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P-element-induced mutation and quantitative variation in *Drosophila melanogaster*: lack of enhanced response to selection in lines derived from dysgenic crosses.

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Summary

Dysgenic and non-dysgenic base populations were made by reciprocal crossing of Harwich (P) and Canton-S (M) strains. From each cross, two up and two down selection lines were established, with selection on abdominal bristle number for ten generations. The intensity of selection was 10 out of 50 individuals from each sex. Mean bristle number, phenotypic variation and heritabilities were compared between dysgenic and non-dysgenic populations under selection. Except for an anomalous non-dysgenic downline in which a mutation of large effect occurred, all lines showed similar responses to selection. These results contrast with the results reported by Mackay (1984, 1985) in which substantial increases were obtained for response to selection, phenotypic variation and heritability in the dysgenic compared to non-dysgenic lines. There are some indications that the higher response in our aberrant non-dysgenic downline is the result of transposition. Possible explanations for the occurrence of transposition and dysgenesis in the lines derived from non-dysgenic crosses are discussed.

1. Introduction

Induction of quantitative genetic variation is of interest to investigators generally for two major reasons. First, the new genetic variation generated by induced mutations may be used in directional selection to avoid an early plateau. Thus, it is of direct relevance to plant and animal breeding. Second, it may help in finding out more about the nature of variation in quantitative traits, and their relationship to natural selection and evolution.

Clayton & Robertson (1955), Kitagawa (1967) and Hollingdale & Barker (1971) showed that radiation increased mutation rate and hence response to selection in inbred lines of *Drosophila*. However it is considered (Enfield, 1986) that radiation is likely to produce a class of mutations skewed in the unfavourable direction, so radiation treatments are likely to provide only limited information about the contribution of naturally occurring mutations to response to selection.

Until McClintock (1956) provided evidence for mobile DNA within the genome of maize, the possibility of endogenous mutagens within the genome had not been considered. However, insertion mutations caused by transposable elements are now widely known in many organisms, from bacteria and yeast to maize, *Drosophila* and mice (see review articles in Shapiro, 1983). Indeed, one of the very first mutations discovered in *Drosophila*, namely that for white eye colour, is now known to be an insertion mutation (Rubin *et al.* 1982).

Transposable elements are very common in *Drosophila melanogaster* and constitute about 10–20% of the genome (Engels, 1983). They form many families, each of which has its own peculiar structure and behaviour (reviewed by Rubin, 1983). So far, two distinctive families of transposable elements have been discovered in *D. melanogaster* in which a phenomenon of correlated aberrant traits called 'hybrid dysgenesis' is induced in the germline of the hybrids, but only in one direction (reviewed by Sved, 1979; Bregliano & Kidwell, 1983). In the P–M (for paternal and maternal) system, hybrid dysgenesis occurs when a P-strain male is crossed to an M-strain female (Kidwell *et al.* 1977). One of the so called 'dysgenic' traits is elevated rates of mutation caused by accelerated transposition of P elements. The major mechanism of mutation is insertion, but complete or incomplete excision, and chromosomal rearrangements

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and deletions also occur (Engels, 1983). Multiple copies of P elements, which are not identical in size, are present in the P strains. A complete element is 2·9 kbp-long and is similar to the smaller ones in having 31 bp inverse repeats at the termini (O'Hare & Rubin, 1983). A complete P element codes for an enzyme (transposase) which is necessary for transposition (O'Hare & Rubin, 1983; Simmons & Bucholz, 1985). Many of the smaller (incomplete) P elements lack this gene, but they can transpose in the presence of transposase from a complete P element.

The first reports of induction of quantitative genetic variation by means of transposable element-induced mutation came from Mackay (1984, 1985). Using the P–M hybrid dysgenesis system, she was able to obtain approximately a doubling in response to selection in the progeny of dysgenic (M♀ × P♂) compared to non-dysgenic (P♀ × M♂) hybrids. This increase in response was on average about seven times larger than the increase obtained by Clayton & Robertson (1955, 1964), and Hollingdale & Barker (1971) for the same character using radiation treatments.

