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Transposable element-induced polygenic mutations in *Drosophila melanogaster*

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Summary

P-element mutagenesis was used to contaminate M-strain second chromosomes with P elements. The effect of P-element transposition on abdominal and sternopleural bristle scores and on female productivity was deduced by comparing the distributions of these quantitative traits among the contaminated second-chromosome lines with a control population of M-strain second-chromosome lines free of P elements. Estimates of P-element-induced mutational variance, V_m, for these characters are very high, and mutational 'heritabilities' (V_m/V_e, the ratio of mutational variance to environmental variance) are of the same order as heritabilities of these traits from natural populations. P-element-induced mutational variance of abdominal bristle score is roughly two orders of magnitude greater than spontaneous and X-ray-induced V_m/V_e for this trait.

1. Introduction

Many spontaneously arising major morphological mutations in *Drosophila melanogaster* have been shown to be caused by insertions of one of the five currently known families of transposable element in this species (Rubin, 1983). One of these families of element, the P element, is of special interest because it can be mobilized at extremely high frequencies experimentally by crossing strains which have multiple copies of the element (P strains) with strains which have no copy of the P element (M strains) (Bingham, Kidwell & Rubin, 1982). Associated with the transposition of P elements following such interstrain crosses are a number of phenotypic and genetic abnormalities collectively termed hybrid dysgenesis (Kidwell, Kidwell & Sved, 1977), which include greatly enhanced mutation rates. The P–M system of hybrid dysgenesis is therefore equivalent to a powerful biological mutagen, which can be exploited experimentally to induce mutations at any desired locus; insertional mutations thus generated have the added advantage that they may be recovered in the manner described by Bingham, Levis & Rubin (1981) and used to determine the molecular biology of the wild-type locus. This procedure is applicable to loci which jointly determine variation for quantitative traits, and has been applied successfully to generate new mutational variation for abdominal bristle score (Mackay, 1984; 1985) as well as for fitness traits (Yukohiro, Harada & Mukai, 1985; Mackay, 1986; Fitzpatrick & Sved, 1986). In this paper I report an analysis of the extent of mutational variation arising from P-element mutagenesis for three quantitative characters: abdominal and sternopleural bristle scores, and female productivity. The experimental design was that used by Mackay (1986), in which populations of M second chromosomes potentially contaminated by P elements following inter-P and -M strain crosses were compared with respect to the quantitative characters of interest to a control population of M second chromosomes free of P elements.

2. Materials and Methods

(i) *Chromosome lines*

The chromosome lines studied are those described in detail by Mackay (1986). Three series of lines were established as follows.

(1) '*M*' *control lines*. Twenty-three single Canton-S (M cytotype) second chromosomes were made homozygous in an M background. Single Canton-S males were crossed to *Cy/Pm* (M) females (G1), and single G2 male progeny backcrossed to *Cy/Pm* (M) females. G3 *Cy/+* males and females were then crossed *inter se* to produce chromosome lines homozygous for single second chromosomes from Canton-S, balanced against the *Cy* marker. Two replicates of each line were maintained separately from G4.

(2) '*PM*' *contaminated lines*. Fifty-four single Canton-S second chromosomes were made homozygous in a P (Harwich) background following a dysgenic

cross. Single *Cy/Pm* (P) males were crossed to Canton-S females, then single *Cy/+* males were backcrossed to *Cy/Pm* (P) females for eight generations. At G10, *Cy/+* males and females were mated *inter se* to produce lines homozygous for a single, possibly mutated, Canton-S second chromosome balanced against the *Cy* marker. Two replicates of each line were maintained separately from G11.

(3) *'MP' contaminated lines.* Thirty-four single Canton-S second chromosomes were made homozygous in a P (Harwich) background following a non-dysgenic cross. Single Canton-S males were crossed to *Cy/Pm* (P) females, then the procedure followed in the G2 and later generations was exactly as described for the 'PM' contaminated lines.

(ii) *Culture conditions*

Crosses for the extraction of all chromosome lines were set up in vials with approximately 10 ml cornmeal–agar–molasses medium, at 20 °C. Subsequently populations were maintained in $\frac{1}{3}$ pint milk bottles containing approximately 100 ml medium, at 25 °C. Details of population sizes are given in Mackay (1986) (and see below).

(iii) *Quantitative characters*

Three quantitative characters were measured on the 21 M lines, 43 PM lines, and 26 MP lines that were homozygous viable. All lines were scored 14 to 16 generations after the establishment of line replicates.

