MEIOTIC DRIVE IN NATURAL POPULATIONS OF DROSOPHILA MELANOGASTER. VII. CONDITIONAL SEGREGATION- DISTORTION: A POSSIBLE NONALLELIC CONVERSION^{1,2}

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MALES, heterozygous for the *Segregation-distorter* (*SD*) allele (located in or near the centromeric heterochromatin of the right arm of chromosome II) and a standard tester second chromosome, regularly produce a preponderance of functional *SD*-bearing sperm (SANDLER, HIRAIZUMI and SANDLER 1959). Segregation in heterozygous *SD* females, on the other hand, is always normal. It has been found, however, that, for certain *SD* lines, if the *SD*-bearing chromosome is inherited from the female parent, then, in a fraction of F_1 male sibships, only one half of the heterozygous *SD* sons exhibit the phenomenon of segregation-distortion; in the other half of the sons, segregation is normal. In the following generation, all of the males exhibit abnormal ratios irrespective of whether or not their father showed an abnormal ratio. Those females that produce sons, only one half of which distort, are referred to as *conditioned*; the phenomenon is termed *conditional distortion* (SANDLER and HIRAIZUMI 1959).

The genetic basis of the phenomenon of conditional distortion has now been elucidated. The system operates as follows. The X chromosome, in a male carrying *SD*, may become induced into a specific modifier of *SD* such that in the succeeding generations the newly induced X chromosome suppresses segregation-distortion in appropriate tester lines. Thus, if *SD*-bearing males are mated to normal females, the female progeny have two kinds of X chromosomes, a normal X from the mother and a changed X from the father. Such a female is said to be conditioned. Her *SD* sons will be of two types. Those that receive the normal X will be distorters; those that receive the changed X will produce only normal segregation ratios. Both kinds of males, when crossed to normal females, produce, in the next generation, sons all of which receive an unchanged X chromosome from the female parent and therefore, if *SD*, produce abnormal ratios.

The evidence for this interpretation, and other questions related to the phenomenon of conditional distortion is presented below.

A demonstration of conditional distortion: The *SD* line that was used to investigate the question of conditional distortion is the *SD*-bearing chromosome, *R(SD)-4*. This chromosome is a recombinant between *SD-72* (a line originally

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collected in nature and containing an inversion in IIR) and the standard *cn bw* tester chromosome (a normal chromosome II carrying the mutants cinnabar and brown). The exchange giving rise to *R(SD)-4* took place proximal to the inversion in *SD-72*, so that *R(SD)-4* is inversion free and is marked by the mutant allele *bw*. In addition, *R(SD)-4* has been backcrossed to the standard *cn bw* line for many generations (passing *R(SD)-4*, however, through males only) so that the genetic background is standardized. Crosses of *R(SD)-4/cn bw* males by *cn bw* females gives rise, in every generation, to the standard semistable distribution of *k* values (SANDLER and HIRAIZUMI 1960). The parameter *k* is defined as the proportion of functional *SD*-bearing gametes produced by a heterozygote.

When, however, *R(SD)-4/cn bw* males are crossed to *In(2LR)Cy/cn bw* females (the Curly chromosome being a standard second chromosome balancer and, in this stock, having been backcrossed for many generations to the standard *cn bw* stock to insure uniformity of genetic background) and the *R(SD)-4/In(2LR)Cy* female progeny crossed individually to *cn bw* males, two types of *R(SD)-4/cn bw* male sibships are recovered—those in which all of the males give distorted ratios (the mother being referred to as “unconditioned”) and those in which only half of the sons distort (the mothers then being termed “conditioned”). The results of such a series of matings are shown in Figure 1. Histogram A shows the standard semistable distribution for *R(SD)-4* inherited through males; histogram B shows the distribution of *k* values of the sons of conditioned females (the mean *k* value slightly higher than 0.50 exhibited by the nondistorting males is almost certainly accounted for by the relative inviability of flies homozygous for the mutants *cn* and *bw*); histogram C shows the distribution of *k* values of the sons of unconditioned females; and histogram D shows the distribution of *k* values of the sons of those males showing no distortion in histogram B. It can be seen (1) that unconditioned females produce male progeny apparently not different from males receiving this *SD*-bearing chromosome from a male parent (that is, histograms A and C are very similar); (2) that the distorting males of conditioned females give a completely standard distribution (the right side of histogram B is similar to histograms A and C); (3) that recovery, in the next generation, is complete (histogram D is similar to A, C, and the high side of histogram B); and (4) that induction does not always occur even when it obviously could.

The formal basis of conditional distortion: The phenomenon of conditional distortion does not occur if the female through which *SD* is passed carries a compound X chromosome so that the X in the male progeny is patroclinous. The compound X chromosome used in these studies is a reversed acrocentric compound marked by the recessives, yellow and forked (symbol: $\gamma f=$). Thus, single *R(SD)-4/cn bw* males were doubly mated both to free-X females carrying *In(2LR)Cy/cn bw* and to $\gamma f=$ /Y females also carrying *In(2LR)Cy/cn bw*. These compound-X-bearing females have been backcrossed to the standard *cn bw* stock for some generations so that the genetic background is again from the

FIGURE 1.—A demonstration of the phenomenon of conditional segregation-distortion. Histogram A = $R(SD)-4$ inherited from male parents; B = $R(SD)-4$ inherited from conditioned female parents; C = $R(SD)-4$ inherited from unconditioned female parents; D = $R(SD)-4$ sons of the nondistorting males recorded in histogram B. N = total males tested; $\bar{k}$ = unweighted mean k value.

standard stock. From each mating, $In(2LR)Cy/R(SD)-4$ females were collected and crossed to $cn bw$ males. From these crosses, $R(SD)-4/cn bw$ male sibships were obtained from individual females and tested for segregation-distortion. The results of these experiments are given in Figure 2.

