THE DICHOTOMOUS ACTION OF Y CHROMOSOMES ON THE EXPRESSION OF POSITION-EFFECT VARIATION¹

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POSITION-EFFECT variation exhibited by the light locus in *Drosophila melanogaster* (first described by SCHULTZ and DOBZHANSKY 1934) has remained a puzzling case of variation because of the anomalous action of heterochromatin on its expression. SCHULTZ (1936) showed that the absence of a Y chromosome in a male exhibiting light variation caused less mutant tissue in the eye as compared with a male carrying a Y, and in flies with extra Y's more mutant tissue was present. This, of course, is diametrically opposed to the findings of the effect of Y chromosomes in modifying variegated expression caused by position effects involving the white locus in the same species (first reported by GOWEN and GAY 1933).

Since the opposite modifying effect of Y chromosomes on white and light variation is a well-established fact, the possibility was raised (BAKER and SPOFFORD 1959) that the Y chromosome might be multifunctional; i.e., certain regions of the Y chromosome might contain enhancers of pigmentation in the white-variegated system, whereas other regions might contain suppressors of pigmentation in the light-variegated system. This hypothesis was open to experimental test since it had been shown (BAKER and SPOFFORD 1959) that fragments of Y chromosomes have varying degrees of effectiveness in enhancing pigmentation in white-variegated flies. Thus one could ask the question as to whether or not the fragments which were most effective in enhancing pigmentation in white-variegated eyes were different from the fragments most effective in suppressing pigmentation in the light-variegated flies. A statement of an alternative hypothesis would be that there is but a single group of modifiers on the Y, but this group acts in opposite manner in the two systems. The data to be presented strongly support the alternative hypothesis and even suggest that the dichotomous action of the Y modifiers is on the same pigment forming system in the light- and white-variegated eyes.

MATERIALS AND METHODS

The rearrangement used to produce white variation was $w^{m264-58a}$, an insertion of about 20 salivary chromosome bands (3B3-4 to 3D5-6) into the centro-

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meric heterochromatin of IIIL (SUTTON 1940; DEMEREC 1940). This rearrangement is carried as a duplication, $Dp(w^m)$, the X chromosomes being structurally normal for this region. Two states of the duplication were used: Dp^a (HESSLER 1961; SPOFFORD 1961) and Dp^s (BAKER and HUBBY, in manuscript; COHEN 1962). These states are distinguished by two facts: Dp^a produces relatively little pigment in the variegated eyes and passage of the duplication through the father (as compared with transmission through the mother) greatly enhances pigment production in the offspring; whereas, Dp^s produces variegated eyes that are heavily pigmented and there is little or no parental-source effect.

Variegated expression of the light (*lt*) locus was produced by $T(2;3)lt^{m100}$, a reciprocal translocation induced in Oregon-R males which were X-irradiated with 3000r on January 25, 1960 by R. A. SPIELER. One break is in the centromeric heterochromatin of IIL, presumably between *lt* and the centromere, and the other at the end of the 97F region near the tip of IIIR. This rearrangement produces a variegated eye when heterozygous with the mutant allele of light. It is homozygous lethal.

Flies with five different constitutions of Y chromosomes were studied in the lt^m system and in both states of the w^m system. These Y constitutions were: $sc^s \cdot Y$, a Y chromosome containing all necessary male fertility factors and the tip of $In(1)sc^s$ attached to Y^L and thus containing the wild-type allele of yellow (MULLER 1948); $sc^{s1} \cdot Y^L-2$; $Y^s: \gamma^+ bb^+-5$; $Y^s: \gamma^+ bb^+-7$ (these Y fragments are described in BAKER and SPOFFORD 1959); and no Y chromosomes.

