DIFFERENTIAL SENSITIVITIES AND THE TARGET OF HEAT-INDUCED RECOMBINATION AT THE BASE OF THE *X* CHROMOSOME OF *DROSOPHILA MELANOGASTER*

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ABSTRACT

The effect of heat on two small adjacent segments at the base of the *X* chromosome was examined. Recombination in the two segments delimited by recessive lethals was measured after treatment with 30° and 34°.Both segments were sensitive at 30°, while only the proximal one responded to 34° treatment. When the same segments were studied in structural heterozygotes (for deletions) the relative increase in recombination was greater, suggesting that heat exerts its effect on the "pairing" rather than the "exchange" components of crossing over. The effect of *c (3) G*/+ on the same segments in both homozygous and heterozygous structurals was studied. The results indicate that this meiotic mutant mediates its effect on a step different than that affected by heat.

ONE of the difficulties in experiments aimed at determining factors affecting chromosomal recombination is the differential response of chromosomal segments to various treatments. Heat treatment and interchromosomal effect are prominent examples (PLOUGH 1917 a, b; LUCCHESI and SUZUKI 1968; SCHULTZ and REDFIELD 1951). In order to study the magnitude of possible errors made by looking at long chromosomal segments (i.e., pooling effect), two very short adjacent segments at the base of the *X* chromosome were studied for their response to two temperature treatments.

The results suggest that the more proximal segment, thought to be part of the proximal heterochromatin, is equally sensitive to both 34° and 30° heat treatments. The adjacent, more distal segment, corresponding to the euchromatic part of the *X*, is preferentially sensitive to 30°, with very low response to 34°.

There is some experimental support for subdividing recombination into two major components, "pairing" and "exchange" (see LINDSLEY and SANDLER 1974).

The set of experiments used to define preferential sensitivities of the two segments at the base of the *X* chromosome were designed so as to attempt to distinguish experimentally between the two hypothetical components. The rationale behind the experiment is the following:

Suppose that two conditions which affect the level of crossing over are applied simultaneously. If they act on independent aspects of recombination, their combined effect might be expected to be the product of their individual effects,

whereas if they act on the same process some interaction might be expected. For the specific experimental test, the assumption is made that sequential heterozygosity* reduces the level of recombination by interfering with the "pairing" process.

A temperature shock which increases recombination in sequential homozygotes is expected to exert the same proportional increase (in the same segment) in a sequential heterozygote if it acts on the "exchange" process, or for that matter on any component unaffected by sequential heterozygosity. The finding that temperature causes proportionally greater increases in recombination in sequential heterozygotes than in homozygotes leads to the tentative conclusion that the effect of increased temperature upon recombination is mediated through "pairing". The system has been further used to see whether increased recombination brought about by heterozygosity for *c(3)G* (HINTON 1966) is mediated through the step sensitive to temperature.

MATERIALS AND METHODS

The region of the *X* chromosome used in these studies is that defined by the *Ymal*$^+$ duplication (LIFSCHYTZ and FALK 1968). Subdivision of the region into two segments has been justified elsewhere (LIFSCHYTZ 1971). The distal euchromatic segment (I) consists of 17 complementation units and is 1.5 recombination units long. The proximal heterochromatic segment II is only 0.75 recombination units in length, and the number of complementation units is more disputable (LIFSCHYTZ, in preparation; SCHALET 1973; FALK 1973 SCHALET and LEFEVRE 1974). In any case, however, the distance (in recombination units) between *l(1)E54* (unit 17) and *l(1)Q463* is the largest observed for the proximal region, so that the exact location of *l(1)Q463* in our complementation map is irrelevant for the present discussion. Details of all deficiencies and mutations used are to be found in LIFSCHYTZ (1971), and descriptions of other mutants and chromosomes are presented in LINDSLEY and GRELL (1968). The combinations and map location of the lethals used in this study are illustrated in Figure 1.