These results clearly indicate how powerful the mutagenic aspects of hybrid dysgenesis might be in generating new genetic variation for metric traits.

However, other attempts to generate enhanced response to selection in lines derived from dysgenic crosses have not been successful. For example, Morton & Hall (1985) obtained a higher response to selection for Malathion resistance in their non-dysgenic lines, using the same strains of flies as Mackay, but a different crossing procedure. In a separate experiment, Shi (1986) used a 'single' MR element on chromosome 2 and a complex crossing programme involving balancer chromosomes, to generate dysgenic crosses and non-dysgenic controls in each generation. Selection for sternopleural bristle number failed to detect any significant difference between dysgenics and non-dysgenics.

This paper reports results of an experiment carried out as an attempt to clarify further the differences between lines established from dysgenic and non-dysgenic hybrids in respect to hybrid dysgenesis-induced mutation for abdominal bristle number in *D. melanogaster*. With one exception, the experimental design and protocol are identical to those of Mackay (1984).

2. Materials and methods

(i) Drosophila *strains*

Harwich: a strong P strain, originating from Dr M. G. Kidwell.

Canton-S: a long-established laboratory M strain.

sn^w (M): an M cytotype stock which has only two defective P elements, inserted in the singed locus (Engels, 1984).

$y^2sn^3ras^2v$: a multiply marked *X*-chromosome stock, M in the P–M system. For description of the genes see Lindsley & Grell (1968).

C(1)DX yf/sn^w(ii) Π2: an attached-*X* chromosome carrying the *sn^w* gene. This stock has the Π2 genetic background and is a strong P stock (Engels, 1984).

(ii) *P-factor activity tests*

(*a*) *sn^w test*. P-factor activity of the Harwich stock was assessed by crossing 10 Harwich males with 10 *sn^w* (M) females (Engels, 1984), and the destabilization rate of the *sn^w* gene was determined by crossing 10 replicates of two F_1 male progeny to attached-*X* chromosome females and estimating the frequency of *sn^+* and *sn^e* phenotypes among male offspring.

(*b*) *Direct mutation test*. Ten sets of one or two hybrid males from crosses of Canton-S and Harwich were crossed to 10 *$y^2sn^3ras^2v$* females and transferred twice to new bottles at 4-day intervals. Daughters were then screened for *sn^e* bristle phenotype (Green, 1984). This is a controlled test of the ability of a P stock (Harwich) to induce high frequencies of visible mutations in dysgenic crosses with an M stock (Canton-S), but not in the reciprocal crosses.

(iii) *Cytotype tests*

(*a*) *sn^w test*. Ten Canton-S females were crossed to 10 *sn^w* (P) males, and 10 replicates of two F_1 females were test-crossed to *$y^2sn^3ras^2v$* males. The female and male progeny were then screened for *sn^e* mutants. This test was used to verify the cytotype of the Canton-S strain. The same test was also performed on females from selection lines at G5 and G10.

(*b*) *Ovarian dysgenesis test*. Dysgenic and non-dysgenic crosses were verified by reciprocal crossing of Harwich and Canton-S at 29 °C, and by testing fertility of the individual female progeny as described by Engels (1979*a*). Similarly, cytotype of the flies from selection lines was also determined at G10. In this case females from the selection lines were crossed to P males (Harwich) at 29 °C and daughters were tested as above.

(iv) *Estimation of mutation rates*

Mutation rates and their standard errors were estimated as described by Engels (1979*b*). Wilcoxon–Mann–Whitney's Rank Sum Test (Steel & Torrie, 1981), based on 10–20 replicates per treatment, was used to test significance of temperature effects on mutation rates.

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(v) In situ *hybridization preparations*

Salivary glands were extracted from third instar larvae of Harwich and Canton-S, which had been grown in uncrowded conditions at 18 °C. Slides were made in a standard manner as described by Pardue (1986). Chromosomes were hybridized, using pπ 25·1 labelled with ^3H by nick translation as probe (O'Hare & Rubin, 1983), according to techniques described by Pardue (1986).

