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# Extrachromosomal control of mutability in *Drosophila melanogaster*

**(hybrid dysgenesis/cytoplasmic heredity/insertion mutations/unstable genes)**

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**ABSTRACT** **Hybrid dysgenesis is a syndrome of germ-line aberrations including, e.g., sterility and mutation, found in certain interstrain hybrids of *Drosophila melanogaster*. Previous studies of sterility have shown that elements responsible for dysgenesis may reside on all major chromosomes, but that their dysgenesis-causing ability is controlled by an unknown extrachromosomal factor. Dysgenic hybrids also give rise to unstable visible mutations thought to be DNA insertions at certain sensitive loci. One such unstable allele at the *singed bristle* locus, designated *sn*$^{w}$, was found to mutate at extraordinary rates exceeding 50%. This instability was shown to be under the same extrachromosomal control as hybrid dysgenesis itself. That is, the mutability of *sn*$^{w}$ was reversibly suppressed when placed in the background cytotype known to prevent sterility and other characteristics of hybrid dysgenesis. These results suggest that *sn*$^{w}$ may represent an insertion at the *singed* locus of a hypothetical gene responsible for hybrid dysgenesis.**

Several independent lines of research have recently led to the discovery of a remarkable set of chromosome–cytoplasm interactions in *Drosophila melanogaster* (1–3). These interactions, known as hybrid dysgenesis, result in profound germ-line aberrations in certain interstrain hybrids. The dysgenic traits include temperature-sensitive sterility in both sexes, high frequencies of mutations and chromosome rearrangements, male recombination, and distortion of transmission ratios and sex ratios among progeny. Hybrid dysgenesis can be recognized by its reciprocal cross effect. That is, most strains can be classified as either P (paternally contributing) or M (maternally contributing) such that hybrids from crosses of the form M♀ × P♂ show dysgenic traits that are reduced or absent in the reciprocal hybrids and never seen in nonhybrids.

Using female sterility as an indicator of hybrid dysgenesis, studies have shown that the dysgenic state is caused by chromosomal factors carried by the P strains (typically strains recently taken from nature) which interact with extrachromosomal factors (4). The chromosomal component may be present on all three major chromosomes of P strains. For example, the X, second, and third chromosomes of $\pi_2$, an inbred wild strain, cause sterility among daughters of M females with probabilities 0.4, 0.6, and 0.1, respectively. These chromosomes act approximately independently in combinations and may cause sterility regardless of which parent they came from, provided the appropriate extrachromosomal component is present. Individuals possessing this extrachromosomal dysgenesis-inducing component are said to be of the "M cytotype"; those lacking it are of the "P cytotype." Therefore, the $\pi_2$ chromosomes are quite harmless within the $\pi_2$ strain itself, which has the P cytotype.

The M cytotype, which is common only in laboratory strains but probably occurs occasionally in nature (W. R. Engels and C. R. Preston, unpublished data), can be thought of as either the absence of an extrachromosomal suppressor of the dysgenic state or the presence of a necessary component. Although experiments have not been able to distinguish between these two possibilities, they have shown that the cytotype is a self-reproducing property transmitted through the female line for at least three generations. Ultimately, however, after enough generations, the cytoplasmic state is determined by the chromosomes. Furthermore, the chromosomal determinants of cytotype are polygenic and, like the P property, present on all three major chromosomes. Thus, the P chromosomes of the $\pi_2$ strain, which can cause sterility, can also prevent it within the strain by bringing about the P cytotype.

The symbols P and M refer to one of two distinct, perhaps related, systems of hybrid dysgenesis (5). The other, known as the I-R system (I is paternally contributing and R is maternally contributing), is similar in most respects to the P-M system, but can be distinguished from it by differences in the physiological details of the sterility it induces and by the fact that in the I-R system dysgenic effects are apparently limited to females, whereas both sexes are affected by P-M interactions.

The presence of the P property and of the cytotypic determinants at multiple chromosomal locations suggests that mobile DNA sequences analogus to insertion elements, plasmids, and episomes in prokaryotes may be involved. (However, see ref. 6 for an alternative explanation.) This hypothesis is strengthened by two other lines of evidence. First, the I-R system displays a phenomenon called "chromosomal contamination" (7, 8) by which R chromosomes can be transformed into the I type. This transformation occurs only in the dysgenic state—that is, in females with R cytoplasm and at least one I chromosome. Presumably, this event represents the insertion of I "factors" into R chromosomes.