Histogram A shows the k value distribution of the sons of those males mated to normal, free X females which were unconditioned. The results from the corresponding crosses to compound X-bearing females are given in histogram B. The results from conditioned females are shown in histogram C (free X) and the corresponding results from compound X females in histogram D.

It is clear from these data that, while the free X daughters of these males may be either conditioned or unconditioned, the compound X-bearing daughters produce only distorting sons. Formally, then, the phenomenon of conditional distortion is suppressed in compound X and Y-bearing females. It may be noted that

FIGURE 2.—The suppression of conditional distortion in compound X and Y-bearing females. Histogram A = the sons of unconditioned free X females; B = the sons of compound X-bearing females carrying the same *SD*-bearing chromosomes as in A; C = the sons of conditioned free X females; D = the sons of compound X-bearing females carrying the same *SD*-bearing chromosome as in C.

this same result has been obtained utilizing a simple attached-X rather than the reversed acrocentric compound X.

This suppression of conditional distortion in compound X females and the equality of distorting and nondistorting sons from conditioned free X females (Figure 1; histogram B) suggested that the X chromosome that the female inherited from her father with the *SD*-bearing chromosome II might be changed and that those of her sons that receive the changed X (i.e. the X chromosome from the maternal grandfather) do not distort. Thus it may be imagined that in an *SD* male, the X chromosome is induced to become a specific modifier of *SD* such that in succeeding generations it inhibits segregation-distortion.

In order to test this hypothesis directly, the following experiments were performed. First, individual *R(SD)-4/cn bw* males were doubly mated both to

$\gamma f := Y$; *cn bw/cn bw* females and to free X *cn bw/cn bw* females and the resulting *R(SD)-4/cn bw* sons from each cross tested for distortion by crossing them to free X females. The results of these experiments are given in Figure 3.

FIGURE 3.—Conditional distortion through males. Histogram A = the sons of *R(SD)-4* fathers mated to free X females; B = the sons of these same fathers mated to compound X and Y-bearing females; C = the sons of *R(SD)-4* fathers mated to free X females; D = the sons of these same fathers mated to compound X and Y-bearing females.

Here, histograms A and C are the k value distributions of the sons of the cross to free X females. Histograms B and D show the two kinds of results from crosses to compound X-bearing females. Histogram A is the control for histogram B; histogram C is the control for the results shown in histogram D.

It can be seen that all of the males from the free X female cross distort (which is, of course, expected since this is the standard mating by which the *SD* stock is kept) while from the compound X female set, the sibships are either all distorting or else all nondistorting. The sons of those males showing no distortion in this generation were also tested and, in the next generation, they all distorted normally. Thus recovery is complete in this case also. It seems clear, therefore, that the phenomenon of conditional distortion does not require that *SD* pass

through a female for the reason that in these experiments the *SD*-bearing chromosome was inherited only through males throughout the experiment.

More important, however, is the fact that males receiving their X chromosome from their *SD*-bearing male parent exhibit conditional distortion—but since an entire male sibship inherits the same X chromosome, the sibships are nonsegregating.

It is interesting, nevertheless, to note that even in unconditioned sibships from males mated to XX/Y females, there are occasional low *k* values (about 15 to 20 percent) which are not found in the free X controls. It seems, therefore, that some changed X's are produced in sibships containing predominantly uninduced X chromosomes. This point will be considered again below.

A second set of experiments designed to test the hypothesis that changed X's are responsible for the nondistorting males of conditioned females was as follows. Single *R(SD)-4/cn bw* males were crossed with Muller-5/+; *cn bw/In(2LR)Cy* females. The Muller-5 chromosome is a standard X chromosome balancer marked by the dominant mutant Bar. In this stock, this chromosome had been repeatedly backcrossed to the standard *cn bw* stock to insure genetic uniformity. It has been found that Muller-5 carries a suppressor of distortion that is unrelated to the present investigation. The nature of modifiers of segregation-distortion will be reported on in detail in a subsequent report. Because of this modifier, however, it is not possible to determine whether a Muller-5 chromosome has become changed by virtue of being with *SD*. However, the Muller-5 chromosome is used solely to provide genetic markers for identifying the paternal and maternal X chromosomes in conditioned females, so its behavior with respect to *SD* is irrelevant. Thus from the cross, *R(SD)-4/cn bw* males by Muller-5/+; *In(2LR)Cy/cn bw* females, Muller-5/+; *R(SD)-4/In(2LR)Cy* females were collected and crossed individually to *cn bw* males. From among these progeny, +/Y; *R(SD)-4/cn bw* males were collected and tested for distortion by crossing to free X *cn bw* females. The results of these crosses are given in Figure 4.

It can be seen that such male sibships, which contain only the one X chromosome ultimately derived from the *SD*-bearing maternal grandfather contain either all distorting (histogram U for unconditioned) or all nondistorting (histogram C for conditioned) males showing that it is indeed the grandpaternal X chromosome that is always present in the nondistorting sons of conditioned females. It should be mentioned that again, in the next generation all the males distort.