Females of the genotype $y^2\ v\ f\ l^L+/+++++l^R$ (l^L and l^R denoting left and right positioned lethals, both covered by the *Ymal*$^+$ duplication) were obtained by crossing males bearing one

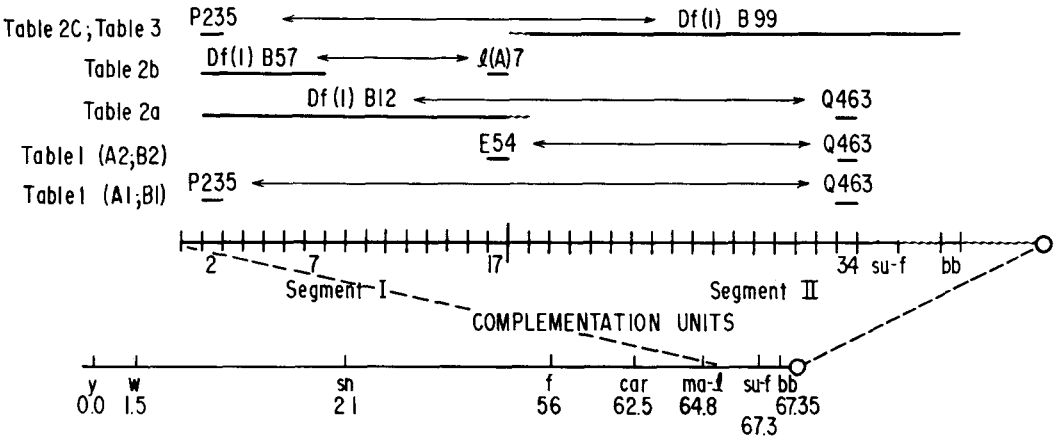

FIGURE 1.—Map locations of the *X*-chromosome lethals used in this study.

* Heterozygous for a deficiency-bearing chromosome in this case.

of the lethals to females carrying the other lethal balanced over *FM6*. Virgin females collected over a 10-hour period were treated with 30° for 4 days or with 34° for one day, with the control females being kept at 25° for the same period. These particular treatments were chosen on the basis of earlier experiments with Drosophila, where they had been found effective in inducing a heat response of recombination (PLOUGH 1917a; GRELL and CHANDLEY 1965; CHANDLEY 1968). The treated and control females were mated to an excess of *Basc/ Y M5* males to ensure immediate insemination and uniform egg desposition. The brooding pattern varied as described for each experiment. Since the only surviving F_1 males result from recombination between the two lethals, recombination was estimated by scoring the number of male progeny among total progeny. In the second series (Table 2) the number of females in both control and experiment was estimated by weight, with the total weight for each scoring day (and brood) standardized against that of an accurately counted sample of 300 to 500 females.

RESULTS

Heat response in structural homozygotes

In this series (Table 1, Figure 2) recombination was measured for pairs of point lethals, one pair [*P235/Q463*] covering both the euchromatic and heterochromatic segments (I and II) and the other [*E54/Q463*] the heterochromatic segment alone (see Figure 1). The response of the euchromatic segment was determined by subtracting that of the heterochromatic one from the total.

It is seen that both heat treatments produce a significant increase in recombination in broods derived from cells that were in meiosis at the time of treatment (5–8 days) (see GRELL and CHANDLEY 1965; GRELL 1973).

Since we are concerned with the relative effect in the two segments and not in the absolute effect of temperature on recombination, accelerated meiotic rate, if it exists, is irrelevant. The unexpected rise in recombination for late broods of A1 and A2 crosses may reflect an effect carried over into meiosis by gonial cells. Examination of the peak of the temperature effect shows that the 34° treatment resulted in 2½-fold increase in the combination in region II. The 30° treatment resulted in a 4-fold increase. Subtraction of these effects from that observed over the whole region (the two experiments were conducted concomitantly) shows that segment I is relatively less sensitive. 34° had only a slight effect and the 30° treatment resulted in a twofold increase.

Heat response in sequential heterozygotes

Lethals were made heterozygous with deletions for different segments of the region. The structural variants used were as follows:

	Defining $l(1)^L$	Defining $l(1)^R$	*Tested segment*
Exp a	*Df(1)B12*	*l(1)Q463*	II
Exp b	*Df(1)B57*	*l(1)A7*	I (proximal part)
Exp c	*l(1)P235*	*Df(1)B99*	I (mostly distal part)

Both 34° and 30° treatments were used again and females were brooded for eight two-day periods. The first two broods were not scored and results therefore apply to days five to sixteen. Controls for 30° and 34° treatments were done separately but were homogeneous and were pooled to give the figures in Table 2 and Figure 3.