The other line of evidence concerns the putative X-chromosome insertion mutations produced by dysgenic males (9, 10), particularly at the *singed bristle* (*sn*) locus. These alleles revert or mutate to different alleles of *sn* at frequencies near $10^{-3}$. Such events are interpreted as either excision or some other alteration of the inserted sequence. In this paper, I describe an allele designated *sn*$^{w}$ (*weak singed*) produced on the $\pi_2$ X chromosome by a dysgenic hybrid male. This allele is highly unstable, mutating at rates even greater than 50%. Furthermore, this instability is under extrachromosomal control, with *sn*$^{w}$ losing its mutability when in the P cytoplasm. Thus, the extreme instability of *sn*$^{w}$ appears to be directly related to the dysgenic state itself. I also show that the *de novo* production of visible X-chromosome mutations, including *singed*, obeys the reciprocal cross rule and is therefore under extrachromosomal control.

## MATERIALS AND METHODS

**Stocks and Crosses.** A standard technique for studying visible mutations on the X chromosome involves the use of compound-X strains in which females carry a normal Y chromosome plus two X chromosomes joined to a single centromere.

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When these females are mated to normal males, the free X chromosome is passed intact from father to son and can be observed in the hemizygous state through successive generations. Males receive one set of autosomes, a Y chromosome, and cytoplasm from their mothers.

Two M strains carrying the compound-X known as *C(1) DX,yf* with the mutations *yellow body* and *forked bristles* (11) were used. One, *C(1)DX,yf;CS* has a genetic background derived from the common laboratory stock, *Canton S*. The other, *C(1)DX,yf;cn bw*, has the eye color markers *cinnabar* (*cn*) and *brown* (*bw*) on chromosome 2 separated by about 50 map units. The free X in this stock carries a temperature-sensitive lethal mutation from M. Simmons that facilitates virgin collecting, but is not involved in these experiments.

The P strain known as $\pi_2$ (12) was derived from a Madison natural population in 1975 and inbred for many generations. To obtain a P strain carrying the compound X chromosome, a female from the *C(1)DX,yf;CS* stock was mated to a $\pi_2$ male and her offspring were backcrossed to $\pi_2$ for 10 more generations to ensure that essentially all of the genetic background is of $\pi_2$ origin. Tests of sterility have shown that females of this stock, designated *C(1)DX,yf;*$\pi_2$, are of the P cytotype.

Unless otherwise stated, all flies were grown at 25°C on standard cornmeal/molasses medium, and progeny emerging until the sixteenth day were scored.

**Statistical Methods.** All measurements of mutation rate, transmission frequency, etc. were obtained as averages over many families (progeny of individual males). Standard goodness-of-fit or likelihood ratio procedures were used wherever possible to test for nonbinomial or "clustered" distributions. However, for those cases where the expected numbers were small enough to render these methods unreliable, the *P* value was calculated by a Monte Carlo technique modified from that of Lewontin and Felsenstein (13). Where no clustering is evident, frequencies appear as the average weighted by family size with its binomial standard error. For clustered distributions, unbiased procedures (14) were used to avoid overestimating the precision. To test for differences between the two reciprocal crosses, either Fisher's exact test or the rank-sum test was used depending on whether or not clustering was evident. However, when neither test was appropriate because of the presence of clusters along with a large proportion of ties, a "conservative" test was used in which all but one member of each cluster in the dysgenic class but not the reciprocal class was discarded before proceeding with Fisher's exact test.

## RESULTS

### Origin and instability of $sn^w$

Dysgenic hybrid males from the cross *C(1)DX,yf;cn bw*♀ × $\pi_2$♂ were backcrossed to *C(1)DX,yf;cn bw* females in an experiment originally designed to detect male recombination and X-Y translocations. Confirming previous work (9), many visible mutations, particularly at the *singed* and *Beadex* loci (11), appeared among the male progeny. To date, 52 independent *sn* mutations have been detected with a continuum of phenotypes ranging from extreme types, with all bristles twisted and abnormal thoracic hairs, to mild ones, with slightly waved bristles or hooked tips. Most have been tested for complementation with a known *sn* mutant, and all were allelic. Further confirmation of previous reports was provided by the observation that many of these alleles were unstable, producing exceptional progeny at frequencies between $10^{-3}$ and $10^{-2}$.