(vi) *Crossing and selection programme*

Reciprocal dysgenic (10M♀♀ × 10P♂♂) and non-dysgenic (10P♀♀ × 10M♂♂) crosses were performed between Harwich and Canton-S. Selection was commenced in the F_1 (G0). The number of bristles on the last abdominal segment was scored on 50 randomly chosen individuals of each sex, selecting the 10 highest and the 10 lowest scoring males and females to establish up and down lines. Similarly, in each subsequent generation, 50 females and 50 males were scored in each line, and the 10 highest (from the uplines) and the 10 lowest (from the downlines) ranking flies from each sex were selected to be the parents of the next generation. Two sets of the above crosses were made at the same time so as to establish two concurrent replicate selection lines in each direction. After generation 10, selection was relaxed for 20 subsequent generations. During the relaxation of selection, at generations 20 and 30, the same character was scored on 50 females and 50 males randomly chosen from each line, in order to determine whether the genes providing response were associated with adverse fitness effects.

(vii) *Culture medium and temperature*

Flies were reared on cornmeal–treacle–agar–yeast medium cultures seeded with live yeast, in $\frac{1}{4}$ pint bottles. 30 ml vials were used for some tests. Temperature was kept in the range of 23–24 °C during the experiment. At this temperature, not only was gonadal dysgenesis insignificant, but more transposition of the P elements was expected than at lower temperatures (Engels, 1983).

3. Results

Results of all tests carried out for verification of the strains, and checks on the base populations and selection lines are summarized in Table 1. The main points which can be drawn from this table are: (1) The Canton-S and Harwich strains behaved consistently as M and P strains respectively. (2) The base populations of the selection lines, i.e. G0 hybrids, were in their proper state with respect to dysgenic traits. (3) In the dysgenic lines, the cytotype had changed substantially by generation 5, and dysgenesis had virtually ceased by generation 10, as shown by the sn^w and ovarian dysgenesis tests of cytotype.

In situ hybridization results are shown in Fig. 1. The only site of hybridization for Canton-S is at 17C. Since pπ 25·1 contains a complete P element and some flanking *Drosophila* DNA from the 17C region, this hybridization is to be expected. No other sites were detected. In contrast, at least 20–22 sites of strong hybridization are present on Harwich chromosomes, confirming multiple copies of P elements in our sample of this strain.

The mean response to selection of dysgenic and non-dysgenic lines for abdominal bristle number over

Table 1. *P-factor activity and cytotype of parental stocks, and cytotype of selection lines at G0, G5 and G10*[a]. *The total numbers of flies scored are shown in parentheses*

	P-factor activity		Cytotype	
Populations	sn^w test (% mutation)	Mutation test (% mutation)	sn^w test (% mutation)	Ovarian dysgenesis test (% infertile females)
Parental stocks				
Canton-S[b]	0·66 ± 0·66 (553)	0 (4051)	24·12 ± 2·94 (1758)	99 ± 1 (96)
Harwich[c]	50·10 ± 6·72 (330)	0·08 ± 0·04 (9427)	0·16 ± 0·17 (2177)	—
Selection lines (pooled across 4 replicates)				
G0 (M♀ × P♂)	—	—	16·44 ± 6·24 (1441)	—
G0 (P♀ × M♂)	—	—	0·96 ± 0·45 (3592)	—
G5 (M♀ × P♂)	—	—	3·40 ± 1·20 (5340)	—
G5 (P♀ × M♂)	—	—	1·48 ± 0·84 (3104)	—
G10 (M♀ × P♂)	—	—	0·28 ± 0·23 (4680)	0 (384)
G10 (P♀ × M♂)	—	—	1·04 ± 0·42 (5089)	0 (384)

[a] The methods used for assessing each population are fully described in the Materials and methods section.
[b] Serves as control for P-factor activity tests.
[c] Serves as control for cytotype test.