Abdominal bristle score. The bristle count on the posterior abdominal sternite was recorded for 10 male and 10 female homozygous flies, and for 10 male and 10 female *Cy/+* heterozygous flies from each replicate of all homozygous viable lines.

Sternopleural bristle score. The sum of the bristle counts on the left and right side sternopleural plates was recorded for 10 male and 10 female homozygous flies, and for 10 male and 10 female *Cy* heterozygotes from each replicate of all homozygous viable lines.

Female productivity. Groups of three wild-type females (for homozygous productivity) or 3 *Cy* heterozygote females (for heterozygous productivity) from each replicate/line were placed in vials together with two wild-type and two *Cy* heterozygote males from the same line, and allowed to mate and oviposit for 4 days. The adult flies were then removed, and the total number of progeny emerging after 14 days was the measure of 'productivity' used (which includes male mating and female choice components of fertility as well as female egg-laying and egg-to-adult viability). Productivity measurements were recorded for 20 vials with wild-type females, and 20 vials with *Cy/+* females, from each replicate of all homozygous viable lines.

3. Results and Discussion

(i) *Means and variances of quantitative characters in control and contaminated chromosome lines*

The distributions of homozygous and heterozygous line means for the two bristle traits and for female productivity among the populations of contaminated and uncontaminated second chromosomes are shown in Figs. 1–3. Some of the features differentiating the distributions of control and contaminated second chromosomes with regard to fitness and its components (Mackay, 1986) are repeated for these three quantitative characters. For every trait observed, there is an apparent similarity in the distributions of MP- and PM-derived contaminated chromosomes. Both populations of contaminated chromosomes consistently exhibit an increase in variance when compared to the M-derived control populations, although this is rather less striking for the two bristle characters and female productivity than was previously observed for the fitness traits.

Statistical summaries of these distributions are presented in Tables 1 (means) and 2 (variance components). Any difference in overall mean performance for these characters between the contaminated and uncontaminated populations of homozygous chromosomes here cannot be attributed to the effects of transposition, since observations were made on individual animals (and not relative to a standard, as was the case for the fitness measurements), and the genetic background of individuals bearing M-derived second chromosomes is both more variable and different from that of individuals with contaminated second chromosomes. However, an increase in variance among homozygous contaminated chromosome line means for a trait when compared to the uncontaminated controls may be construed as evidence for the occurrence of transposition-induced mutations affecting that trait. Joint inspection of Tables 1 and 2 therefore leads to the interpretation that transposable element-induced mutations have occurred affecting these three traits, since the component of variation among homozygous contaminated lines in all but one instance exceeds that of the uncontaminated controls. Paradoxically, the variation among MP-derived lines is consistently greater than that among PM-derived lines. Contaminated between-replicate components of variance for the three traits are also much inflated compared to the control between-replicate components, and the pattern is such that the PM-derived lines have greater between-replicate variance than MP-derived lines.

(ii) *Estimation of mutational variance*

Estimation of the magnitude of transposable-element-induced mutational variance from these data is confounded by the differences in background genotype