From these results taken together then, the hypothesis that in *SD*-carrying males the X chromosome may become a specific inhibitor of segregation-distortion in subsequent generations, may be taken as demonstrated.

We may note an additional point about the phenomenon of conditional segregation-distortion. It seems clear that the change in the X chromosome is *specific induction*. Three arguments effectively eliminate the possibility that the results reported are the consequence of segregating modifiers of segregation-distortion. First, the background genotype, including the X chromosomes, is uniformly

FIGURE 4.—The effect of the grandpaternal X chromosome inherited through a female. Histogram U = those grandpaternal X chromosomes associated with unconditioned behavior; C = those grandpaternal X chromosomes associated with conditioned behavior.

from the *cn bw* stock. Thus, if there were modifiers of some sort segregating in the *cn bw* stock that suppress distortion, these modifiers would express themselves, in the same way irrespective of whether *SD* is inherited from the male or female parent. Second, those heterozygous *SD* males that transmit the changed X (i.e. that produce conditioned females) are themselves distorters indicating that they do not carry any suppressors of distortion. Finally, the complete recovery of the ability to distort after crossing to free X females eliminates the possibility of any segregating modifiers on the Y chromosome, or indeed on any chromosomes other than the X. It therefore seems inescapable that in an *SD* male, there is specific induction of a modifier of distortion on the X chromosome.

Additional observations on conditional distortion: It has been found previously that the *SD* region is complex (SANDLER and HIRAIZUMI 1960a). It may be thought of as consisting of two separable elements: (1) the *SD* locus itself that causes an effective break in its homolog, which break results in the nonfunctioning of *SD*⁺-bearing spermatocytes or spermatozoa and thus leads to abnormal genetic ratios, and (2) an *Activator of SD*, *Ac(SD)*, that is necessary, in coupling with *SD*, in order that *SD* operate. The *SD Ac(SD)* complex apparently resides in a small chromosomal aberration that is immune to *SD* action, resulting in complete insensitivity of *SD*-bearing chromosomes to the action of *SD* and thus also essentially "directing" the *SD* chromosome to break its homolog instead of itself.

It is of interest, in this connection, to inquire as to which element or elements are necessary in order that the changed X chromosome be generated. Accordingly, males carrying *cn bw* and a chromosome bearing the *SD* subelement but not *Ac(SD)* and only a small part of the associated aberration, *SD*ⁱⁿ, (SANDLER and HIRAIZUMI 1960a) were crossed to *cn bw/In(2L)Cy cn bw* (*In(2L)Cy* carries only the left arm *Cy* inversion and is distortable). *SD*ⁱⁿ/*In(2L)Cy cn bw* female progeny were crossed to *R(SD)-4/cn bw* males and the *R(SD)-4/In(2L)-Cy cn bw* male progeny were tested. In five conditioned families there were pro-

duced 38 males showing the usual amount of distortion and 45 males showing approximately 1:1 segregation ratios. Therefore, it can be concluded that the *SD* sub-element alone can generate changed X chromosomes.

An experiment has been performed for the purpose of defining the difference between a conditioned and an unconditioned female. The question to be answered is whether an unconditioned female is one that has not received a changed X chromosome from her father or whether such a female is one that has received a changed X, but also carries an unresponsive *SD* chromosome so that the induced X cannot function. In general, then, we may inquire whether the difference between the conditioned and unconditioned state is defined by the state of the X chromosome or of *SD*.

To answer this question, the following experiment was performed utilizing in addition to stocks already mentioned, *SD-5* (an original *SD* line collected in nature that contains two inversions and a lethal in IIR). The two inversions prohibit crossing over in the right arm, between *SD-5* and its homolog (SANDLER, HIRAIZUMI and SANDLER 1959). Single *R(SD)-4/cn bw* males were doubly mated both to $\gamma f: = /Y; cn bw/cn bw$ females and to *SD-5/cn bw* free X females. From each of these matings, *R(SD)-4/cn bw* males were collected and tested for segregation-distortion. The results of these experiments are given in Figure 5.

Histograms A and C show the *k* value distributions of the sons of *R(SD)-4* males crossed to compound X-bearing females. Only the sons of males that produced distorting progenies were chosen, although the other type of sibship was present. Histogram B shows the distribution of *k* values of the sons of the same males used in histogram A, but mated, in this case, to *SD-5/cn bw* free X females. Histogram D corresponds in the same way to histogram C.

From these results, it is clear that a conditioned female is defined by the possession of an X chromosome that is changed. This is so for the reason that even when the *SD*-bearing chromosome and the X chromosome together in a male exhibit the unconditioned behavior (histograms A and C), the same *SD* exhibits the typical conditioned (or else unconditioned) behavior in the presence of an X chromosome from a different *SD* line.

These experiments, it might be mentioned, also show that a modified X chromosome can inhibit the distorting action of a different *SD* chromosome from that which engendered the change in the X so that the specificity of the induced modifier is not restricted to the particular *SD* that generated it. It may be noted that this experiment (and the previous one with *SDⁱⁿ*) is further evidence that *SD* itself does not have to pass through a female in order that conditional distortion occur.