However, one phenotypically intermediate mutant, designated $sn^w$, displayed instability of an entirely different order of magnitude, closer to the "supermutable" alleles studied by Golubovsky (15). When $sn^w$ males were mated to *C(1) DX,yf;CS* or *C(1)DX,yf;cn bw* females, three discrete classes of sons appeared in more or less equal frequencies. These are $sn^w$, $sn^e$ (extreme singed), and $sn^+$ (normal bristles). This mutability contrasts with the induction of new mutations by its much greater frequencies and by the discrete rather than continuous distribution of phenotypes produced. The alleles, $sn^e$ and $sn^+$, were also observed to mutate, but at frequencies much lower than $sn^w$.

This behavior, which was observed through 17 generations of backcrossing to *C(1)DX,yf;CS* or *C(1)DX,yf;cn bw* females, is exemplified in the following experiment: From a single $sn^w$ male mated to *C(1)DX,yf;cn bw* females, 34 $sn^w$, 18 $sn^e$, and 36 $sn^+$ sons were obtained. Each was then mated to compound-X females to produce the three classes of sons, as shown in Table 1. The average frequencies of the various kinds of mutational changes in this experiment (top half of Table 2) were typical.

Not included in Table 2 were 4 of the 88 parental males that appeared to be exceptional. Three of these (families 23, 44, and 78 in Table 1) were classified as $sn^w$, $sn^e$, and $sn^+$, respectively,

Table 1. Instability of $sn^w$, $sn^e$, and $sn^+$ alleles

| $sn^w$ father | | | | $sn^e$ father | | | | $sn^+$ father | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ID* | $sn^w$ | $sn^e$ | $sn^+$ | ID | $sn^w$ | $sn^e$ | $sn^+$ | ID | $sn^w$ | $sn^e$ | $sn^+$ |
| 1 | 12 | 8 | 36 | 35 | 0 | 45 | 2 | 53 | 0 | 0 | 84 |
| 2 | 18 | 23 | 33 | 36 | 0 | 64 | 1 | 54 | 0 | 1 | 85 |
| 3 | 32 | 34 | 37 | 37 | 0 | 61 | 3 | 55 | 0 | 0 | 82 |
| 4 | 38 | 10 | 8 | 38 | 0 | 58 | 4 | 56 | 0 | 0 | 89 |
| 5 | 58 | 14 | 21 | 39 | 0 | 49 | 1 | 57 | 0 | 0 | 58 |
| 6 | 41 | 22 | 8 | 40 | 0 | 70 | 4 | 58 | 0 | 1 | 85 |
| 7 | 17 | 55 | 14 | 41 | 2 | 57 | 1 | 59 | 1 | 7 | 103 |
| 8 | 6 | 28 | 45 | 42 | 0 | 76 | 4 | 60 | 0 | 0 | 73 |
| 9 | 13 | 14 | 31 | 43 | 0 | 62 | 9 | 61 | 0 | 0 | 92 |
| 10 | 23 | 7 | 22 | 44† | 3 | 83 | 48 | 62 | 0 | 0 | 129 |
| 11 | 54 | 15 | 29 | 45 | 0 | 66 | 3 | 63 | 0 | 3 | 95 |
| 12 | 33 | 11 | 20 | 46 | 0 | 73 | 6 | 64 | 0 | 1 | 103 |
| 13 | 18 | 26 | 37 | 47 | 0 | 72 | 4 | 65 | 0 | 0 | 105 |
| 14† | 90 | 0 | 0 | 48 | 0 | 72 | 3 | 66 | 0 | 0 | 107 |
| 15 | 28 | 28 | 46 | 49 | 0 | 61 | 5 | 67 | 1 | 0 | 93 |
| 16 | 53 | 12 | 14 | 50 | 2 | 118 | 5 | 68 | 3 | 0 | 99 |
| 17 | 26 | 13 | 35 | 51 | 1 | 101 | 5 | 69 | 0 | 0 | 116 |
| 18 | 9 | 35 | 29 | 52 | 0 | 87 | 4 | 70 | 1 | 0 | 89 |
| 19 | 23 | 3 | 36 | | | | | 71 | 1 | 0 | 99 |
| 20 | 9 | 17 | 56 | | | | | 72 | 0 | 1 | 97 |
| 21 | 52 | 44 | 26 | | | | | 73 | 0 | 0 | 81 |
| 22 | 62 | 18 | 29 | | | | | 74 | 0 | 2 | 98 |
| 23† | 0 | 0 | 90 | | | | | 75 | 0 | 0 | 77 |
| 24 | 22 | 15 | 32 | | | | | 76 | 0 | 0 | 92 |
| 25 | 29 | 46 | 23 | | | | | 77 | 0 | 0 | 123 |
| 26 | 45 | 23 | 20 | | | | | 78† | 65 | 34 | 24 |
| 27 | 36 | 29 | 35 | | | | | 79 | 0 | 0 | 138 |
| 28 | 32 | 2 | 14 | | | | | 80 | 0 | 0 | 77 |
| 29 | 48 | 41 | 22 | | | | | 81 | 0 | 0 | 117 |
| 30 | 41 | 27 | 63 | | | | | 82 | 0 | 2 | 111 |
| 31 | 50 | 28 | 52 | | | | | 83 | 0 | 0 | 128 |
| 32 | 37 | 19 | 44 | | | | | 84 | 0 | 0 | 68 |
| 33 | 38 | 40 | 48 | | | | | 85 | 0 | 0 | 112 |
| 34 | 57 | 25 | 53 | | | | | 86 | 0 | 0 | 130 |
| | | | | | | | | 87 | 0 | 0 | 104 |
| | | | | | | | | 88 | 0 | 0 | 144 |