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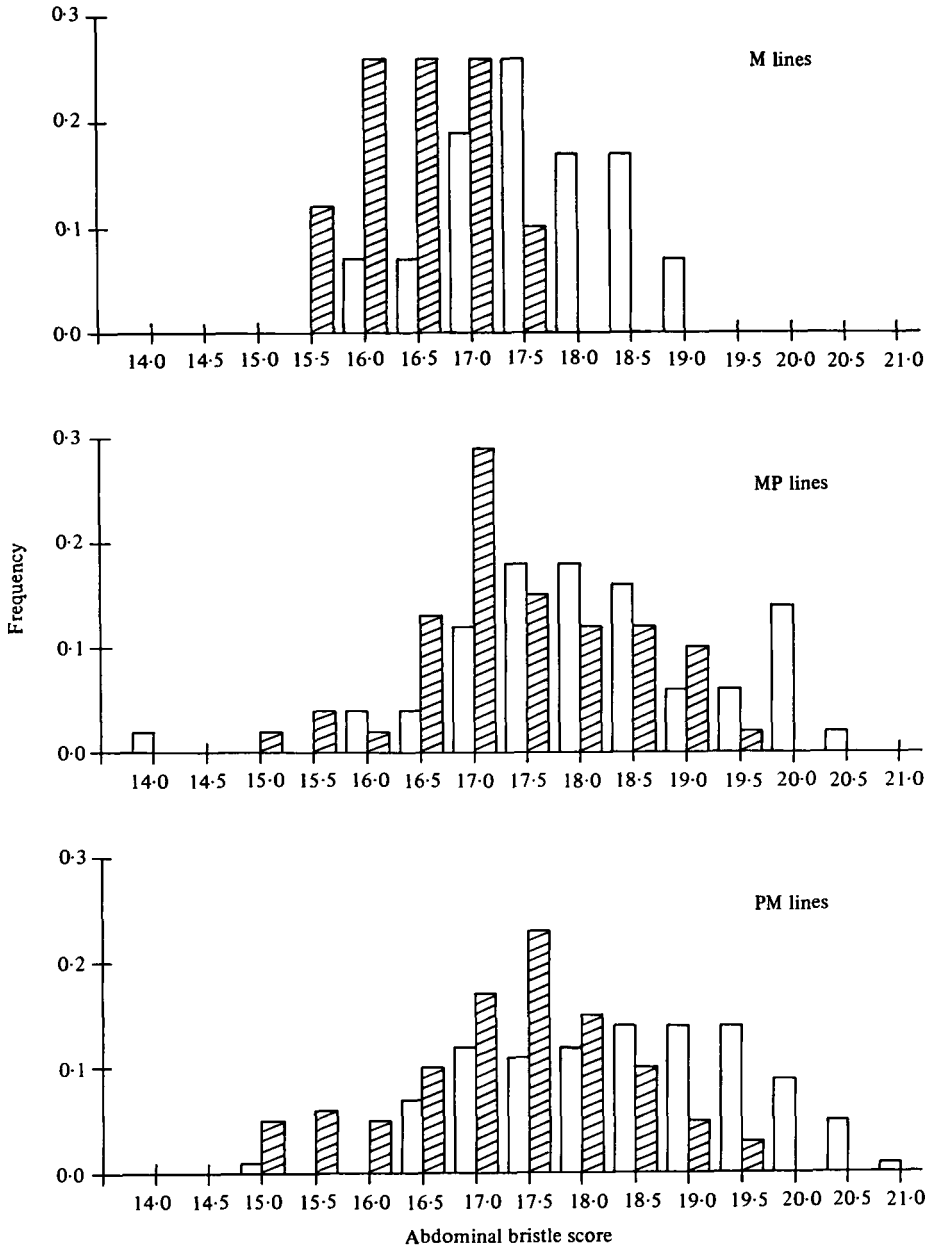

Figs. 1–3. Distributions of line means among the uncontaminated (M lines) and contaminated (MP and PM lines) populations of second chromosomes. The open bars represent homozygous line means, and the cross-hatched bars depict heterozygous line means.
Fig. 1. Distributions of homozygous and heterozygous abdominal bristle score.

between the control and contaminated lines, and also by the uncertain knowledge of over how many generations transposition occurred. One can certainly infer from the data that the accepted maxim that transposition is negligible in the P cytotype is false. However, an approximate estimate of V_m, the mutational variance, can be obtained by deducing the expected genetic composition of the lines and relating this to the observational components of variance.

Consider the derivation of each of the control lines (Mackay, 1986). In the first generation (G1) single males were crossed to marked *Cy/Pm* second chromosome balancer females, and at G2 a single *Cy* heterozygote male was backcrossed to three females of the balancer strain. Subsequently 6 male and female *Cy* heterozygotes were crossed *inter se* (G3), and at G4, two samples each of 20 male and female *Cy* heterozygotes were used to initiate two replicate populations which were then maintained for 14 generations with 40 males and females each generation. This crossing scheme preserves intact a single second chromosome of the control (M) strain, but the remainder of the genome is of mixed M and *Cy* strain origin. At G2 the genotypic constitution of the control lines is that the second chromosome, which represents 40% of the genome, is entirely of M-strain origin; the *X* chromosome, which is about 20% of the genome, is entirely of *Cy* strain origin; and the third and fourth