TABLE 1

Heat responses in structural homozygotes

		Days	1–2	3–4	5	6	7	8	9	10	11
Experiment A1		No. Females	7,425	9,523	5,202	5,010	4,369	3,143	3,845	3,190	1,992
P235/Q463	Control	No. Males	88	105	55	66	41	31	44	34	35
Region I + II		% Rec.	2.37	2.20	2.11	2.43	1.88	1.94	2.28	2.13	3.51
Units 2–34			±0.24	±0.21	±0.28	±0.31	±0.30	±0.35	±0.34	±0.36	±0.58
		No. Females	5,967	11,925	6,898	7,522	5,173	4,413	3,397	7,062	2,615
	34°	No. Males	64	111	73	139	100	83	42	105	54
		% Rec.	2.14	1.87	211	3.69	3.86	3.75	2.47	2.97	4.13
			±0.26	±0.16	±0.24	±0.31	±0.38	±0.41	±0.38	±0.27	±0.56
Experiment A2		No. Females	7,595	7,270	3,330	2,426	2,439	2,203	1,509	2,596	
E54/Q463	Control	No. Males	24	28	17	12	17	6	14	16	
Region II		% Rec.	0.63	0.77	1.02	0.99	1.39	0.54	1.86	1.23	
Units 17–34			±0.13	±0.14	±0.24		±0.32	±0.22	±0.48	±0.30	
		No. Females	9,251	12,405	5,103	2,885	3,481	2,659	2,161	4,114	
	34°	No. Males	38	64	67	16	23	26	25	44	
		% Rec.	0.67	1.03	2.63	1.11	1.32	1.96	2.31	2.14	
			±0.12	±0.13	±0.30	±0.26	±0.26	±0.38	±0.44	±0.32	
Experiment B1		No. Females	3,879	8,038	6,240		5,681		3,065		
P235/Q463	Control	No. Males	61	90	64		62		34		
Region I + II		% Rec.	3.22	2.23	2.05		2.18		2.21		
Units 2–34			±0.41	±0.23	±0.25		±0.27		±0.38		
		No. Females	5,756	6,027	5,099		5,121		6,734		
	30°	No. Males	80	97	174		155		109		
		% Rec.	2.79	3.21	6.82		6.05		3.23		
			±0.31	±0.32	±0.51		±0.48		±0.31		
Experiment B2		No. Females	7,772	7,107	6,044		5,865		3,952		3,530
E54/Q463	Control	No. Males	31	29	20		21		18		8
Region II		% Rec.	0.80	0.82	0.66		0.69		0.91		0.5
Units 17–34			±0.14	±0.15	±0.15		±0.15		±0.20		±0.16
		No. Females	14,147	12,047	11,141		7,869		6,903		5,591
	30°	No. Males	58	105	173		114		84		37
		% Rec.	0.82	1.74	2.87		2.90		2.43		1.32
			±0.11	±0.17	±0.22		±0.27		±0.26		±0.11