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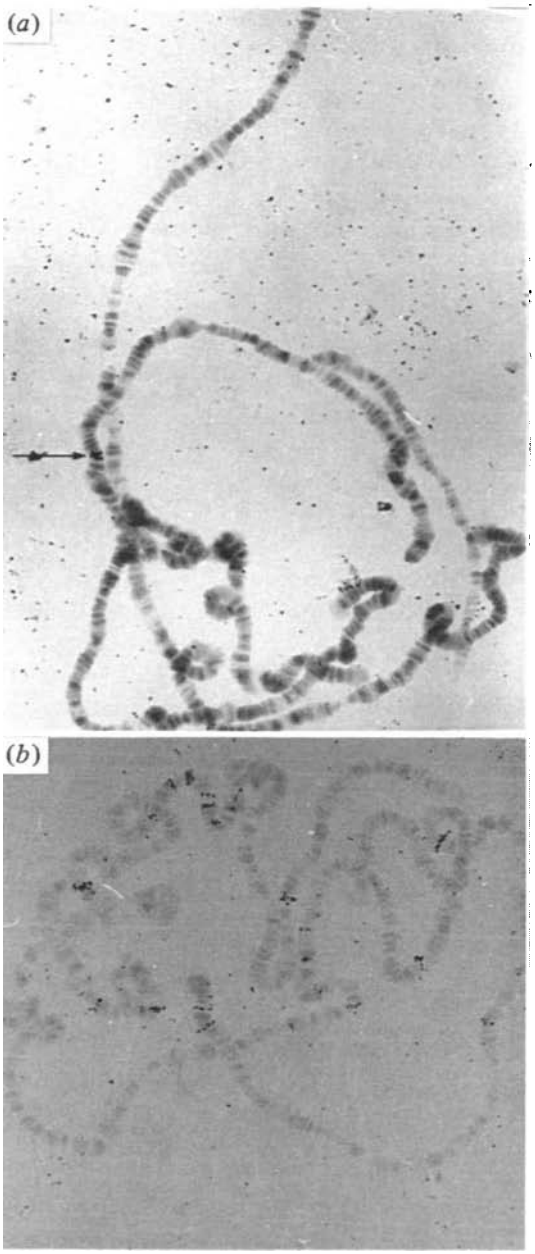

Fig. 1. *In situ* hybridization to salivary gland chromosomes of original Canton-S (*a*) and Harwich (*b*) stocks. Arrow shows the 17C position on the Canton-S *X* chromosome.

ten generations of selection is shown in Fig. 2(*a* and *b*). It is clear from the graphs that there is no extra response to selection in the dysgenic compared to the non-dysgenic lines. In fact, the only line that gave a substantial additional response was one of the non-dysgenic downlines, henceforth called the aberrant non-dysgenic line.

Fig. 2(*c* and *d*) shows variances of the dysgenic and non-dysgenic lines. Again, except for the aberrant non-dysgenic downline, all lines behaved similarly.

Data showing the fate of the mean bristle number of the selection lines during relaxation of selection is also shown in Fig. 2(*a* and *b*) for dysgenic and non-dysgenic lines respectively. Clearly there is little tendency for the mean of the selected lines, including the aberrant non-dysgenic line, to revert towards the base population means.

The final analysis made on the selection data was estimation of realised heritabilities of the selection lines, which were calculated from the regression of the total response on cumulative selection differentials (Hill, 1972). This gave an average realised heritability of 0·173 for dysgenic and 0·267 for non-dysgenic lines. The latter reflects the higher response of the aberrant non-dysgenic downline. It was not possible to estimate standard errors of these heritabilities, as the phenotypic variances were shown by Bartlett's test (Steel & Torrie, 1981), to be inhomogeneous across generations.

What was the fate of the non-dysgenic lines during the course of selection? Results of the cytotype test at G5 show an average mutation rate of $1{\cdot}48 \pm 0{\cdot}84\,\%$ for the sn^w gene introduced into the cytoplasm of the females from the non-dysgenic lines. This value, although lower than the average mutation rate obtained for their dysgenic contemporaries ($3{\cdot}40 \pm 1{\cdot}20\,\%$), shows an increase when compared to their performance at G0 ($0{\cdot}96 \pm 0{\cdot}45\,\%$). More interesting are the results of the same test at G10. Here a higher value was obtained for the non-dysgenic than for the dysgenic lines ($1{\cdot}04 \pm 0{\cdot}42$ *vs.* $0{\cdot}28 \pm 0{\cdot}23\,\%$), suggesting that transposition is not fully repressed in the non-dysgenic lines.