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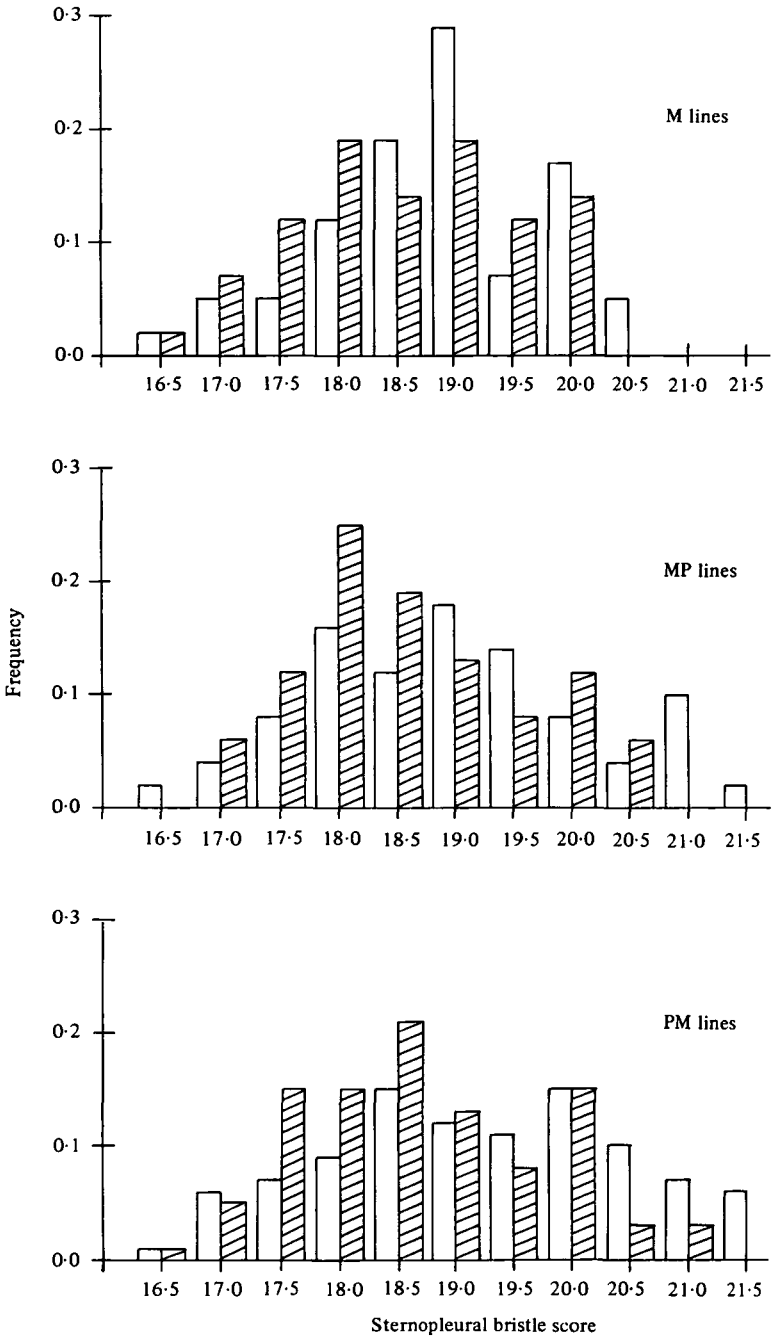

Fig. 2. Distributions of homozygous and heterozygous sternopleural bristle score.

chromosomes, which comprise the remaining 40% of the genome, are a mixture of 25% M and 75% *Cy* strains.

Under the additive model, the expected autosomal variance between lines is $2F\,V_g$ (Falconer, 1981), where F is the inbreeding coefficient, and V_g the genetic variance in the base population, which in this case consists of the M and *Cy* strain genotypes in the above proportions. The expected between-line variance contributed by the X chromosome is less straightforward to determine. In Drosphila the phenomenon of dosage compensation operates at the transcriptional level in males, such that genes on the single X chromosome of homozygous males are regulated to produce the same amount of product as the two female copies (Baker & Belote, 1983). A consequence of this is that the additive variance contributed by X-linked loci in males is twice as large as that in females (James, 1973). Therefore the contribution of X-linked variation in Drosophila to variation among inbred lines is $FV_g♂$ for males, and $2FVg♀$ for females, and since $V_g♂ = 2V_g♀$, the variation expected among inbred X chromosomes is $2FV_g♀$ for both sexes. (Note that if the mechanism of dosage compensation is by random X-inactivation, the variation between inbred X chromosomes is not the same for both sexes, but is $2FV_g♀$ for males and $FV_g♀$ for females.)