The experiment was designed to reduce the variability in expression always associated with position-effect variegation. An individual male bearing a particular Y chromosome was pair-mated successively to females carrying the lt^m , the Dp^a and the Dp^s rearrangements. The precise genotypes of the parents and the offspring analyzed from these crosses are presented in Table 1. With the exceptions noted below, the only data used in the analysis were taken on offspring from males all three of whose matings were fertile. The straw locus (*stw-2*, 55.1) was particularly helpful in marking the $lt stw^s$ chromosome since there is only 0.1 percent recombination between *stw* and *lt*. Therefore, flies bearing the trans-

TABLE 1

Genotype of attached-X females being compared and their parents

Parents	$\frac{+}{Y}; lt^m/lt stw^s \text{ } \varnothing$	$\frac{\gamma w/sc^s \cdot Y; Dp^a}{+} \text{ } \varnothing$	$\frac{\gamma w/sc^s \cdot Y; Dp^s}{+} \text{ } \varnothing$
$Y^s f \gamma \cdot Y^L \gamma^+ / sc^s \cdot Y;$ $lt stw^s \text{ } \delta$	$\frac{+}{+}/sc^s \cdot Y;$ $lt^m/lt stw^s$	$\frac{\gamma w/sc^s \cdot Y;}{lt stw^s/+}; Dp^a+$	$\frac{\gamma w/sc^s \cdot Y;}{lt stw^s/+}; Dp^s/+$
$*X \cdot Y-F/Y^F;$ $lt stw^s \text{ } \delta$	$\frac{+}{+}/Y^F;$ $lt^m/lt stw^s$	$\frac{\gamma w/Y^F;}{lt stw^s/+}; Dp^a+$	$\frac{\gamma w/Y^F;}{lt stw^s/+}; Dp^s/+$
$Y^s f \gamma \cdot Y^L \gamma^+ / 0;$ $lt stw^s \text{ } \delta$	$\frac{+}{+}/0;$ $lt^m/lt stw^s$	$\frac{\gamma w/0;}{lt stw^s/+}; Dp^a+$	$\frac{\gamma w/0;}{lt stw^s/+}; Dp^s/+$

* Three Y^F 's were used: $sc^{s1} \cdot Y^L-2$, $Y^s: \gamma^+ bb^+-5$, and $Y^s: \gamma^+ bb^+-7$; the complementary $X \cdot Y-F$'s were, respectively, $\gamma \cdot f \cdot Y^s$, $g^2 B \cdot Y^L$ and $B \cdot Y^L$.

† Homozygous $lt stw^s$ offspring from these crosses were also analyzed as controls.

location could be distinguished even though in some genotypes the eyes were phenotypically light. Complications of parental-source effects (SPOFFORD 1961) were eliminated by the experimental design since all three rearrangements were contributed only by the mothers to their daughters whose pigments were to be measured.

Four-day old flies were decapitated and their heads squashed on Whatman No. 1 chromatographic filter paper. The drosopterins pigments and associated pteridines were separated by descending chromatography in propanol plus seven percent ammonia (2:1) solvent. The dried sheets were examined in ultra-violet light and the spots were circled which contained the drosopterins, sepia pteridine, and the "Himmelblau" substances (2-amino-4-hydroxypteridine and biopterin). These spots were cut out and eluted in one cc of one percent NH_4OH for two hours. After removal of the paper, the fluorescence was measured by a Farrand (Type A) photofluorometer using the following filters: primary filter—Corning No. 9863, secondary filters—Corning No. 3389 plus Bausch and Lomb interference filters No. 33-78-55 for drosopterins and sepia pteridine, No. 33-78-45 for the Himmelblau substances. The standard was 1 μg of anthranilic acid per cc of one percent NH_4OH and was kept frozen until two hours prior to use. The fluorometer was adjusted to give a reading of 20 on the 0-100 scale for one cc of the standard. The amount of fluorescence of appropriate paper blanks has been subtracted from all readings presented.

Complete progeny counts were made on all crosses in order to measure the penetrance of pigmentation in flies carrying the rearrangements. This is a relatively sensitive measure of differential effects of Y fragments in the white-mottled system when the level of pigmentation is low, e.g., in the Dp^a crosses.