Distribution of three types of sons from crosses between *C(1)DX,yf* females and single males ($sn^w$ or $sn^e$ or $sn^+$). All 88 parental males came from one mating of *C(1)DX,yf;cn bw*♀♀ × $sn^w$♂.

* Identification number of parent.

† Parental male considered to be exceptional (see text).

Table 2. Frequencies of the three types of chromosomes produced by M and P cytotype males (% ±SD)

| Parent | Offspring | | | Sample |
|---|---|---|---|---|
| | $sn^w$ | $sn^e$ | $sn^+$ | size |
| M cytotype | | | | |
| $sn^w$ | 37.7 ± 2.6 | 26.0 ± 2.3 | 36.2 ± 2.2 | 2810 |
| $sn^e$ | 0.4 ± 0.2 | 94.5 ± 0.6 | 5.1 ± 0.6 | 1261 |
| $sn^+$ | 0.2 ± 0.1 | 0.5 ± 0.2 | 99.3 ± 0.3 | 3508 |
| P cytotype | | | | |
| $sn^w$ | 99.9 ± 0.06 | 0.1 ± 0.06 | 0 | 2086 |
| $sn^e$ | 0 | 100 | 0 | 659 |
| $sn^+$ | 0 | 0 | 100 | 1087 |

Results of matings between *C(1)DX,yf;cn bw* females and single males of the indicated cytotype and *singed* allele.

on the basis of phenotype, but produced progeny typical of one of the other classes. The somatic cells were apparently different from the germ line due to changes during development. The fourth exception (family 14 of Table 1) was phenotypically indistinguishable from $sn^w$, but failed to display instability. Subsequent tests showed that this loss of instability was permanent.

As Table 1 shows, there were eight families (excluding those considered exceptions) in which either a $sn^e$ or a $sn^+$ father produced one or more sons phenotypically similar to $sn^w$. These were test-crossed to determine whether the instability characteristic of the original $sn^w$ allele had also returned with the phenotype. High levels of mutability appeared in only three of them (families 41, 51, and 71 in Table 1), but further tests are needed to determine whether they are distinguishable from the original $sn^w$.

Of the 8027 offspring in Table 1, 11 were somatic mosaics in which one or more bristles differed from the rest. Two of these were sterile, and the rest, when mated to compound-X females, produced a single class of sons resembling one of the two bristle types.

Clustering was detected among progeny of the nonexceptional $sn^w$ and $sn^+$ males ($P < 0.001$) but not of the $sn^e$ males ($P = 0.83$), indicating that premeiotic events are involved. Besides varying from one $sn^w$ male to the next, the mutation frequencies can also change during the lifetime of individual males. This point was demonstrated by providing each of four newly emerged $sn^w$ males with a fresh harem of *C(1)DX,yf;cn bw* females every 48 hr for as long as they remained fertile, then scoring all progeny produced by each harem. Tests for heterogeneity through time were positive ($P \leq 0.05$) in three of the four males, but there was no overall tendency for these frequencies to either increase or decrease with age. This result could be explained by premeiotic mutations or by variation among stem cells.

## Cytoplasmic suppression of $sn^w$ instability

Is the extreme instability of $sn^w$ an intrinsic property of the gene or does it, like hybrid dysgenesis, require the M cytotype? Under the latter hypothesis we would expect to see suppression of the instability among $sn^w$ sons of P-cytotype females. In fact, dramatic suppression occurred under exactly those circumstances, as shown by the following experiments.