In order to determine whether the temperature at which our selection experiment was conducted had any adverse effect on fertility in the dysgenic line, dysgenic and non-dysgenic crosses were made at room temperature (23–24 °C), and at 29 °C. Table 2 shows results of the fertility test of the female progeny developed and hatched at the above temperatures. These results show that no significant ovarian dysgenesis occurs at 23–24 °C.

P-factor activity of the Harwich males and the cytotype of the G0 females were determined at 20 and 23–24 °C using the sn^w tests as described before. In agreement with Engels (1983), Table 3 shows a marked increase in the P-factor activity of the Harwich males with increasing temperature. Temperature effect was not significant for the cytotype tests.

4. Discussion

Clearly, there are three general differences in the responses to selection obtained in this experiment, when compared with the experiments reported by Mackay (1984, 1985). First, our dysgenic lines did not give increased response to selection. In general, responses in our dysgenic and non-dysgenic lines were very similar (and indeed were almost identical to the responses obtained in Mackay's non-dysgenic controls), with the exception of an aberrant non-dysgenic downline which gave greatly increased response. Second, the increased response of the aberrant non-

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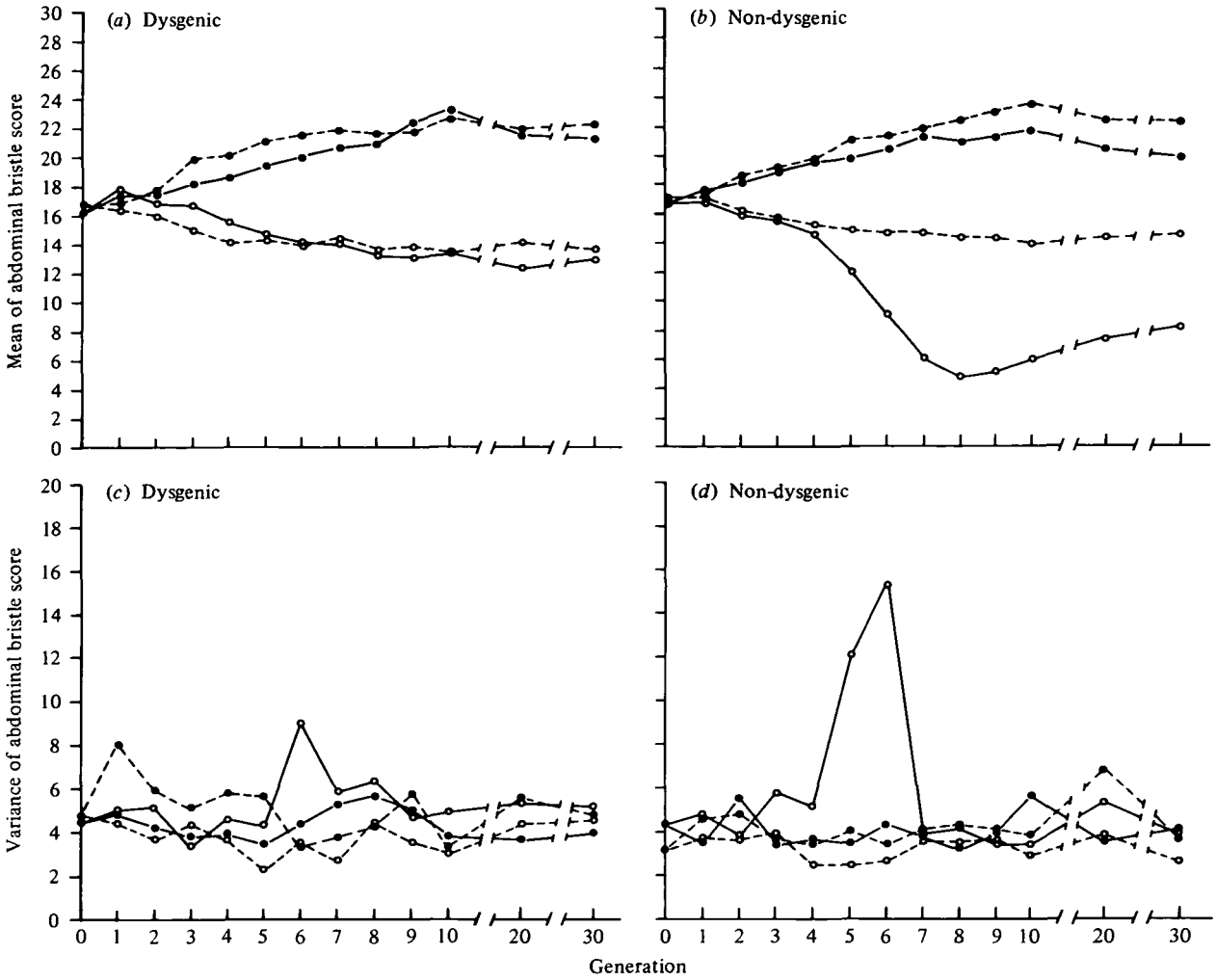