RESULTS

The experiments were designed primarily for the purpose of obtaining evidence on the question whether those Y fragments most effective in enhancing pigmentation in white-variegated eyes were the ones also most effective in suppressing pigmentation in eyes exhibiting light variegation.

The data presented in Table 2 indicate the relative amounts of drosopterins produced in females by the three variegation systems as well as the amount of these pigments in the heads of daughters homozygous for light. An analysis of variance gives no indication of significant differences in the amount of drosopterins between light daughters having the five different Y chromosome constitutions: the mean value is 3.70. There is no detectable amount of drosopterins or the other pteridines in flies homozygous or hemizygous for white.

The Y fragments are arranged in the table in order of their effect in decreasing the amount of pigment in light-variegated flies. The amount of pigment varies in these flies from 19 fluorometric units when no Y chromosome is present to less than five units with $sc^s\cdot Y$; whereas, the Dp^s state of the white-variegated flies produces far less than one unit with no Y and over 14 units with the $sc^s\cdot Y$. In flies with very high fluorometric values, the eyes often cannot be visually dis-

TABLE 2

Fluorometric measurements of drospterins in attached-X females with different Y chromosomes

Male Number	M	lt^m SE	No.	M	lt SE	No.	M	lt^m-lt SE	M	$Dp^a(lt^m)$ SE	No.	M	$Dp^a(lt^m)$ SE	No.
No Y														
1	19.35±0.97	17		3.12±0.40	8		16.23±1.05		No pigment			Only 37 heads		
4	21.09±2.43	11		3.68±0.46	7		17.23±2.47		No pigment			from all families		
11	19.89±2.08	9		5.00±0.41	4		14.89±2.12		No pigment			produced		
16	19.91±0.97	11		3.57±0.37	7		16.34±1.04		No pigment			measurable		
17	18.40±1.94	5							No pigment			amounts of		
19	19.90±1.62	10		3.50±0.56	6		16.40±1.71		No pigment			pigment.		
20	18.67±2.60	3		3.25±0.24	4		15.42±2.62		No pigment					
26	16.00±0.94	8		4.67±0.33	3		11.33±1.00		No pigment					
Lumped	19.38±0.59	74		3.72±0.18	39		15.66±0.62		No pigment			0.68±0.12	37	
Ys:y+ bb+-7														
4	9.92±0.84	13		4.52±0.32	8		5.67±0.89		No measurable			2.25±0.40	20	
5	6.50±0.72	10		3.43±0.29	7		3.07±0.75		amount of			4.20±1.09	5	
16	6.20±0.80	5		3.00±0.00	2		3.20		pigment.			12.59±0.82	27	
17	6.59±0.59	17		3.54±0.48	13		3.05±0.76		No measurable			3.69±1.33	13	
18	9.28±0.94	7		4.00±0.63	5		5.28±1.14		amount of			9.10±0.68	21	
26	6.67±1.20	3		3.00	1		3.67		pigment.			10.92±0.93	12	
Lumped														
Low	6.51±0.37	35		3.50±0.31	20		3.01±0.49		No measurable			3.00±0.52	38	
High	9.70±0.64	20		4.15±0.30	13		5.55±0.70		amount of			*11.03±0.51	60	
									pigment.					
sc^{Sl}.Y^{L-2}														
4	6.00±0.63	13		3.83±0.71	6		2.17±0.95		0.76±0.22	17		10.78±1.22	18	
6	5.28±0.46	18		3.62±0.17	8		1.66±0.49		1.06±0.20	16		14.81±0.72	21	
8	5.00±0.58	11		4.00±0.32	5		1.00±0.66		0.88±0.22	16		12.24±0.92	17	
12	5.21±0.46	14		3.67±0.33	9		1.54±0.57		1.12±0.22	17		16.56±0.52	18	
15	4.80±0.45	10		3.67±0.24	9		1.13±0.51		1.06±0.22	18		10.67±2.73	3	
19	6.53±0.56	17		3.94±0.30	17		2.59±0.63		0.80±0.14	10		16.33±0.49	6	
Lumped	5.54±0.22	83		3.80±0.14	54		1.74±0.27		0.96±0.09	94		*13.75±0.46	83	
Ys:y+ bb+-5														
2	3.83±0.48	6		3.25±0.24	4		0.58±0.54		0.23±0.10	22		14.62±1.20	8	
7	4.42±0.37	12		2.50±0.17	10		1.92±0.41		0.95±0.20	21		15.00	1	
13	3.75±0.17	8		3.00±0.32	7		0.75±0.35		1.29±0.17	24		12.64±1.20	22	
21	5.62±0.55	13		3.89±0.42	9		1.73±0.69		1.86±0.47	22				
Lumped	4.59±0.26	39		3.13±0.18	30		1.46±0.32		*1.09±0.15	89		13.23±0.92	31	
sc^S.Y														
1									1.20±0.20	5				
6												1.59±0.24	17	
7												11.33±1.38	6	
10	5.20±0.49	5												
12	4.75±0.63	4		6.33±0.88	3		-1.58±1.13							
13	4.38±0.60	8		4.12±1.08	8		0.26±1.23		6.64±0.84	11		15.92±0.48	12	
15									1.78±0.81	9		14.69±1.60	16	
17												13.50±1.51	8	
18	6.00±0.75	8		3.00±0.45	5		3.00±0.88							

