e11}\text{——}fa^{g}\text{——}spl\text{——}N^{Co}\text{——}N^{60g11}\text{——}nd^{2}$$

The mutants *y*, *sc*, *z*, and w^a to the left of Notch and *rb* to the right were used in various combinations to determine the direction of crossing over if an exchange occurred between an *Ax* and a mutant site at Notch.

TABLE 1

The number and types of recombinant chromosomes obtained from heterozygotes of Ax^{59d} *with other mutant sites at the Notch locus*

1 sc z + + Ax^{59d} +/+ + w^a fa^g + rb ♀ × y w^a fa^g rb ♂

(8) sc z + + + rb
(3) + + w^a fa^g Ax^{59d} +
*(1) sc z + + +

Tested chromosomes = 19,100
Recombination = .058%

2 sc z + Ax^{59d} +/+ + spl + rb ♀ × w^a fa^{no} spl rb ♂

(1) + + spl Ax^{59d} +
*(1) sc z spl Ax^{59d} +

Tested chromosomes = 32,100
Recombination = .003%

3 y w^a fa^g Ax^{59d} + +/+ w^a + + N^{Co} rb ; Dp/+ ♀ × w^a fa^g fa^{no} rb ♂

(1) + w^a + + + +

Tested chromosomes = 25,200
Recombination = .008%

4 y w^a fa^g Ax^{59d} + +/+ w^a + + N^{60g11} rb ; Dp/+ ♀ × w^a fa^g fa^{no} rb ♂

(4) + w^a + + + +

Tested chromosomes = 25,200
Recombination = .032%

5 y w^a fa^g Ax^{59d} + +/+ + + + nd^2 rb ♀ × nd^2 rb ♂

(7) + + + + + +

Tested chromosomes = 36,600
Recombination = .038%

Dp/+ indicates the presence of *Dp (1;2) 51b7*.
* Exceptionals not associated with recombination between outside markers, and not used for the calculation of recombination values.

The results of recombination experiments utilizing Ax^{59d}, recessive visibles and recessive lethals at Notch are summarized in Table 1. Proceeding from left to right within the Notch gene and from top to bottom in Table 1, *Ax* is to the right of fa^{g}. It also locates to the right of *spl*, but is more closely linked to *spl* than to fa^{g}. The experiments with N^{Co} indicate that Ax^{59d} lies a short distance to the left of this recessive lethal and can be represented as a mutant site between *spl* and N^{Co}. The observations that Ax^{59d} also lies to the left of N^{60g11} and nd^{2}, but is more loosely linked to these two mutant sites, supports the conclusion.

Similar recombination experiments were performed with Ax^{59b}, except that the recessive lethal N^{Co} was not utilized (Table 2). Proceeding as before, the experiments indicate that Ax^{59b} is located to the right of both fa^{g} and *spl*, but is more closely linked to the *spl* mutant. No recombinants were detected with N^{60g11}, although they might appear in an enlarged recombination experiment. If Ax^{59b} is closely linked to N^{60g11}, one would expect to find recombinants in the progeny of Ax^{59b}/nd^{2} heterozygotes and the *Ax* mutant site at a position to the left of nd^{2}. As

TABLE 2

The number and types of recombinant chromosomes obtained from heterozygotes of Ax^{59b} *with other mutant sites at the Notch locus*