The experiments with *SDⁱⁿ* given above indicate that a male does not actually have to exhibit segregation-distortion in order to induce an X chromosome. This is so for the reason that the *SDⁱⁿ/cn bw* males used in that experiment show normal, 1:1, ratios (SANDLER and HIRAIZUMI 1960a). A further check on this point made use of the fact that *SD/In(2LR)Cy* males show no distortion (SANDLER, HIRAIZUMI and SANDLER 1959). In this case, *R(SD)-4/In(2LR)Cy* males

FIGURE 5.—A demonstration of the changed state of the X chromosome. Histogram A = the sons of $R(SD)-4$ males crossed to compound X and Y-bearing females selected to be unconditioned; B = the $R(SD)-4$ sons of these same males crossed to $SD-5/cn\ bw$, free X females; C = the same as in "A"; D = the $R(SD)-4$ sons of the same males as in "C" crossed to $SD-5/cn\ bw$, free X females.

were crossed to $cn\ bw/In(2LR)Cy$ females, and the F_1 $R(SD)-4/In(2LR)Cy$ female progeny were tested to see whether any were conditioned. Conditioned females were found in this case, confirming the conclusion that an SD male can induce the X chromosome whether or not he actually exhibits segregation-distortion.

A final question about conditional distortion to be considered is the fate of an induced X chromosome in the absence of SD . To determine this, $R(SD)-4/cn\ bw$ males were mated to $cn\ bw/In(2LR)Cy$ females, and the F_1 $R(SD)-4/In(2LR)Cy$ females were crossed individually to $cn\ bw/cn\ bw$ males. From this cross, $R(SD)-4/cn\ bw$ males were tested to determine whether the female was conditioned or not, and, from the conditioned females in this same cross, $cn\ bw/In(2LR)Cy$ males (two or three per female) were crossed to $\gamma\ f::Y; R(SD)-4/In(2LR)Cy$ females. From this cross, $R(SD)-4/cn\ bw$ males were tested for segregation-distortion. The control consisted of testing similar males from the

TABLE 1

The behavior of induced and not induced X chromosomes after one generation in males without SD. The origin of the males in each set in the table is given in the text

<i>k</i>	Set I	Set II	Set III
0.43	...	...	14.63
0.46	...	...	9.76
0.49	...	...	26.83
0.52	...	...	17.07
0.55	...	...	14.63
0.58	...	...	12.20
0.61	...	...	2.44
0.64	...	...	0.00
0.67	...	...	2.44
0.70	...	...	...
0.73	...	2.08	...
0.76	...	2.08	...
0.79	1.16	2.08	...
0.82	0.00	0.00	...
0.85	2.33	2.08	...
0.88	1.16	2.08	...
0.91	3.49	0.00	...
0.94	3.49	2.08	...
0.97	88.37	87.50	...
N	86	48	41
$\bar{k}$	0.99	0.98	0.52

unconditioned grandmothers. Pedigrees were kept. The results are given in Table 1.

From each of four unconditioned *R(SD)-4/In(2LR)Cy* females, two or three *cn bw/In(2LR)Cy* males were collected and crossed to the compound X *SD* females. These yielded *R(SD)-4/cn bw* test males—the *k* value distribution of which is given in the first column (Set I) of the table. It can be seen that this is the standard semistable distribution indicating that the X chromosome from unconditioned females is unchanged. From four conditioned females, ten *cn bw/In(2LR)Cy* males were also collected (again two or three per female) and their *R(SD)-4/cn bw* sons tested for *k*. Here, two different kinds of sibships were observed. From five of the males, the sibships produced the usual semistable distribution. The *k* value distribution from these males is given in the second column (Set II) of the table. This is undoubtedly the distribution from the unchanged (i.e. grandmaternal) X chromosome from a conditioned female and indicates that nothing happens to that X in such females. Finally, the other five *Cy* sons produced a distinctly different kind of *R(SD)-4* male sibship—the *k* value distribution of which is given in the last column (Set III) of Table 1. This almost certainly corresponds to the behavior of the induced X after one generation in males lacking *SD*.

From these results it is clear that, for one generation at least, the induced modifier on the X chromosome remains unchanged. This is shown both by the observation that one half (five out of ten) of the sons of conditioned females show low k distributions among their progeny, and also by the fact that the low k distributions themselves vary uniformly about a k value equivalent to that characteristic of the changed X in the first generation.

Evidence for "conditioning states" of SD: The $R(SD)$ -4 stocks used throughout the studies reported here were kept by selecting, in every generation, one or two single $R(SD)$ -4/*cn bw* males and backcrossing these to *cn bw* females. We have observed, during the two years that these studies were carried out, at least three (and possibly more) distinct kinds of results: (1) for some generations at a time, the $R(SD)$ -4 males would produce only unconditioned daughters; (2) for some generations, only conditioned daughters are observed; (3) most often, about 15–30 percent of the females are conditioned. From these observations, it seems reasonable to suppose that there are at least three different kinds of *SD* males—each defined by the proportion of induced X's that it transmits to its progeny.