The expected genetic composition of the component

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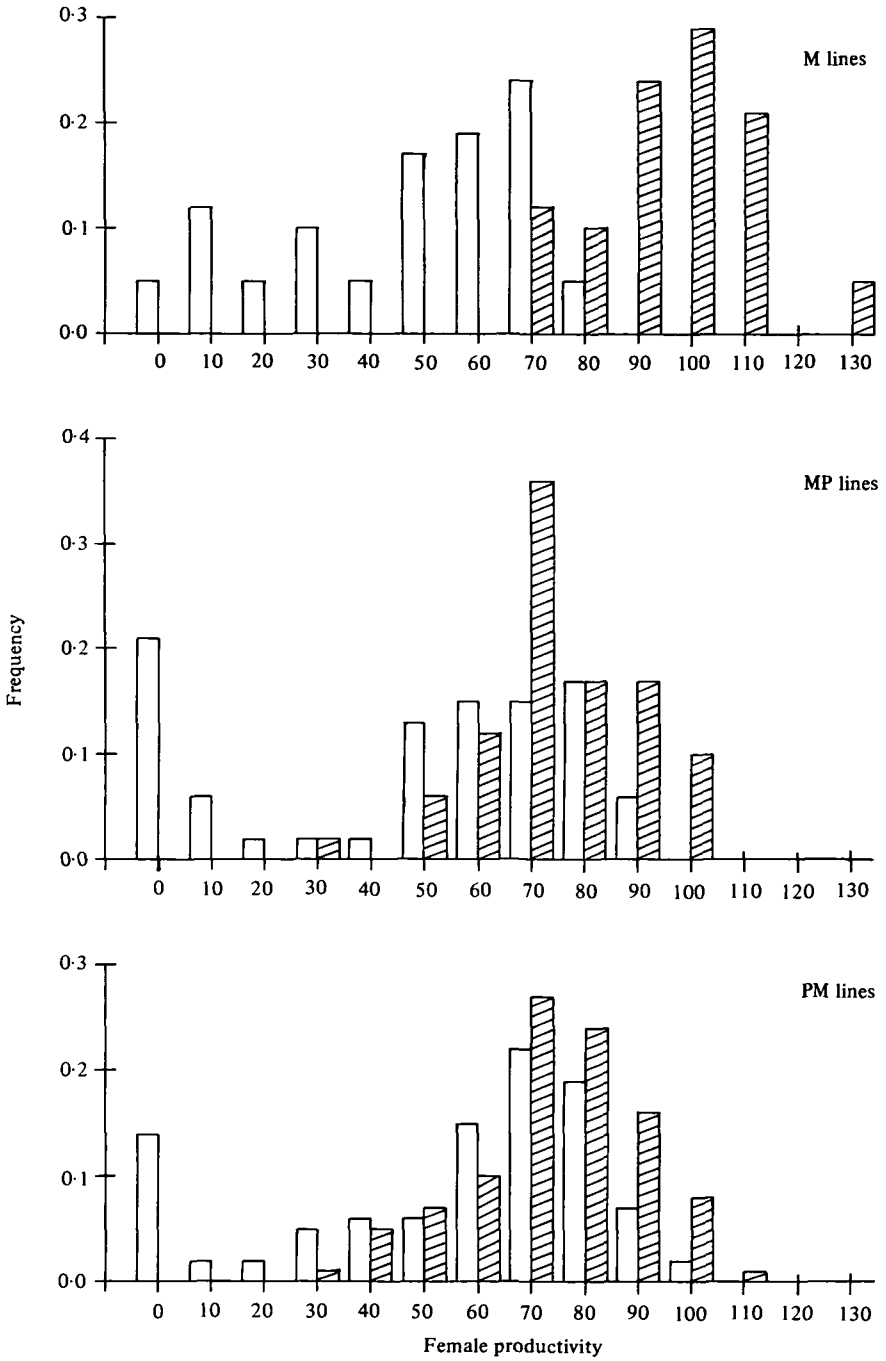

Fig. 3. Distributions of homozygous and heterozygous female productivity.