1	$y^{2}\ z\ +\ +\ Ax^{59b}\ +/+\ +\ w^{a}\ fa^{g}\ +\ rb$ ♀ × $y\ w^{a}\ fa^{g}\ rb$ ♂	
	(8) $y^{2}\ z\ +\ +\ +\ rb$	Tested chromosomes = 23,200
	(3) $+\ +\ w^{a}\ fa^{g}\ Ax^{59b}\ +$	Recombination = .047%
2	$y^{2}\ z\ +\ Ax^{59b}\ +/+\ +\ spl\ +\ rb$ ♀ × $y\ w^{a}\ spl\ rb$ ♂	
	(1) $y^{2}\ z\ +\ +\ rb$	Tested chromosomes = 32,200
	(1) $+\ +\ spl\ Ax^{59b}\ +$	Recombination = .006%
3	$y\ w^{a}\ fa^{g}\ Ax^{59b}\ +\ +/+\ w^{a}\ +\ +\ N^{60g11}\ rb$; $Dp/+$ ♀ × $w^{a}\ fa^{g}\ fa^{no}\ rb$ ♂	
	(0) Recombinants	Tested chromosomes = 40,400
4	$y\ w^{a}\ fa^{g}\ Ax^{59b}\ +\ +/+\ +\ +\ +\ nd^{2}\ rb$ ♀ × $nd^{2}\ rb$ ♂	
	(8) $+\ +\ +\ +\ +\ +$	Tested chromosomes = 51,100
	*(2) $+\ +\ +\ +\ +\ rb$	Recombination = .031%

$Dp/+$ indicates the presence of *Dp (1;2) 51b7*.

* Exceptionals not associated with recombination between outside markers, and not used for the calculation of recombination values.

indicated in Table 2, the expectation is confirmed; Ax^{59b}, like Ax^{59d}, localizes within the presently defined limits of the Notch gene.

Because these two *Ax*'s were isolated as mutants of independent origin upon irradiation of mature sperm (GREEN, personal communication), it is logical to suspect that they represent separable *Ax* mutant sites in the Notch gene, and the data of Tables 1 and 2 support this view, although falling short of actual proof. The failure of Ax^{59b} to recombine with N^{60g11} suggests that the *Ax* site is quite close to the *N*, and if it is, Ax^{59b} must be separable from and to the right of Ax^{59d}. As indicated earlier, a direct test for recombination in Ax^{59d}/Ax^{59b}; *Dp(1;2)51b7* females is precluded by the relatively great inviability and infertility of the heterozygotes, but appropriate crosses involving Ax^{59b} and N^{Co} might eventually prove the point in a different manner. In any event, two independently isolated *Ax's* are positioned within the Notch gene.

As shown in Tables 1 and 2, a few exceptionals that were nonrecombinant for peripheral markers were isolated in these experiments. One *sc z spl* Ax^{59d} coupled mutant combination was detected (Table 1, cross 2), and from appropriately marked fa^{g}/Ax^{59d} heterozygotes, one *sc z* chromosome was noted (Table 1, cross 1). With Ax^{59b}, two *rb* exceptionals were found (Table 2, cross 4). The paucity of data relevant to the occurrence of these exceptionals does not call for additional discussion except to note that events of a similar nature are commonly detected at a low frequency in recombination experiments involving Notch.

Some pertinent phenotypic comparisons became possible when *spl* was coupled to either Ax^{59b} or Ax^{59d}. As indicated in Table 1, two cases of the coupled condition *spl* Ax^{59d} were detected, one in which the origin of the double mutant was associated with exchange of peripheral markers, and one that was not. Similarly, the coupled mutant chromosome *spl* Ax^{59b} associated with exchange was isolated as shown in Table 2. All three coupled mutants were detected in females that had inherited a chromosome carrying *spl* from the male parent; all were Abruptex, and with reference to the eye phenotype associated with *spl*, they were extreme split, that is to say more aberrant than *spl/spl* homozygotes. The observation that *spl Ax/spl* + expressed the split phenotype to a greater degree than split homozygotes was less surprising when it was subsequently discovered that the genotype *spl Ax/*+ +also was phenotypically split, but somewhat less mutant than *spl/spl* females. In other words, when the recessive *spl* is coupled to an *Ax*, it behaves as a dominant, and since *spl Ax/*+ + is phenotypically split-Abruptex, whereas + *Ax/spl* + expresses only Abruptex, the expected results of the *cis-trans* comparisons are reversed.