Additional evidence on this point is provided by the results of crossing $R(SD)$ -4 males to compound X females. Here, two kinds of results have been observed: either all the sons of a single male crossed with compound X females exhibit no distortion (Figure 3; histogram D) or else a small fraction do (Figure 3, histogram B). The former presumably correspond to males that produce only conditioned daughters (although this conclusion was not checked directly). The latter result requires consideration. A comparison of histograms A and B in Figure 3 reveals that about 20 percent of the males from the compound X female cross exhibit lower k values than the corresponding free X cross (in spite of the fact that both sets of males result from precisely the same fathers by double mating). It was considered possible that males that produce sons showing the distribution of histogram B, Figure 3, would produce the typical 15–30 percent conditioned females. Accordingly, the daughters of males whose sons (from a mating to γf = females) showed a distribution similar to histogram B, Figure 3, were tested. It was indeed found that of 37 females tested, seven were conditioned. Thus, the two kinds of results given in Figure 3 illustrate two of the possible "conditioning states" of *SD*. The state giving no induced X's was not observed in this experiment.

Although the proportions of low k values agree between the compound X and free X (through female) crosses, the k values themselves do not. A conditioned female produces 50 percent sons with normal 1:1 segregation ratios, while the lower k values in histogram B, Figure 3, range from 0.50 to more than 0.85. This matter requires further study, but it seems likely that the induced X is somehow stabilized in a female. The entire question of the fate of the induced X in females and the matter of conditioning states is under additional study.

On the differences among different SD lines: Until this point, all of the experiments have utilized the *SD*-bearing recombinant chromosome, $R(SD)$ -4. This chromosome is typical of recombinants between the original *SD* line, *SD*-72, and

cn bw but differs markedly from other types of *SD* lines in its response to the specifically modified X chromosome.

There were two different types of *SD* lines originally collected in nature—*SD-5* (that contains two inversions and a lethal in IIR) and *SD-72* (that contains one inversion and no lethal). It has already been shown that *SD-5* (and thus presumably all *SD* lines) regularly generate changed X chromosomes in the same way as *R(SD)-4* (see Figure 5 and accompanying text). The effect of such changed X chromosomes on the behavior of *SD-5* and *SD-72*, however, is very much less marked than it is on *R(SD)-4*. Thus Figure 6 shows the results of

FIGURE 6.—The results of passing *SD-72* and *SD-5* through males and females.

passing *SD-5* and *SD-72* through females as compared with males. It is clear that whereas there is a slight lowering of the k values in males that receive their *SD*-bearing chromosome from the female parent, there is no evidence for the complete suppression of segregation-distortion such as is observed in the case of *R(SD)-4*.

The typical recombinant between *SD-5* and *cn bw* results from an exchange

distal to the inversions and the lethal so that the *SD*-bearing chromosome, symbolized *R(SD-5)* followed by an identifying number, carries both inversions and the lethal. Recombination between *SD-72* and *cn bw*, on the other hand, takes place proximal to the inversion so that these *SD*-bearing recombinants, symbolized *R(SD)* followed by an identifying number, contain no gross rearrangements. In the case of either type of recombinant, the *k* value distribution will vary somewhat from male to male (in which case the line is referred to as "semi-stable") or the male to male variation may be very wide (the line then being termed "unstable"). The semistable and the unstable states differ from the original, "stable", state in that the recombinant *SD* chromosome has lost by crossing over a stabilizing modifier, *St(SD)*, located at the tip of IIR. A semistable line can become unstable without further recombination. The evidence bearing on the matter of stability has been presented by SANDLER and HIRAIZUMI (1960).

Samples of the various kinds of recombinants have been tested for their response to changed X chromosomes by comparing the distribution of *k* values when the *SD*-bearing chromosome has been inherited from females as compared with males. The results are given in Table 2. It can be seen that in the case of

TABLE 2

The distribution of k values of recombinant SD-bearing chromosomes inherited from the male, as compared with the female, parent. The entries are the proportion of males falling into each k value interval

<i>k</i>	R(SD-36)-1*		SD-5 Recombinants			R(SD-5)-18		R(SD)-8		SD-72 Recombinants			R(SD)-5	
	♂ ♂	♀ ♀	♂ ♂	♀ ♀		♂ ♂	♀ ♀	♂ ♂	♀ ♀	♂ ♂	♀ ♀ †	♀ ♀ †	♂ ♂	♀ ♀ †
0.43	...	0.86	...	...	...	...	...	...	7.50	...	6.45	...	13.04	
0.46	...	3.42	...	...	...	...	...	1.12	5.00	0.97	4.84	...	0.00	
0.49	1.54	2.56	...	0.83	...	...	...	0.00	10.00	0.00	9.68	...	21.74	
0.52	6.15	2.56	...	0.83	...	...	...	0.00	5.00	0.00	14.52	...	0.00	
0.55	3.08	11.11	...	0.00	...	...	...	3.37	7.50	0.00	6.45	...	17.39	
0.58	3.08	5.13	1.45	0.00	...	...	...	4.49	0.00	0.00	11.29	...	0.00	
0.61	3.08	3.42	0.00	0.00	...	...	...	3.37	0.00	0.00	1.61	...	4.35	
0.64	4.62	2.56	0.00	0.83	...	0.81	...	5.62	2.50	0.00	6.45	...	0.00	
0.67	1.54	6.84	0.72	1.65	...	0.00	...	4.49	5.00	0.97	0.00	...	0.00	
0.70	6.15	2.56	1.45	3.31	...	0.00	...	11.24	0.00	4.85	0.00	...	0.00	
0.73	4.62	3.42	0.72	4.96	0.78	0.00	...	4.49	2.50	2.91	0.00	...	0.00	
0.76	7.69	2.56	0.72	4.96	0.00	0.00	...	3.37	2.50	1.94	0.00	...	0.00	
0.79	6.15	4.27	0.72	7.44	0.00	0.81	...	0.00	0.00	6.80	0.00	...	0.00	
0.82	4.62	0.00	1.45	12.40	0.78	0.81	...	7.89	5.00	8.74	1.61	...	0.00	
0.85	6.15	1.71	5.07	9.92	1.55	0.81	...	6.74	2.50	11.65	0.00	1.85	0.00	
0.88	3.08	1.71	5.80	7.44	6.98	1.63	...	11.24	0.00	19.42	0.00	8.33	0.00	
0.91	10.77	5.98	11.59	17.36	3.88	8.94	...	16.85	7.50	15.53	3.23	9.26	0.00	
0.94	6.15	8.55	28.26	9.09	18.60	13.82	...	5.62	2.50	9.71	3.23	20.37	0.00	
0.97	21.54	30.77	42.03	19.01	67.44	72.36	...	10.11	35.00	16.50	30.65	60.18	43.48	
Total ♂ ♂	65	117	138	121	129	123		89	40	103	62	108	23	
$\bar{k}$	0.81	0.79	0.94	0.91	0.97	0.90		0.81	0.77	0.88	...	0.95	...	