Fig. 2. Results of the selection experiment depicted graphically. (*a*) and (*b*) show the means and (*c*) and (*d*) the variances of the dysgenic and non-dysgenic selection lines, during 10 generations of selection and 20 generations of relaxation. Up and down selection lines are shown by dots and circles respectively. Solid lines represent replicate 1 and dashed lines replicate 2.

dysgenic downline in this experiment started at G5 and ceased at G7. In contrast, the increased responses to selection in Mackay's dysgenic lines were apparent as early as G2 in most cases, and continued as far as G10. Finally, while the mean of our aberrant non-dysgenic line remained almost unchanged after 20 generations of relaxation, the rate at which the mean of Mackay's dysgenic selection lines returned towards the base population mean, during the relaxation of selection, was quite rapid (Mackay, 1985). This implies that in contrast to Mackay's dysgenic lines, the increased response in our line was not associated with strong adverse effects on fitness. This might suggest a qualitative difference in the nature of the mutations or mutational process.

The pattern of phenotypic variance over time was also different in the two experiments. First, our dysgenic lines did not show increased phenotypic variance. This is consistent with the lack of increased response. Secondly, in our aberrant non-dysgenic line, variance returned to its original value as soon as the response ceased, while it remained at its elevated values for Mackay's dysgenic lines, even when the responses reached selection plateaux.

What are the possible explanations for these differences? Extensive checks on the strains, and maximum care in carrying out the experiment as similarly as possible to Mackay (1984), leave only a few minor factors to be considered as possible agents which may have contributed to these differences.

Among the possible environmental factors, temperature is the most apparent difference between the two experiments. It has been reported that temperature can be an important cause of change of cytotype in dysgenic hybrid females if developed and/or aged at temperatures of 25 °C or higher (Ronsseray *et al.* 1984; Ronsseray, 1986). It appears that such temperatures indirectly affect transposition rate by causing an early switch to P cytotype. However, the temperature which was used in this experiment, namely 23–24 °C, was below this threshold, and so far, no indication of significant adverse effect of temperature has been

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Table 2. *Results of the ovarian dysgenesis tests at room temperature (23–24 °C) and at 29 °C for dysgenic and non-dysgenic crosses. Ninety-six (96) female progeny were tested in all cases*

Cross	Ovarian dysgenesis (%) 23–24 °C	29 °C
Canton-S♀ × Harwich♂	0	99 ± 1
Harwich♀ × Canton-S♂	0	10 ± 3
Canton-S♀ × Canton-S♂ (control)	0	6 ± 2
Harwich♀ × Harwich♂ (control)	0	51 ± 6

Table 3. *P-factor activity of the Harwich males and cytotype of the G0 females judged by the mutation rate (percent) of the* sn^w *gene at 20 °C and 23–24 °C. The numbers of flies scored are shown in parentheses*