No such reversal occurs in the fa^{g}–*Ax* comparison; fa^{g} *Ax/*+ + is Abruptex, and + *Ax*/fa^{g} + is facet-glossy and Abruptex, although the expression of fa^{g} is diminished. Heterozygotes fa^{g} *Ax*/fa^{g} + are phenotypically double mutant.

The reversal of the *cis-trans* comparison seen with *spl* and *Ax* was puzzling, especially since the recombination experiments clearly indicated that the *N*'s, the recessive visibles at Notch and the *Ax*'s were allelic mutant sites in the same gene. Further consideration of the problem did, however, suggest an interpretation relevant to the genetic nature of the two *Ax*'s and identified what

must be the essential difference between recessive lethal Notches and Abruptexes. Since the mutant phenotype of split, a recessive visible, is discernible in the *cis* condition *spl Ax*/+ +, a gene product marked simultaneously with *spl* and *Ax* must be present. This, in turn, implies that, when the gene carries a mutant site for either of these two *Ax* mutants, unlike the case for recessive lethal *N*'s, it does make a functional product, albeit so aberrant that at 25°C homozygotes and hemizygotes fail to survive.

To explain the unexpected expression of *spl* in *cis* with *Ax*, it seems reasonable to suppose that, given two allelic mutants each capable of synthesizing a functional but aberrant polypeptide, the associated phenotypes might be altered when coupled in the *cis* condition. Said differently, two lesions simultanously present in one gene can alter the typical expression of one or both. Certainly the actions of both lesions are modified in the case of intragenic suppressors, although, unlike the situation for *spl* and *Ax*, one is dealing initially with a loss of function associated with the individual mutants, and a restoration of partial or complete function in the coupled condition. In our case, both *Ax* and *spl* make aberrant products, and when coupled, the action of *Ax* enhances the recessive *spl* to the point where it behaves as a dominant, but there is no obvious effect of *spl* on *Ax*. This enhancement of *spl* is slightly less surprising, yet the basic cause remains obscure, when one knows that *spl* has the potentiality for enhancement as demonstrated by its interaction with the autosomal dominant Enhancer-split.

The view that, in the presence of *Ax*, a highly aberrant but partly functional polypeptide is synthesized can explain the lethality of *Ax/N* heterozygotes and the quite different phenotypes recognized as Abruptex and Notch associated with the genotypes *Ax*/+ and *N*/+, respectively. With *Ax/N*, the presence of *N* in one 3C7 band is associated with lack of a functional polypeptide, while *Ax*, in the other band, makes a highly aberrant product in place of the N^+ substance that would normally occur; consequently, the heterozygous condition is lethal. Heterozygotes *Ax*/+ are phenotypically aberrant because one gene in 3C7 functions normally, and the other produces an altered polypeptide that interferes with normal development, culminating in the expression of Abruptex. The *N*/+ combination (with either a cytologically deficient *N* or a point mutant *N*) is phenotypically Notch because the product of one of the two genes is absent or not functional.

Further support relevant to the genetic nature of these *Ax*'s and *N*'s derives from a comparison of phenotypes when the two mutants are present in genomes that also have *Dp(1;2)51b7*. In males of the genotype *N; Dp(1;2)51b7*, one 3C7 band in the *X* chromosome marked by the Notch recessive lethal fails to function, but an additional functional 3C7 is carried in the autosome and covers the lethality. Since one functional 3C7 is the normal situation for a hemizygous male, the flies are phenotypically wild type rather than Notch. Substitute *Ax* for *N* in the same genome, yielding *Ax; Dp(1;2)51b7* males, and note the difference: The recessive lethality is covered, but the Abruptex phenotype is expressed. The autosomally transposed 3C7 provides the necessary N^+ substance, lethality is circumvented, but the *X*-linked *Ax* still produces an altered product that brings

forth the aberrant phenotype. Indeed, the Abruptex expression in these males is strikingly similar to that in *Ax*/+ females, a seemingly logical observation since both genomes are heterozygous for *Ax* and its normal allele, but a consideration of dosage compensation could have inclined one to expect a lesser degree of similarity.