* *SD-36* is the same type as *SD-5*.

† Conditioned females only were chosen for this line.

recombinants from *SD-5* type lines the response to the changed X chromosome is similar to that of the original *SD-5* line, while in the case of *SD-72* recombinants, such as *R(SD)-4*, the response is (1) extreme and (2) independent of whether the recombinant is semistable or unstable.

Two tests were performed to determine whether some of the nonreactivity of the original *SD* lines to the changed X was the result of the presence of *St(SD)* on the stable *SD*-bearing chromosomes. Thus *R(SD)-4/In(2LR)Cy* conditioned females (selected on the basis of the *k* value distribution of their sons) were crossed to *cn bw/St(SD)* males and the *R(SD)-4/cn bw* and *R(SD)-4/St(SD)* sons were tested for distortion. The origin of *St(SD)*-bearing chromosomes can be found in SANDLER and HIRAIZUMI (1960). These results are presented in Table 3. It is clear that whereas the control mating, *R(SD)-4/cn bw*, shows the normal conditioned behavior the experimental set, *R(SD)-4/St(SD)*, shows no complete suppression of distortion. Similarly, a *R(SD)-4* chromosome, onto which *St(SD)* has been placed by crossing over, was made heterozygous with *In(2LR)Cy* in females and these females crossed to *cn bw* males. The resultant *R(SD)-4, St(SD)/cn bw* males were tested for distortion. The results are shown in Figure 7. Here again there is no evidence for completely suppressed distortion. It is clear, therefore, that *St(SD)* causes a nonreactivity of *SD* to the specifically modified X chromosome.

This observation satisfactorily accounts for the results from *SD-5*, *SD-72* and

TABLE 3

Conditioned R(SD)-4/In(2LR)Cy females were crossed to males heterozygous for St(SD) and cn bw. The F₁ R(SD)-4/St(SD) and R(SD)-4/cn bw males were collected and tested for distortion

<i>k</i>	<i>R(SD)-4/cn bw</i>	<i>R(SD)-4/St(SD)</i>
0.43	3.23	
0.46	3.23	
0.49	12.90	
0.52	16.13	
0.55	12.90	
0.58	6.45	
0.61	9.68	
0.64		
0.67	3.23	
0.70	0.00	
0.73	3.23	3.57
0.76	0.00	0.00
0.79	0.00	3.57
0.82	0.00	0.00
0.85	0.00	14.29
0.88	0.00	0.00
0.91	6.45	14.29
0.94	0.00	10.71
0.97	22.58	53.57

N = 20

 $\bar{k} = 0.54$

N = 11

 $\bar{k} = 0.92$

N = 28

 $\bar{k} = 0.94$

FIGURE 7.—The response of $R(SD)-4$ carrying the stabilizing modifier, $St(SD)$, to the specifically modified X chromosome.

the recombinants from $SD-72$. It fails to explain, however, the nonreactivity of recombinants from $SD-5$, since these too lack $St(SD)$ but are nevertheless non-reactive. Accordingly it must be supposed that either (1) $SD-5$ carries a non-reactive allele of SD or (2) there exists, on $SD-5$, an additional nonreactivity modifier proximal to $St(SD)$. This question has been resolved by testing a rare type of recombinant from $SD-5$, $R(SD-5)-32$. This recombinant carries neither the inversions nor the lethal indicating that the recombination between $SD-5$ and $cn bw$ took place between cn and the proximal break point of the proximal inversion. The recombinant line is unstable.

Conditional distortion, in the case of $R(SD-5)-32$, was tested by doubly mating $R(SD-5)-32/cn bw$ males to homozygous $cn bw$ free X and $\gamma f:=Y; cn bw/cn bw$ females and testing the F_1 $R(SD-5)-32/cn bw$ males for distortion. These results are presented in Table 4. It can be seen that the males resulting from the compound X cross yield either a distribution of k values not different from the free X cross or all nondistorting sons as in the compound X crosses recorded above for $R(SD)-4$. Consequently, it is evident that $R(SD-5)-32$ does react to the changed X in the same way as $R(SD)-4$, and therefore $SD-5$ does not contain a nonreactive allele of SD . Accordingly $SD-5$ must be supposed to carry an additional, more proximally placed, modifier of conditional segregation-distortion. Whether this is a simple modifier or some action of the inversions themselves is not known.