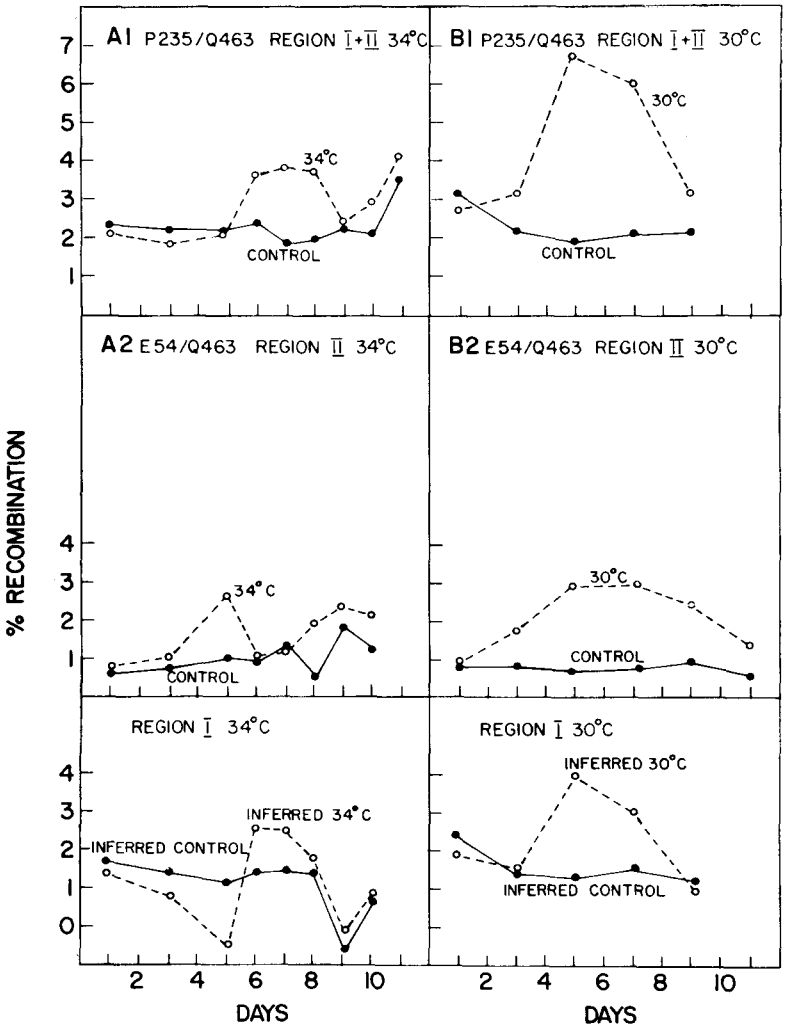

FIGURE 2.—Heat response in structural homozygotes.

The comparisons available are (1) the response of the two segments over a 12-day period to the two temperatures, and (2) the heat response of the segments under different levels of recombinational restricitons imposed by the various deficiencies. (Thus *Df(1)B99* reduces recombination in the studied segment to about 10% of the normal, while *Df(1)B12* and *Df(1)B57* reduce it to about 40–50% of the normal rate.)

The data presented in Table 2 (Figure 3) show a gradient in response to 34° treatment. The proximal heterochromatic segment (Exp't. a) is the most sensitive, the proximal part of segment I (Exp't. b) shows much reduced response, and the distal part of segment I (Exp't. c) does not show a response significantly

TABLE 2

Heat response of segments I and II in structural heterozygotes

Broods / Days		III 5–6	IV 7–8	V 9–10	VI 11–12	VII 13–14	VIII 15–16–17
Experiment A				*Df(1)B12/l(1)Q463*			
	No. Females	5,571	8,232	5,660	7,315	6,966	9,202
34°	No. Males	22	29	37	63	27	27
	% Rec.	0.789	0.704	1.307	1.72	0.785	0.586
		±0.166	±0.130	±0.214	±0.216	±0.418	±0.112
	No. Females	3,524	3,619	3,982	3,587	3,944	4,515
30°	No. Males	16	19	28	26	21	11
	% Rec.	0.906	1.052	1.40	1.45	1.06	0.49
		±0.226	±0.240	±0.264	±0.282	±0.230	±0.144
	No. Females	8,700	7,528	6,938	6,560	6,780	10,750
Control	No. Males	12	11	12	14	12	13
	% Rec.	0.275	0.292	0.345	0.426	0.350	0.241
		±0.078	±0.088	±0.096	±0.102	±0.100	±0.066
Experiment B				*Df(1)B57/l(1)A7*			
	No. Females	10,214	12,282	9,866	9,700	6,664	11,200
34°	No. Males	11	22	31	34	24	22
	% Rec.	0.214	0.358	0.628	0.701	0.720	0.393
		±0.064	±0.076	±0.112	±0.118	±0.146	±0.082
	No. Females	18,574	11,443	10,464	9,353	6,950	10,030
30°	No. Males	58	46	63	45	18	21
	% Rec.	0.624	0.803	1.204	0.962	0.518	0.410
		±0.080	±0.118	±0.150	±0.142	±0.120	±0.090
	No. Females	12,088	19,534	21,438	15,972	14,702	16,670
Control	No. Males	13	22	31	31	35	33
	% Rec.	0.215	0.225	0.289	0.394	0.476	0.390
		±0.058	±0.046	±0.050	±0.070	±0.080	±0.068
Experiment C				*l(1)P235/Df(1)B99*			
	No. Females	5,744	7,364	8,610	4,670	4,625	4,970
34°	No. Males	7	10	18	6	7	4
	% Rec.	0.243	0.257	0.418	0.257	0.302	0.160
		±0.090	±0.082	±0.098	±0.104	±0.114	±0.080
	No. Females	9,466	12,890	9,100	7,665	3,143	11,275
30°	No. Males	41	53	35	24	9	8
	% Rec.	0.866	0.822	0.76	0.626	0.573	0.141
		±0.134	±0.112	±0.128	±0.123	±0.190	±0.048
	No. Females	9,560	12,522	9,240	7,250	11,257	8,711
Control	No. Males	4	8	12	11	15	7
	% Rec.	0.083	0.128	0.25	0.303	0.26	0.160
		±0.040	±0.044	±0.072	±0.090	±0.066	±0.060