Test	Population	Mutation rate (%) 20 °C	23–24 °C	R.S.T.[a]
P-factor activity	Harwich	28·05 ± 2·17 (751)	48·30 ± 2·25 (715)	$P < 0{\cdot}01$
Cytotype	G0 (M♀ × P♂)	4·93 ± 1·25 (2612)	16·44 ± 6·24 (1441)	n.s.
Cytotype	G0 (P♀ × M♂)	0 (3232)	0·96 ± 0·45 (3592)	n.s.

[a] Wilcoxon–Mann–Whitney's Rank Sum Test of the effect of temperature.

reported in this range. Furthermore, previous workers (Engels, 1983) as well as the present results of the mutation tests performed parallel to this experiment (see results), have indicated that more transpositional mutations are expected as temperature moves towards 24 °C. Therefore, if anything we should have expected an even greater additional response in our dysgenic lines than Mackay observed in hers.

Preston & Engels (1984) have reported significant but low transpositional activities within the Π2P strain. There is some evidence to suggest that the Harwich stock is also transpositionally unstable. For example, when flies from this stock are raised at 28 °C, they show a relatively high level of sterility (51 %), which appears indistinguishable from ovarian dysgenesis (Table 2). Artificial selection for bristle traits within an inbred Harwich population has also led to a much greater mutational heritability than is usually expected from spontaneous mutations (Mackay, 1987*b*). If these are due to within-strain dysgenesis then it is quite likely that Harwich sub-populations have diverged with respect to the number and position of P elements. This divergence could be sufficient to account for the difference between our results and those of Mackay.

Another question which may be put forward relates to the nature and cause of the higher response obtained in our aberrant non-dysgenic downline. There are two possibilities: first, it may be due to a favourable mutation of large effect that arose *de novo* by some unknown mechanism. Although feasible in long term selection experiments with larger population sizes (Frankham, 1980), this seems very unlikely after only 5 generations in a population of this size (Hill, 1982). The second possibility is that the response in the non-dysgenic downline is in fact due to hybrid dysgenesis-induced mutation, that is from P-element transposition. Non-trivial dysgenesis for putative dysgenic traits has already been observed in early generations of some non-dysgenic crosses (Kidwell *et al.* 1977), but to a much less extent than in dysgenic crosses. More recent reports (Kidwell *et al.* 1981; Kiyasu & Kidwell, 1984) also showed an increase in P-factor activity in the progeny of non-dysgenic crosses, implying an increase in the number of P elements. Evidence is also available which shows very high levels of induction of recessive lethals in non-dysgenic crosses, equal to that in dysgenic crosses (Mackay, 1986). More interesting are the results of a series of recent experiments by Mackay and her colleagues (Mackay, 1987*a*, *b*). In these experiments which also extend to the I–R system, enhanced transposition and hence accelerated polygenic mutation is almost as high in the non-dysgenic derived lines as for the dysgenic derived lines. These observations all support the second suggestion, namely that P-element-induced mutation is a possible cause of higher response in the non-dysgenic downline.

Finally, it seems that the results of this experiment add another dimension to the problems of P element

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regulation in the P–M hybrid dysgenesis system, namely apparent transient dissipation of P cytotype in non-dysgenic lines. A recent study by Sved (1987) has shown that in contrast to M cytotype, which can persist for several generations in the presence of P chromosomes, the abolition of P cytotype is immediate as soon as all P chromosomes are removed. Accordingly, a possible explanation for the occurrence of transposition in non-dysgenic crosses may be dilution of P chromosomes by M chromosomes in this cross. If transposition is resisted by P cytotype, which is in turn highly dependent on P chromosomes, then partial substitution of the P chromosomes by M chromosomes may lead to partial breakdown of P cytotype, hence allowing transpositon to some extent.

What is the fate of cytotype, and how much transposition is likely to occur in the following generations of a non-dysgenic cross? These questions are yet to be answered, but are being addressed by experiments currently in progress.

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