DISCUSSION

It is clear that SD has the special property of inducing a specific inhibitor of its own action on the X chromosome. From the arguments presented in this report, particularly the fact that the very males that transmit the specifically

modified X chromosome themselves began life with an unchanged X, it is evident that this is specific induction as opposed to segregating modifiers in the *cn bw* stock. It is possible, however, that X chromosomes could be found that are not inducible in this way. If this is true, then it is conceivable that the other chromosomes in the *cn bw* stock (that is the Y chromosome and chromosomes III and IV) are simply not inducible but that stocks could be found in which chromosomes other than the X would be specifically modified by *SD*. That such inductions do not occur in the *cn bw* background follows immediately from the fact that males showing normal segregation ratios occur only as sons of *SD* females and not as sons of *SD* males (if it is supposed that the changed property is dominant; if, on the other hand, the induced property is recessive, then there could be inductions of other chromosomes that would not be detected in these experiments). In general, then, there is no reason from this analysis to conclude that *SD* and some section of the X chromosome are particularly related. The relationship exhibited here may simply be a consequence of the specific genetic background and experimental design that happens to have been utilized.

It is interesting to inquire just when, in an *SD* male, the X chromosome becomes changed. The answer to this question at this time is not at all clear. At first sight it would seem as though the change must occur after meiosis, for, should it have been completed before meiosis, the male in which it occurred would show

TABLE 4

The sons of R(SD-5)-32 males crossed to (A) free X females, (B) compound X and Y-bearing females and yielding an unconditioned distribution, and (C) compound X and Y-bearing females and yielding a conditioned distribution

k	A	B	C
0.43	...	...	8.21
0.46	...	...	13.43
0.49	...	...	12.69
0.52	...	6.90	22.39
0.55	1.52	0.00	17.91
0.58	6.06	6.90	12.69
0.61	3.03	13.79	8.21
0.64	7.58	0.00	1.49
0.67	3.03	3.45	2.24
0.70	7.58	10.34	0.75
0.73	3.03	3.45	...
0.76	6.06	3.45	...
0.79	7.58	10.34	...
0.82	7.58	6.90	...
0.85	7.58	0.00	...
0.88	10.61	0.00	...
0.91	12.12	10.34	...
0.94	10.61	6.90	...
0.97	6.06	17.24	...
Total $\delta \delta$	66	29	134
$\bar{k}$	0.81	0.78	0.54

a normal segregation ratio. On the other hand, if the change in the X chromosome occurs either during or after meiosis, then it is not immediately evident why all, or almost all, of the X's from a given male are, in some instances at least, specifically modified. It seems that there is no way of deciding between these alternatives and that all that can be said is that either the X chromosome becomes changed early in ontogeny but for some reason the phenotype does not manifest itself until the succeeding generation or that the change takes place during or after meiosis and that the inducing mechanism may, nevertheless, work in every germ cell.

The stabilizing modifier, *St(SD)*, apparently has two distinct functions. On the one hand it stabilizes the action of *SD* at a high level of activity (SANDLER and HIRAZUMI 1960), and, on the other, it imparts a high degree of nonreactivity of *SD* to the effect of the specifically modified X chromosome. It might initially be imagined that these are two manifestations of the same activity of *St(SD)* which is simply to enhance the distorting action of *SD* under all circumstances. The true situation, however, while possibly this simple, is probably somewhat more complex. It has been shown above that in addition to *St(SD)* there is another modifier on *SD-5* affecting the response of *SD* to the changed X. This additional modifier does not affect stability since *R(SD-36)-1*, for example, is extremely unstable but nevertheless does not react to the changed X (see Table 2). Thus, irrespective of the nature of *St(SD)*, specific modification of the response of *SD* to the changed X chromosome does occur (this is specific modification of specific modification!). It seems most reasonable, therefore, that *St(SD)* also specifically modifies the response of *SD* to the changed X, and therefore, that *St(SD)* does indeed have two functionally distinct actions. It should be mentioned however, that there is no way in these experiments to distinguish between two functions of *St(SD)* versus the possibility of another modifier closely linked to *St(SD)* having the second function.

It is immediately evident that the equality of distorting and nondistorting sons of conditioned females implies that the specific modifier induced on the X chromosome by *SD* is a single locus. This is so for the reason that if more than one locus were either necessary or sufficient to inhibit distortion, the segregation into two classes would depart from equality. It would be interesting therefore to determine the location of this induced modifier. However, a number of marked X chromosomes isolated for this purpose all contained modifiers of distortion (as does the Muller-5 chromosome) which made them useless for this purpose. When, moreover, attempts were made to separate the marker from the modifier, the results were difficult to interpret, for it was uncertain that a marked chromosome lacking modifiers had been produced. For this reason, it was considered reasonable to defer mapping the induced modifier until the location and behavior of the already existing modifiers is worked out.