Eight two-day broods were sampled in all cases. Only the last six were actually counted. In Figure 3, figures significantly different from control values are indicated.

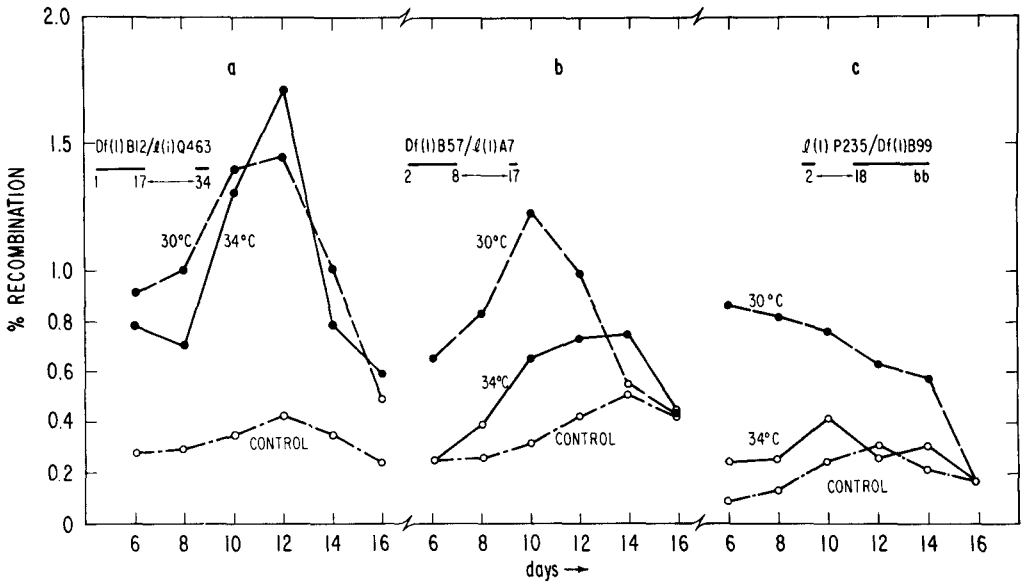

FIGURE 3.—Heat response in structural heterozygotes.

different from the control level. All three regions show a significant response to the 30° treatment.

In addition, a gradient in the time of response to 30° is evident. The earliest peak response is found in the distal region of segment I (brood three and four), the peak occurring later in the more proximal regions (brood five in proximal segment of I and brood six in segment II). Whether the same trend occurs with the 34° is hard to say because of the different response exhibited by the three segments.

As regards the heat response of the sequential heterozygosity *per se*, in Exp't. a, crossing over was reduced to an average of 40% of the normal (0.3–0.4% compared with 0.8%). On heat treatment an increase of about 2½-fold was observed in the homozygote at 34°, compared with 4–5-fold increase, stretching over a longer period, in the sequential heterozygote. The amplifying effect is less obvious in the 30° treatment, but the overall response is similar. In the proximal section of segment I (Exp't. b) recombination was similarly reduced to about 40% of the normal (0.3% compared with 0.8%. The increase in the homozygote at 30° was about 2-fold compared with a 4-fold increase in the heterozygote in the peak brood. A much weaker effect was of course observed in the 34° treatment.

Structural heterozygosity in the distal segment (Exp't. c) reduces recombination to less than 10% of the normal value (average 0.15% compared with 1.5%) and an 8–10-fold increase was obtained at 30°; the weighted average increase in broods 3,4 and 5 was about 7-fold compared with a 2-fold increase—and for two broods only—in the sequential homozygote. It seems, therefore, that the magnitude of the differential response depends on the extent of reduction exerted by

the deletion. (This in turn reflects, of course, the nature of the deletion and the genetic length of the region in which crossing over is measured.) Along with the proportional higher response exhibited by the sequential heterozygote, this result supports the hypothesis that the increase due to heat treatment is mediated through the "pairing" component of crossing over.