When comparisons similar to those just described are extended to females, the interpretation of *Ax* mutants still holds. *N*/+; *Dp(1;2)51b7* heterozygotes are phenotypically wild type because two functional 3C7 bands are present as in a normal female. *Ax*/+; *Dp(1;2)51b7* heterozygotes have one *X*-chromosomal locus making the aberrant product, the females are thereby Abruptex, although, as expected, the mutant expression is somewhat diminished compared with *Ax*/+ because of the presence of two N^+ loci. Females *N*/*N*; *Dp(1;2)51b7* are viable but phenotypically Notch; only one functional 3C7 band is present, whereas two are required for normality. As previously noted, *Ax*/*Ax*; *Dp(1;2)51b7* females are quite inviable and infertile; they also have an extreme Abruptex phenotype because two of the three 3C7 bands present are producing the altered product.

As noted in a previous report (WELSHONS 1965), our interpretation of the point mutant *N*'s led to the conclusion that a *N spl* coupled mutant chromosome should be phenotypically indistinguishable from *N* + since in both conditions the single gene product is absent or nonfunctional. Support for this illation was obtained when we acquired a new N^{64d6} that had been induced on a chromosome already carrying *spl* (JUDD, personal communication). Cytological observation revealed that the salivary chromosome was normal, thereby eliminating the possibility of mutation to *N* by deletion of 3C7, and suggesting the origin of a coupled mutant combination by mutation to *N* in a gene with a pre-existing *spl*. Proof was obtained when *spl* was separated from the *N* in appropriate recombination experiments.

Additional support for our interpretation of the genetic nature of *N*'s and *Ax*'s can be obtained by the use of coupled mutants and the incorporation of Enhancer-split into appropriate genotypes. *E(spl)* is inherited as an autosomal dominant. It is a powerful enhancer, capable of converting *spl*/+ heterozygotes, normal in appearance, into females phenotypically split to the same degree as seen in *spl*/*spl* homozygotes. If one starts with homozygous *spl* females or hemizygous mutant males, then, upon addition of *E(spl)*, the aberrant phenotype is even more extreme.

When *N* is coupled to *spl*, and *E(spl)* is introduced into the genome, the heterozygotes N^{64d6} *spl*/+ +; *E(spl)*/+ fail to express the split phenotype, whereas *spl*/+; *E(spl)*/+ females will do so. This result is interpreted to mean that the *N* site will not allow the synthesis of a functional polypeptide and that, since *spl* represents a second lesion in the same gene, there will be no product marked by *spl* available for interaction with *E(spl)*. If our interpretation relating to the genetic nature of the *Ax*'s and the probable cause of the unexpected reversal of the *cis-trans* comparison is correct, then one would expect *spl* coupled with *Ax* to respond to the enhancer because an aberrant but partly functional product is synthesized. The expectation is fully realized; *spl Ax*/+ +; *E(spl)*/+ females

show enhancement of split and, since *spl* already acts as a dominant when coupled to *Ax*, the split phenotype is more extreme than in *spl*/+; *E(spl)*/+ females.