TABLE 2—Continued

Male Number	M	lt^m SE	No.	M	lt SE	No.	lt^m-lt SE	M	$Dp^a(w^m)$ SE	No.	M	$Dp^s(w^m)$ SE	No.
19									8.35 ± 1.30	17		2.00 ± 0.54	18
20		4.80 ± 0.37	5		4.25 ± 0.24	4	0.55 ± 0.45		1.45 ± 0.61	11			
25		4.00 ± 0.45	5		3.40 ± 0.60	5	0.60 ± 0.75		1.88 ± 0.61	8		2.07 ± 0.71	15
Lumped													
Low		4.91 ± 0.27	35		4.04 ± 0.42	25	0.91 ± 0.44		1.61 ± 0.33	33		1.88 ± 0.26	50
High									7.68 ± 0.86	28		14.33 ± 0.73	42

* Analysis of variance indicates lack of homogeneity (one percent level) among the offspring from different males. lt^m = light variegated females, lt = light females (not carrying rearrangement), w^m = white variegated females. M = mean fluorometric reading, SE = standard error of the mean, No. = number of heads. See Table 1 for details of genotypes.

tinguished from wild type, especially in lt^m flies. This table also illustrates the great difference in level of pigmentation observed between the two states of the white duplication.

Let us turn our attention now to the action of the Y fragments themselves. A considerable bimodality exists in the data from lt^m and Dp^s daughters carrying Y^{s-7} , and in the Dp^a and Dp^s daughters having the $sc^s \cdot Y$. This variation is not associated with differing activity of a given Y fragment since a single father carrying one Y^{s-7} , e.g., No. 4, produced daughters in the high category of lt^m eyes and in the low category of w^m eyes. Another father, No. 18, had daughters with high levels of pigmentation in both lt^m and w^m eyes. We do not know the basis of this variation but it is not relevant to the main question of this study. An analysis of variance shows that, insofar as the lt^m eyes are concerned, the high and low categories with Y^{s-7} are internally homogeneous, and a t-test indicates that even the mean amount of pigment present in the low class of Y^{s-7} (6.51) is significantly higher (5% level) than the amount of pigment with $sc^{s1} \cdot Y^L$ (5.54) which, in turn, has significantly more pigment than the lt^m daughters carrying Y^{s-5} (4.59). Therefore, the pigmentation seriation for the lt^m series runs:

$$0 > Y^{s-7} > sc^{s1} \cdot Y^L > Y^{s-5} = sc^s \cdot Y.$$

The data for Dp^a show just the reverse trend as is evident not only from Table 2, but perhaps even more strikingly when one considers the penetrance of mottling in terms of the percent of daughters that show any pigment (50 percent would indicate full penetrance):

$$0 (0\%) < Y^{s-7} (11\%) < sc^{s1} \cdot Y^L (38\%) = Y^{s-5} (39\%) < sc^s \cdot Y (48\%).$$