From the standpoint of the evolution of the phenomenon of segregation-distortion, conditional distortion is of interest in two connections. In the first place, it would seem that the ability of *SD* to cause a specific change on the X is, from

the standpoint of *SD* itself, selectively disadvantageous. Thus this is very unlikely to have evolved in response to selection and therefore is very likely to be an integral part of *SD*. That is, it seems reasonable that potential distorting ability implies the ability to induce the X chromosomes. The fact that the *SD* subelement itself, can induce the X also supports this notion. It is, however, immediately evident why the modifiers of the phenomenon of conditional segregation-distortion should have persisted. Given their action, the ability of *SD* to change the X chromosome into a specific inhibitor of its own action becomes relatively unimportant because in nature all of the chromosomes carry the modifiers of *SD*'s response to the specifically modified X chromosome.

In this general connection an additional point may be noted. It has been found that stocks either from the laboratory or those collected in nature contain numerous modifiers of segregation-distortion (SANDLER and HIRAIZUMI 1959 and unpublished). These modifiers probably may be located on any of the chromosomes of the complement. It is not unreasonable that these modifiers are present in populations as a consequence of selection against distortion during a prior history with *SD*. Indeed, the fact that *SD* has had a long evolutionary history has been argued by SANDLER and HIRAIZUMI (1959, 1960), HIRAIZUMI, SANDLER and CROW (1960) and most cogently by MANGE (1961), who reported on independent collection of *SD* from a natural population in Lower California. It is probable, therefore, that modifiers of segregation-distortion arise in natural populations and are caused to increase in frequency by virtue of natural selection (HIRAIZUMI, SANDLER and CROW 1960). It also may be that these modifiers arise specifically in response to the *SD* element. It is not impossible that the specific modification induced on the X chromosome (or, indeed, on any chromosome) could, in some cases, prove permanent or it could be that specific modification repeated over a number of generations, as would happen in natural populations in which *SD* was fairly common, would finally result in permanent modifiers of the sort observed now. Evidently, a matter such as this cannot be rigorously resolved (particularly, since the modifiers observed have properties rather different from those of the induced X, the observed heritability of the induced modifier on the X is not immediately relevant), but it is worth noting that the phenomenon of conditional segregation-distortion opens the possibility that *SD* engenders its own modifiers.

It may be noted that the conditional distortion system itself and the intricacy of *SD*'s response to this phenomenon (that is the development of specific modifiers) suggests a long evolutionary history of segregation-distortion.

It is interesting to note that regular, heritable, specific inductions of alleles are observed in maize in the case of the phenomenon of paramutation (BRINK 1958), the apparently similar changes at the *B* locus (COE 1959) and the well-known modifier of *a₁*, *Dt* (RHOADES 1938). Although there is a definite similarity between these cases in maize and the phenomenon of conditional distortion, it is not yet clear just how—if at all—these various phenomena are to be analogized.

Finally, the phenomenon of conditional segregation-distortion is, most prob-

ably, a case of "nonallelic conversion"; that is, an instance of a heritable, directed, gene change that cannot readily be imagined to come about by any kind of copy-choice mechanism.

SUMMARY

In males carrying the *Segregation-distorter* element (*SD*) the X chromosome may become changed into a specific inhibitor of segregation-distortion. It has been shown that if *SD* males are crossed to normal free X females and the *SD*-carrying female progeny crossed to normal males, then among the heterozygous *SD* grandsons only one half exhibit segregation-distortion; the other half, those receiving their X chromosome from the *SD*-carrying maternal grandfather, show normal 1:1 segregation ratios. In the next generation, however, all of the males receive their X chromosome from normal females, and hence all exhibit segregation-distortion. Using marked X chromosomes, it is possible to show directly that the chromosome responsible for the suppression of distortion is the X chromosome from the maternal grandfather.

That this is specific induction is shown first by the fact that the male that produces either sons that do not distort (if the male is crossed to compound X females) or daughters that produce sons, half of which do not distort (if the male was crossed to free X females), himself exhibits the phenomenon of segregation-distortion. Secondly since the *SD* line is kept by backcrossing heterozygous *SD* males to the same standard tester stock generation after generation, the X chromosomes received by a male from his mother are a sample of precisely the same X chromosomes that are delivered by a heterozygous *SD* female when such a cross is made. Thus if this were not specific induction of a modifier on the X chromosome, it would be expected that males that do not distort would be produced as frequently as the sons of *SD* males as of the sons of *SD* females which is not the case.

This phenomenon of induction on the X chromosome occurs apparently in all *SD* lines. However, the response of *SD* to the specifically modified X differs from line to line. In particular, it has been found that there are modifiers that cause *SD* to be relatively nonreactive to the specifically modified X. One such modifier is the stabilizer of *SD*, *St(SD)*, that has been previously shown to reduce male to male variability in segregation ratios in *SD* lines.

The exact nature of the conditioned state is not understood. It is known that the state is defined by the X chromosome having been changed in an *SD* male. Apparently, *SD* males will transmit either all induced X's or a small fraction of induced X's or, possibly, no induced X's. How such males differ from one another is not at present understood.

Various other properties of the phenomenon of conditional segregation-distortion and some of the evolutionary possibilities of this phenomenon are discussed.

Finally, the phenomenon of conditional segregation-distortion exhibits two unique properties: (1) that the *SD* element induces a change on the X chromo-

some which in turn modifies the action of *SD*; and (2) this specific induction appears to be stable and comes about presumably without physical contact between *SD* which is on the second chromosome and the induced site on the X so that the usual copy-choice interpretation of conversion phenomena seems rather unlikely.

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