If such is the case the system may be used for classification of mutants affecting recombination as to whether or not they modified "pairing" or "exchange". This was attempted using the mutant genotype known to increase recombination in Drosophila, namely *c(3)G/+* (HINTON 1966). The effect of *c(3)G* on segment I was studied both in structural homozygotes and in heterozygotes for *Df(1)B99*. For the crosses involving heterozygous females, the mutant was combined with *l(1)P235* as follows:

$$\frac{y^2\ v\ f\ l(1)P235}{FM6}\ ;\ \frac{c(3)G\ sbd}{TM3}\ \&\ \frac{y^2\ v\ f\ l(1)P235}{Ymal^+}\ ;\ \frac{c(3)G\ sbd}{TM3}$$

The stock was expanded and maintained through selection against homozygous *c(3)G sbd* in each generation (the homozygous females were checked for the presence of the mutant by measuring the nondisjunction frequency of the *X* chromosomes in their progeny). Stock females were regularly checked for a concealed *Y mal*$^+$ chromosome by crossing to attached *XY/O* males and testing the progeny for fertility. In the final crosses, *y*^{2} *v f l(1)P235/Ymal*$^+$ males, heterozygous or homozygous for *c(3)G sbd*, were crossed to *Df(1)B99* females to yield *c(3)G/+*; *y*^{2} *v f l(1)235/+ + + +* *Df(1)B99* females. They were in turn crossed to *Basc/Y* males, and the progeny were scored (in this case by counting) for the rare recombinant males. Because of the known effect of *c(3)G* on nondisjunction, and in order to avoid overestimation of the recombination frequency, every F_2 recombinant male from the cross involving *Df(1)B99* was tested for the presence of a lethal-bearing *X* or the *Ymal*$^+$ chromosome by crossing to a female heterozygous for *Df(1)Q219*, which fails to complement both parental lethals and is covered by *Ymal*$^+$. (Actually, the precautions taken in constructing the stocks had rendered this test unnecessary.)

As shown in Table 3, heterozygosity with respect to *c(3)G* increased crossing

TABLE 3

The effect of c(3)G/+ *on recombination in structural homozygote or heterozygote for segment I*

	Number females	Number males	Percent recombination	Control
E54/Q463; *c(3)G/+* (17–34)	17,041	98	1.15	0.78*
P235/1A7; *c(3)G/+* (2–17)	24,778	349	2.8	1.53*
P235/B99; *c(3)G/+* (2-Df17-bb)	29,335	39	0.29	0.17*

The control figures for these experiments are taken from previous work (LIFSCHYTZ 1971) since the brooding pattern was the same. The reader may compare them with the average controls for the same segments given in this work.

over in segment I approximately 2-fold when lethal point mutations at unit 2 (*P235*) and 17 (*E54*) were used. The response in sequential heterozygotes was of the same order as that found for the same region in sequential homozygotes.

DISCUSSION

From the early attempts to study heat effect on recombination (PLOUGH 1917a, b; 1921) it became clear that various chromosomal regions react differentially to heat. Although our first experiment (sequential homozygotes) suffers from lack of complete orthogonality, the difference between the two segments (at least in terms of the peak brood) is obvious. The use of sequential heterozygosity amplified the responses and confirmed that segment I (the euchromatic one) is preferentially sensitive to 30° treatment and nearly insensitive to 34°. Segment II, on the other hand, is equally sensitive to both treatments. Since the whole region is no more than 2½ recombinational units long, pooled responses are expected when longer regions are studied. The danger is especially high where heterochromatic and euchromatic segments are included within a long region. The fact that a rise in crossing over as a result of heat effect is characteristic of proximal heterochromatic regions was already established by STERN (1926, 1933). Thus most of the 34° response in the *car–y*$^{+}$ segment often studied in this respect might be attributed to the proximal or even intercalated heterochromatin in this region (see LIFSCHYTZ 1971).