Females from the *C(1)DX,yf;*$\pi_2$ stock were mated to $sn^w$ males (families 1–4 in Table 1) to produce the usual three classes of sons whose cytotype should now be P. Each of 21 $sn^w$ sons was then mated to *C(1)DX,yf;cn bw*, and the progeny were scored. As shown in the bottom half of Table 2, the instability was essentially gone, with virtually all their male progeny being $sn^w$. Next, note that these males now possess the M cytotype inherited from their mothers and are therefore expected to display the same instability as their grandfathers. Indeed, when these $sn^w$ males were test-crossed, the instability was seen to have returned in full, with each of 22 males tested producing all three classes of sons. The average mutation rates to $sn^e$ and $sn^+$ were 30% ± 6 and 26% ± 5, respectively, in good agreement with the expected rates in Table 2 (top).

The entire cycle was then repeated, this time by doubly mating some of the now-unstable $sn^w$ males to *C(1)DX,yf;*$\pi_2$ and *C(1)DX,yf;cn bw* females. As expected, the sons of *C(1) DX,yf;cn bw* displayed the usual instability, whereas their half siblings with the P cytotype transmitted the $sn^w$ allele faithfully. In all cases, the mutation frequencies as a function of cytotype were consistent with those given in Table 2. Finally, instability was returned to the restabilized $sn^w$ chromosomes by placing them back into M cytotype. These results are all consistent with the hypothesis of extrachromosomal control and are not explicable in terms of autosomal Mendelian suppressors.

It is also of interest that the lower-order instability of the $sn^e$ and $sn^+$ alleles appears to be subject to the same extrachromosomal suppression (Table 2).

## Extrachromosomal control of *de novo* mutation induction

Previous results suggest that *de novo* induction of *singed* and other visible mutations is part of the hybrid dysgenesis syndrome (9, 16) and is suppressed in the offspring of females likely to be of the P cytotype (M. Green, personal communication). The following experiment clarifies this point and demonstrates that the suppression is indeed extrachromosomal by comparing hybrid males from the two reciprocal crosses between *C(1) DX,yf;cn bw* and $\pi_2$. Forty males from each cross were grown at 21°C, then individually mated in coded vials to *C(1) DX,yf;cn bw* females, and the progeny were scored. It is important to note that the two classes of hybrid males have identical chromosomal complements, including the sex chromosomes, so that any differences in their mutability, etc. must be attributable to extrachromosomal effects.

Among the progeny were 10 *sn* and 14 *Beadex* (*Bx*) males, representing at least 17 separate mutational events. (Several other visible mutations were also recovered, but only *sn* and *Bx* were used in the quantitative analysis.) The mutation frequencies in the two reciprocal classes (Table 3) differed significantly in the expected direction ($P < 0.05$). For comparison, the same progeny were also scored for (*i*) X-Y translocations detected as non-*yellow forked* ($y^+f$) females, (*ii*) male recombination between *cn* and *bw*, (*iii*) transmission ratio distortion against the $\pi_2$ second chromosome, and (*iv*) sex ratio distortion against males. Each of these traits is associated with hybrid dysgenesis (17) and, as shown in Table 3, each displayed reciprocal cross effects significant at $P < 0.05$ in the expected direction.

As an additional control, 40 nonhybrid $\pi_2$ males were tested in the same way as the two classes of hybrids. No *sn* or *Bx* mutations were detected (Table 3). Sex ratio distortion and X-Y translocations were also found to be less frequent in the nonhybrids than in either class of hybrids, as would be expected. The differences between the nonhybrids and the P-cytotype hybrids (all three comparisons were significant at $P < 0.05$) are presumably due to partial changes in the cytotype of the latter brought about by the M chromosomes during the development of the fly. This effect is not seen when hybrid dysgenesis is measured by sterility tests, which depend on interactions very early in development (4, 12).

Table 3. Several measures of dysgenesis in hybrids and nonhybrids (±SD)

| Initial cross | *C(1)DX,yf;cn bw*♀ × $\pi_2$♂ | $\pi_2$♀ × *C(1)DX,yf;cn bw*♂ | $\pi_2 \times \pi_2$ |
|---|---|---|---|
| *sn* & *Bx* (♂♂), % | 0.60 ± 0.20* | 0.14 ± 0.05 | 0 |
| $y^+f$ (♀♀), % | 0.45 ± 0.13 | 0.18 ± 0.07 | 0 |
| Male recombination, % | 0.54 ± 0.10 | 0.22 ± 0.05 | — |
| $\frac{(++)}{(++) \& (cn\ bw)}$, % | 45.4 ± 0.9* | 49.4 ± 0.4 | — |
| Males, % | 49.9 ± 1.3* | 56.2 ± 0.4† | 59.9 ± 1.1* |
| Sample size | 5728 | 9042 | 9276 |

* Clustering detected at $P < 0.01$.
† Clustering detected at $P < 0.05$.