of variance among control lines may be derived as follows. The crossing scheme used ensures that the second chromosome is completely inbred ($F = 1$), but the inbreeding coefficient appropriate to the background genotype must be estimated from the effective population sizes (N_e) before replicate divergence. At G2, the N_e for one male and 3 female parents is approximately 3, and at G3, 6 pairs of parents per line gives an $N_e = 12$ (ignoring variation of family size). The total inbreeding before replication is then approximately $F = 0{\cdot}2$ (Falconer, 1981). The inbreeding coefficient for X-linked loci is somewhat higher than for autosomal loci because of the effective bottleneck in males, but this effect is trivial for the level of approximation required here. The total expected between-line variance is then $2F\ V_g(\mathrm{M})$ (0·4) [from chromosome II, for which $F = 1] + 2F\ V_g(Cy)$ (0·5) [from chromosomes X, III and IV, $F = 0{\cdot}2] + 2F\ V_g(\mathrm{M})$ (0·1) [from chromosomes III and IV, $F = 0{\cdot}2$], or $0{\cdot}84\ V_g(\mathrm{M}) + 0{\cdot}2\ V_g(Cy)$. The expected within-line variance at the time of replicate divergence is $(1 - F)V_g$, where $F = 0{\cdot}2$ and V_g is the expected constitution of the background genotype, which is $\frac{5}{6}\ Cy + \frac{1}{6}$ M, giving an expected within-line variance when the lines were

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Table 1. *Mean homozygous and heterozygous performance (±S.E. calculated from variance between lines) for three quantitative characters from contaminated (MP, PM) and uncontaminated (M) second-chromosome lines*

		Character		
	Line derivation	Abdominal bristles	Sternopleural bristles	Female productivity
Homozygous mean	M	17·56 (0·156)	18·81 (0·189)	46·86 (4·961)
	MP	18·13 (0·224)	19·00 (0·213)	47·48 (5·886)
	PM	18·39 (0·165)	19·19 (0·163)	56·42 (3·937)
Heterozygous mean	M	16·47 (0·093)	18·52 (0·192)	95·94 (2·213)
	MP	17·43 (0·140)	18·58 (0·146)	74·82 (2·049)
	PM	17·32 (0·121)	18·68 (0·120)	74·33 (2·008)

Table 2. *Variance components of three quantitative characters from analysis of variance of contaminated (MP, PM) and uncontaminated (M) homozygous and heterozygous second-chromosome lines*

Character	Line derivation	Among lines	Between replicates, within lines	Within replicates	Total
Abdominal bristles	M, homozygotes	0·4134	0·0515	2·8136	3·2785
	M, heterozygotes	0·1571	0·0488	2·1914	2·3973
	MP, homozygotes	0·9369	0·5825	3·0361	4·5555
	MP, heterozygotes	0·0619	0·7538	2·8497	3·6654
	PM, homozygotes	0·7134	0·6618	3·0740	4·4492
	PM, heterozygotes	0·1821	0·7592	2·6802	3·6215
Sternopleural bristles	M, homozygotes	0·6382	0·0850	2·8622	3·5854
	M, heterozygotes	0·6091	0·1953	2·7747	3·5791
	MP, homozygotes	0·7196	0·6358	2·7691	4·1245
	MP, heterozygotes	0·2321	0·4933	3·0111	3·7365
	PM, homozygotes	0·5745	0·8709	3·1274	4·5728
	PM, heterozygotes	0·1086	0·8811	2·8136	3·8033
Female productivity	M, homozygotes	480·21	67·32	121·92	669·45
	M, heterozygotes	0	190·07	311·45	501·52
	MP, homozygotes	823·11	140·94	230·81	1194·86
	MP, heterozygotes	24·62	153·45	313·16	491·23
	PM, homozygotes	539·76	212·85	235·85	988·46
	PM, heterozygotes	89·07	150·05	363·57	606·69

split of $\frac{2}{3} V_g(Cy) + \frac{2}{15} V_g(\mathrm{M})$. The expected variance between replicates, within lines is then $2F$ (V_g within lines), where F is that appropriate to the maintenance of the populations for one generation with $N = 40$, followed by 14 generations with $N = 80$, which is 0·1 (Falconer, 1981). This gives an expected between-replicate variance for the control lines of $0{\cdot}13\ V_g(Cy) + 0{\cdot}03\ V_g(\mathrm{M})$. An estimate of $V_g(\mathrm{M})$, the genetic variance of the control population, is then obtained by equating observational and expected components of variance and solving the two simultaneous equations.