Another difference between the two segments is the timing of the peak response as revealed in experiments A, B and C of Table 2. The more distal the region the earlier is the peak response. Whether this phenomenon relates to the sequence of pairing along the chromosome (see ROBERTS 1970) or to the fact that region II is heterochromatic and I is euchromatic is hard to say. Interestingly enough this sequence of events is correlated with replication time being later at heterochromatic regions.

SCHALET & LEFEVRE (1974) have recently argued that a distinct junction located near the *su-f* gene (see Fig. 1) separates the proximal heterochromatin from the euchromatic part of the *X*. We maintain however, that the genetic behavior of segment II as deduced from this and former work, is best explained as being composed of long heterochromatic stretches, interrupted by mendelian genes. As will be shown elsewhere, there are at least 3 hot points for X-ray induced breaks along this segment. It will be shown that the occurrence of breaks at these points is the result of interaction with a known heterochromatic region.

The premeiotic effect of heat:

The amplification and refinement of the response obtained with the sequential heterozygote system also uncovered a very impressive premeiotic effect. Thus, the rise induced by heat shock reached control level again after only 2 weeks. Although problems of synchronization, dilution and extension of the responsive period are not easy to settle or avoid (see GRELL 1973 for discussion), it is nevertheless hard to attribute such a long-lasting effect to "technicalities". PLOUGH (1917a) observed a persistence of heat effect for 8 days after the

treatment. A long-lasting effect was also observed by WHITTINGHILL (1964) and by THOMPSON (1964), both of whom tended to attribute it to gonial exchanges. However, gonial crossovers may result from unequal exchanges. It is rather hard to envisage this type of exchange taking place in such short segments, encompassing many viable genes and delimited by two lethal mutations, and yet imposing such a proportionally high recombination rate. Also, in Exp't. a (Table 2, Figure 3) where both temperatures are effective, the 4-day 30° treatment reacts the same way as the one-day 34° treatment, and the distribution of recombinants among cultures gives no indication of clustering. This is the case for experiments b and c as well. Moreover, the shape of the curve in all three experiments (Figure 3) is similar. It does not flatten after reaching peak levels but, rather, goes down back to control level, another indication of late-appearing recombinants have no stem cell origin. LAMB (1969) has shown that heat shock given two divisions prior to meiosis enhances meiotic exchanges and FELDMAN (1968) has postulated that meiotic pairing is well correlated with mitotic pairing in wheat. It is tempting therefore, to conclude that recombination efficiency is partly determined in premeiotic cells and that this process is also heat-sensitive.

Heat target during meiosis

The underlying assumption that the deficiency heterozygote reduces nearby exchanges through "pairing" difficulties limits our conclusion to just this "type" of "pairing". We may say nothing regarding all other steps leading to the kind of intimate pairing needed for normal exchange to take place. The results indicate that heat treatment is able to increase 8–10 times the number of sites available for exchange in the short delimited segment that is under the influence of sequential heterozygosity. This might mean that the same degree of extensive pairing takes place also in the treated sequential homozygote, but does not materialize in exchanges, probably because of restrictions put by the "exchange" system. Only when "pairing" is reduced 15-fold (as in Exp't. c, Table 2 and Figure 3) by heterozygosity for deficiency, and subsequently elevated back by heat (while the "exchange" potential remained constant) could this effect be seen. When "pairing" is reduced initially to by 40% of its normal level (Exp'ts. a and b) the rise is proportionally lower (4–5-fold). We conclude therefore that heat-induced crossing over is the result of a preferential effect on the "pairing" component of recombination.

Since deficiency-distributed pairing is materialized only in the already paired chromosome, one should keep in mind that the above conclusion is valid for, and restricted to, the type of pairing impaired by sequential heterozygotes. A broader effect of heat on pairing is suggested by CHANDLEY (1968) in discussing the disruption of distal pairing in the *X* chromosome. Whether or not the "pairing" defined by our experiment bears some relation to the phenomenon of "proximal increase" of crossing over (see CHANDLEY 1968) is questionable.

Interpretation aside, the system is quite useful in classifying agents which increase crossing over into two classes, one which increases crossing over propor-

tionally in sequential heterozygotes and another which does not. We have attempted to classify only the *c(3)G/+* effect. The results show that if *c(3)G/+* increases crossing over through the pairing mechanisms (HALL 1972), it does not do it through the step in pairing disturbed by deficiency heterozygotes.

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