## DISCUSSION

The many aberrant characteristics known to be associated with hybrid dysgenesis all appear to share three common features: (*i*) they are suppressed in the P cytotype, (*ii*) they are primarily limited to the germ line, and (*iii*) they involve premeiotic events, as indicated by either clustering or temperature-sensitive periods early in development. The present results show that the extreme mutability of $sn^w$ displays all three of these features. First, and most important, this instability vanished in males whose mothers were of the P cytotype but was restored in full the next generation when returned to the M cytotype. This cycle can be repeated, apparently indefinitely, indicating that the instability of $sn^w$ is not an intrinsic property of the gene but is the result of interaction with extrachromosomal components of the M cytotype. Second, it can be seen that the mutability of $sn^w$ is vastly greater in the germ line than in somatic cells by noting that virtually all $sn^w$ males of the M cytotype are gonadal mosaics possessing three distinct cell types in roughly equal proportions among germ cells, yet very few somatic mosaics were seen. Finally, the clustered distributions of mutation frequencies among $sn^w$ males and within individual males observed over time indicate the importance of premeiotic events. Therefore, we may consider not only the induction of new unstable mutations, but the instability itself to be part of the hybrid dysgenesis syndrome.

It is quite possible that all previously reported cases of instability at the *singed* locus (10, 15, 18, 19) are under the same sort of extrachromosomal control as $sn^w$ but that it has not been observed because of the exclusive use of laboratory stock females likely to be M cytotype. However, the clustered occurrence of $sn^w$ mutability seems also to apply to Golubovsky's supermutable $sn^{11}$; my analysis of published data reveals pronounced clustering significant at $P < 0.001$. Furthermore, germ-line specificity also seems to be a general feature of unstable *singed* alleles. Although the frequencies of somatic mosaicism observed in some of Golubovsky's crosses (15) are somewhat higher than those reported here, germ-line mosaics are still much more common than somatic ones.

Berg (20, 21) observed that natural populations sometimes undergo marked changes in mutability of *singed* and other loci. One possibility suggested by the present results is that periods of high mutability represent times when P chromosomes more frequently find themselves in M-cytotype flies. For example, changes in population structure might allow females of a previously isolated M subpopulation to mate with surrounding P males and produce mutation-prone dysgenic hybrids.

If, as suggested by Green (9), the unstable *sn* alleles are insertion mutations, then the parallel with chromosomal contamination in the I-R system immediately suggests itself. As mentioned earlier, chromosomal contamination is thought to be an insertion event that takes place only in R cytoplasm. The analogy between this phenomenon and $sn^w$ mutability would imply that the inserted sequence at the *singed* locus is actually the P property itself. It would also imply that molecular events similar to those occurring at the $sn^w$ locus are quite common throughout the genome of dysgenic hybrids, but are not normally observed because they are not associated with phenotypic changes. However, chromosomal contamination differs from $sn^w$ instability in two ways: it occurs only in females and it leaves the donor chromosome unchanged (22). Still, these discrepancies might merely reflect superficial differences between the P-M and I-R systems, and the analogy between the two phenomena remains a useful one.

It is possible to think of hybrid dysgenesis as a family of mobile genes ("P genes") with similar DNA sequences scattered throughout the genomes of the P strains. Other dispersed families of repeated genes in *Drosophila* have already been discovered by molecular methods (23). These genes may become activated and perhaps mobilized in certain cells, particularly germ cells, that possess the M cytotype. The $sn^w$ allele might then represent one such gene, which, by virtue of its position, yields various observable effects on bristles when it undergoes its usual extrachromosomally controlled changes of state.

What is the nature of this extrachromosomal control? The simplest hypothesis is that of a protein repressor produced by the P gene itself. The system would then be similar to the control of the lytic cycle in the temperate bacteriophage λ, and the reciprocal cross effect would be equivalent to zygotic induction. However, one cannot account for the semi-autonomous nature of the transmission of cytotype in terms of simple molecular repressors. Such repressors would have to be self-replicating. If, indeed, $sn^w$ carries a copy of the hypothetical P gene, further study of its mutability promises to be valuable in answering questions such as these.

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