Counts of the offspring of the Dp^s crosses indicate general agreement with the same seriation, the percent of daughters with pigment being:

$$0 (12\%) < Y^{s-7} (36\%) < sc^{s1} \cdot Y^L (52\%) = Y^{s-5} (48\%) = sc^s \cdot Y (54\%).$$

These data may be summarized by stating that the Y fragments most effective in enhancing pigmentation with lt^m position effects are the ones least effective with w^m variegation.

One would be inclined to interpret this result in either of two ways: (1) the pathway for synthesis of the drospterins is different in light-variegated and in white-variegated eyes, or (2) the pathway is the same but the Y fragments act in opposite directions in the two systems. No direct evidence is available to dis-

tinguish the alternatives, but circumstantial evidence casts some doubt on the first. Although the pathway for synthesis of the drosopterins (DP) is not known, the evidence is good that sepia pteridine (SP), and biopterin are involved, possibly as precursors (HUBBY and THROCKMORTON 1960). Figure 1 shows the relation between the amount of SP and the Himmelblau (HB) substances (consistent chromatographic separation of biopterin and 2-amino-4 hydroxypteridine was not obtained) as a function of the amount of DP. The points on the graph are the mean fluorometric values for SP and HB for each of the lumped values for the drosopterins given in Table 2. It is apparent from this graph that the values for light-variegated eyes as well as the homozygous *lt* eyes fall on the same curve as the values for white mottles. Thus there is no evidence indicating that a different pigment forming system is being affected in the *lt^m* and the *w^m* eyes, or for that matter, between *Dp^a* and *Dp^g* eyes.

DISCUSSION

In view of the dichotomous action of the Y chromosome and its fragments on white and light variegation, one might have supposed that there were two groups of modifying factors located on the Y: one group causing increased pigmentation in the *w^m* eyes and another group causing decreased pigmentation in *lt^m* eyes.

FIGURE 1.—The amount of sepia pteridine (SP) and "Himmelblau" (HB) substances (2-amino-4-hydroxypteridine and biopterin) as a function of the amount of drosopterins (DP) in heads of light, white- and light-variegated flies.

The data show that the dichotomous action is maintained by each of the three fragments; therefore, it appears that either there is but one group of modifying factors acting in opposite manner in the two systems, or else the two groups interdigitate in location. In the latter case, if one Y fragment contained an effective group of modifiers enhancing pigment in w^m eyes, the fragment would also have to contain an equally effective group of modifiers suppressing pigmentation in lt^m eyes. Although these experiments do not differentiate between these alternatives, the dual modifier scheme seems less probable since it was shown that the amount of enhancement of pigmentation exhibited by w^m eyes was not a direct function of the amount of chromatin cytologically visible in the fragment (BAKER and SPOFFORD 1959). That is to say, there is a regional differentiation along the Y chromosome in effectiveness of suppressing white variegation and one would hardly expect this regional differentiation to be the same for a different group of light-variegated enhancers.