Now consider the derivation of the two series of contaminated lines, which differ only in the direction of the initial cross (Mackay, 1986). The chromosome extraction procedure was essentially as described above for the control lines, with the exception that 8 generations of backcrossing of single *Cy* heterozygote males to balancer females whose background genotype was Harwich (P) were included prior to replicate divergence. After the 8 backcross generations, the expected genotypic constitution of the contaminated lines is that the second chromosome (40% of the genome) is entirely of M-strain origin, and that the remaining 60% background genotype is of P-strain origin. The second chromosome is completely inbred ($F = 1$), and the background genotype has an expected inbreeding coefficient of 0·2 because of the small population sizes used to found each chromosome line. The component of variation among contaminated lines is therefore $2F\ V_g(\mathrm{M})$ (0·4) [chromosome II, $F = 1$] $+ 2F\ V_g(\mathrm{P})$ (0·6) [background, $F = 0{\cdot}2$] $+ 2t\ F\ V_m$ (0·4), where the latter term represents the contribution to the variance due to the accumulation of mutations in the second chromosome over t generations ($F = 1$). The expected among-lines component is then $0{\cdot}8\ V_g(\mathrm{M}) + 0{\cdot}24\ V_g(\mathrm{P}) + 0{\cdot}8t\ V_m$. The variation within contaminated lines at the time of

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splitting into replicates is $(1-F)\ V_g(\mathrm{P})$, where $F = 0{\cdot}2$. The component of variation between replicates is $2F$ (variation within lines before divergence), where $F = 0{\cdot}1$ is the amount of inbreeding expected from one generation of culture at $N = 40$, followed by 14 generations with $N = 80$, plus a term due to the accumulation of new mutations over the entire genome. From Lynch & Hill (1986), the expected contribution of new additive mutations to variation between lines is $4N\ V_m[(t/2N)-(1-\exp(-t/2N))]$. The expected variation between replicate contaminated lines becomes $0{\cdot}16\ Vg(\mathrm{P})+1{\cdot}45\ V_m$, assuming $t = 15$ generations over which mutations may have occurred subsequent to line divergence. An estimate of V_m, the mutational variance arising each generation, is obtained by substituting the estimate of $V_g(\mathrm{M})$ obtained from the control lines into the expression for the variation between contaminated lines, then equating observational and expected components of variance and solving the two simultaneous equations. The number of generations over which transposition may have occurred during the 8 backcross generations is unknown, so the value of t which minimized the estimate of V_m was chosen to produce the most conservative estimate.

Estimates of transposable element-induced mutational variance for the three quantitative characters assessed are given in Table 3. These estimates are scaled relative to the observed environmental variance appropriate to each trait, which is the average of the within-replicate components of variation of the control and contaminated lines. Mutational 'heritabilities' (V_m/V_e) from the PM lines exceed those from the MP lines by a factor of 2, but all estimates are surprisingly high. The estimates presented for the two bristle traits have been calculated according to the procedure described above, assuming complete additivity of the new mutations. It is possible to estimate the degree of dominance, k (using the terminology of Lynch & Hill, 1986), from the regression of heterozygous score on homozygous score, where the regression coefficient (b) is the covariance of homozygous and heterozygous line means pooled over replicates, divided by the sum of the homozygous variance components among lines and between replicates, and $k = 2(b-0{\cdot}5)$. For abdominal bristle score, the estimates of k are $-0{\cdot}52$ for the MP lines and $-0{\cdot}26$ for the PM lines, and for sternopleural bristle score the estimates are $-0{\cdot}31$ and $-0{\cdot}20$ for the MP and PM lines, respectively. Because the standard errors attached to these coefficients are relatively large, these estimates are consistent with $k = 0$ (additivity) (with the possible exception of the MP abdominal bristle data which show partial recessivity). Since the effect of using these values of k to compute the expected contribution of new mutations to the variation between replicate contaminated lines (Lynch & Hill, 1986) is to increase the estimate of V_m for the two bristle traits, the V_m values produced under the additive model may be considered to be minimum estimates.

Table 3. *Estimates of transposable element-induced mutational variance, expressed as a proportion of the environmental variance (V_m/V_e) for three quantitative characters from contaminated chromosome lines*

Line derivation	Character: Abdominal bristles	Character: Sternopleural bristles	Character: Female productivity
MP	0·067	0·186	(*a*) 0·280 (*b*) 0·188
PM	0·151	0·310	—

The estimates for the two bristle characters were computed assuming complete additivity of the new mutations, and the two estimates for female productivity from the MP lines were computed (*a*) for additive mutations and (*b*) for an average degree of dominance of new mutations of $k = -0{\cdot}87$. The estimate for female productivity from the PM lines was negative for all models.