As noted earlier, SCHULTZ (in MORGAN, SCHULTZ and CURRY 1941) investigated two tandem duplications of the *X* chromosome. *Dp(1;1)Co*, associated with a Confluens phenotype, was duplicated for a number of bands, one of which was 3C7. In this case, the two 3C7 bands on one chromosome are separated by intervening salivary bands. *Dp(1;1)Ax*^{28a} was believed to be a tandem duplication for the single band 3C7, and the duplicated elements would be adjacent. The particularly convincing demonstration that the Confluens phenotype in *Dp(1;1)Co* resulted from the presence of the extra 3C7, rather than from the numerous other bands similarly duplicated, led to the suggestion that the Abruptex phenotype in *Dp(1;1)Ax*^{28a} might be due to a position effect evoked by the adjacency of the two genetic elements, implying that, if it were possible to separate the two bands, each would resume its normal function. Our observations relevant to the action of *Ax*^{59b} or *Ax*^{59d} in the presence of *Dp(1;2)51b7* suggest a plausible alternative interpretation to the position-effect explanation while assuming that *Ax*^{28a} does in fact possess two contiguous, homologous elements. Both *Dp(1;1)Ax*^{28a} and, for example, our recessive lethal combination *Ax*^{59b}; *Dp(1;2)51b7* are then similar genomes in that each has two 3C7 bands. It could be that in the former case one of the two adjacent elements on the *X* is marked by a dominant Abruptex mutant site, whereas the other has a normal function; in the latter instance, *Ax*^{59b} is on the sex chromosome and a functional 3C7 has been transposed to an autosome. The hypothetical mutant site in *Ax*^{28a} could be associated with lethality or semilethality as is *Ax*^{59b}, but it is an unnecessary presumption.

In theory, it is possible to distinguish between the alternative explanations by taking advantage of unequal pairing and exchange that might occur in homozygotes and heterozygotes of *Dp(1;1)Ax*^{28a}, but such information is not presently available.

SUMMARY

Two X-ray-induced Abruptex mutants are represented as mutant sites within the defined limits of the Notch gene. *N*/*Ax* heterozygotes are lethal, suggesting the cessation of a function common to both, but requiring explanation as to why the functional interruption is expressed phenotypically as Notch in one case and Abruptex in the other.—The unexpected results of a *cis-trans* comparison involving *spl* and *Ax*, plus a presumption relevant to cause, suggested that an *Ax* mutant site causes the synthesis of a highly aberrant, partly functional product, whereas, with a *N* site, the product is absent or nonfunctional. Various phenotypic comparisons are in accord with the hypothesis as are observations of coupled mutant combinations in the presence of Enhancer-split.—This work is in harmony with the view that the original *Dp(1;1)Ax*^{28a} possesses two 3C7 bands. The Abruptex phenotype is due to a position effect that is caused by the adjacency of the two genetic elements, or one of the 3C7's is normal in function, whereas the other harbors a mutant site for *Ax*.

LITERATURE CITED

DEMEREC, M., 1939 The nature of changes in the *w–N* region of the *X* chromosome of *Drosophila melanogaster*. Proc. 7th Intern. Congr. Genet. 99–103.

LEFEVRE, JR., G., 1952 *Dp(1;2R)w*^{51b7}. Drosophila Inform. Serv. **26:** 66.

LINDSLEY, D. L. and E. H. GRELL, 1968 Genetic variations of *Drosophila melanogaster*. Carnegie Inst. Washington Publ. **627**.

MOHR, O. L., 1919 Character changes caused by mutation of an active region of a chromosome in Drosophila. Genetics **4:** 275–282. ——, 1923 A genetic and cytological analysis of a section deficiency involving four units of the *X* chromosome in *Drosophila melanogaster*. Z. Ind. Abst. Vererbl. **32:** 108–214.

MORGAN, T. H., J. SCHULTZ and V. CURRY, 1941 Carnegie Inst. Washington Yearbook **40:** 283.

SLIZYNSKA, H., 1938 Salivary chromosome analysis of the white-facet region of *Drosophila melanogaster*. Genetics **23:** 291–299.

WELSHONS, W. J., 1958 The analysis of a pseudoallelic recessive lethal system at the Notch locus of *Drosophila melanogaster*. Cold Spring Harbor Symp. Quant. Biol. **23:** 171–176. ——, 1965 Analysis of a gene in Drosophila. Science **150:** 1122–1129.

WELSHONS, W. J. and E. S. VON HALLE, 1962 Pseudoallelism at the Notch locus in Drosophila. Genetics **47:** 743–759.