It has been previously pointed out (BAKER 1953; GRELL 1959; and SCHNEIDER 1962) that the rather unusual response of light-variegated eyes to the addition or subtraction of heterochromatin is not a characteristic common to all genes normally located in or near centromeric heterochromatin. But still the lt^m case remains an interesting and possibly very instructive illustration of genetic control of gene action. Two structural changes are apparently necessary to produce light variegation: a break in the centromeric heterochromatin of IIL (presumably between lt and the centromere) and the movement of lt to a location at some distance from a centromere (HESSLER 1958). Now the disruption of the continuity of the heterochromatin is a necessary requirement of both the w^m and lt^m type of position effect. Therefore one would be inclined to look for the basis of the differential action of extra heterochromatin in the difference in location of the new site of $R(w^+)$ or $R(lt^+)$ —the former gene usually placed next to disturbed centromeric heterochromatin, the latter moved away from centromeric regions. It is known that disturbed heterochromatin has a spatially limited range of action (spreading effect) and thus the action of the additional heterochromatin may be limited in a like manner. If in the cells of the pertinent tissue all heterochromatic regions pair together as in the chromocenter of a salivary gland nucleus, then one might postulate that extra heterochromatin may help repair only the damaged gene action of those affected genes located near centromeric heterochromatin. Therefore, the impaired action of the $R(w^+)$ might be alleviated since the structural rearrangements producing the position effect typically place the gene close to centromeric regions; whereas, the $R(lt^+)$, at a distance from centromeric regions, would be unaffected.

But why does additional heterochromatin further impair the activity of $R(lt^+)$? One possibility is that the $R(lt^+)$ locus could occasionally pair back into the chromocenter where the undisturbed heterochromatin might ameliorate the gene activity. With extra heterochromatin in the genome, the pairing sites would be satisfied and the lt^+ locus would remain outside of the sphere of influence of the centromeric heterochromatin, thus producing more mutant action. One merit of such a structural hypothesis is that it is testable. For example, it would be

predicted that an X chromosome inversion with a break point to the right of *w* and the other break point sufficiently down in the heterochromatin to bring an appreciable piece of this material next to *w* should produce less pigment in the eye with the addition of extra Y chromosomes, just the opposite of the usual effect of added heterochromatin on white variegation.

DR. EILEEN S. GERSH kindly made the crosses to test this hypothesis. *In(1)rst^s* and *Dp(1;3)N²⁶⁴⁻¹⁰⁰r1* (GERSH 1959) are rearrangements in which the white locus is placed in or adjacent to interrupted heterochromatin at a distance of 16 and 15 numbered sections, respectively, on the salivary chromosome map from centromeric regions. She did not observe white variegation with either the normal or additional numbers of Y chromosomes in the genome, but only in XO males of the constitutions *γrst^scar bb/0* and *γw/0; Dp(w⁺)/+*. These data militate against the hypothesis. Thus one may rule out still another structural hypothesis proposed to explain altered gene action in position effect.

Finally it should be added that the data in this paper allow one to argue strongly against the notion that somatic variegation is the result of somatic mutation *in sensu stricto*. If the areas in the eyes that are mutant were the consequence of somatic mutations of *w⁺→w* or of *lt⁺→lt* then we would have the most unusual phenomenon of certain mutagenic agents (Y fragments) increasing the rate in one system over that found with other agents (other fragments) and concomitantly the same agent decreasing the rate in the other system. There is no precedent for such dichotomous action of one and the same mutagen on two different loci (see BAKER 1963 for a more complete discussion of this problem).

SUMMARY

Concomitant studies were made on the effect of Y chromosome fragments on the expression of position-effect variegation at the light and the white loci of *Drosophila melanogaster*. It was found that those fragments which were most effective in enhancing pigmentation in white-variegated eyes were the ones most effective in suppressing pigmentation in light-variegated eyes. Pigmentation was assayed by photofluorometric measurements of the drosopterin pigments after paper chromatographic separation.

The data support the hypothesis that there is but one group of modifiers on the Y chromosome which affect the expression of variegation and these modifiers act in the opposite manner in the light- and white-variegated systems. Moreover, the data lead to the suggestion that the light and white loci are acting on the same biosynthetic pathway. Thus one is left with the interesting possibility that one group of modifiers may act in an opposite manner on the same biosynthetic pathway in two different variegation systems.

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