Estimates of k for the female productivity data are $-0{\cdot}87$ for the MP lines and $-0{\cdot}49$ for the PM lines. Therefore variation for female productivity is largely recessive (and deleterious when homozygous), which is consistent with the close association of this trait with fitness. Although the female productivity data do not fit an additive model, it can be argued that departures from additivity do not have a large effect where F is small, and the analysis outlined above may be used to estimate V_m for this trait. Alternatively, the value of k obtained from regression of homozygous on heterozygous productivity can be used to calculate the expected contribution of new mutations to the variation between replicate contaminated lines, and this expression used to compute V_m. Estimates of V_m for female productivity produced under both models are given in Table 3 for the MP contaminated lines. The data for this trait from the PM contaminated lines did not fit either model; variation between replicates was too large compared to variation among lines, so all estimates were negative. This may be attributed most reasonably to an accident of sampling, since the line and replicate variance components are based on rather few degrees of freedom.

The estimates of transposable element-induced V_m/V_e presented in Table 3 are extremely high; indeed, they are of the same order as typical heritability estimates of these traits from natural populations (Falconer, 1981). The magnitude of dysgenesis-induced genetic variation can be appreciated particularly when compared to spontaneous and X-ray-induced mutational variation for quantitative characters. Estimates of spontaneous mutational 'heritability' (V_m/V_e) for bristle traits may be derived from experiments in which the response to selection from an initially inbred base is analysed, and also from experiments which determine the extent of divergence

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Table 4. *Estimates of spontaneous and X-ray induced mutational variance, expressed as a proportion of the environmental variance (V_m/V_e), for abdominal bristle score. X-ray-induced V_m/V_e is scaled/1000r/generation*

Authors	Method	$V_m/V_e \times 10^3$ Spontaneous	X-irradiation
Clayton & Robertson, 1955	Selection from inbred base	0·1	4·8
Clayton & Robertson, 1964	(*a*) Selection from inbred base	(i) 4·2[a]	(i) 3·5[b]
		(ii) 1·7[a]	(ii) 1·1[b]
	(*b*) Selection from mass-mated population from inbred base	(iii) 0·4[b]	(iii) 1·2[b]
Kitagawa, 1967	Selection from inbred base	0·4	4·1
Hollingdale & Barker, 1971	Selection from inbred base	1·1	2·6

of originally inbred chromosomes protected from selection by a balancer, due to the accumulation of new mutations. In a review and analysis of the relevant experiments, Hill (1982) suggests that $V_m/V_e = 10^{-3}$ is typical for both bristle traits. Data pertinent to the estimation of X-ray-induced mutational variation for quantitative traits are scanty; estimates of V_m/V_e of abdominal bristle score from experiments which compared spontaneous and X-ray-induced response to selection from an inbred base are given in Table 4. V_m was calculated by joint application of the theory of Lynch & Hill (1986), which gives the expected variance within lines arising from t generations of mutation in a population of size N, which was originally completely isogenic; and the theory of Hill (1982), which gives the expected response to selection from new mutations arising each generation; and summing the separate contributions of spontaneous (and induced, where applicable) mutations to selection response over the different periods of the population's history (see Lynch & Hill, 1986, equation 28). V_e was calculated separately for each experiment by subtracting the estimate of mutational variance from the reported phenotypic variance. X-ray-induced estimates of V_m/V_e for abdominal bristles average $2{\cdot}9 \times 10^{-3}$/1000r/generation; three times greater than the spontaneous rate but two orders of magnitude less than transposable element-induced mutational variance for this trait.

(iii) *Conclusions*

These data are interesting in that they demonstrate the unprecedented power of the P element as a mutagen, when mobilized under the special circumstances of inter-P and -M strain crosses. Although associated with deleterious homozygous fitness effects (Mackay, 1986), the fitness depression is mild compared to the major abnormalities accompanying mutagenesis by chemicals and irradiation, so it is conceivable that variation in sites of insertion of transposable elements observed in natural populations (Montgomery & Langley, 1983) contributes to variation of quantitative characters. There are, however, several problems yet to be resolved. An experimental design such as that used here, which was intended to homogenize the background genotype and stabilize the cytotype to minimize transposition, is clearly unsatisfactory in this regard; for it remains unknown over how many generations transposition occurred; how many transposition events are represented in each line; what is the extent and pattern of transposition in the P cytotype; and what is the nature of the difference in amount and pattern of transposition in the F2 and later generations of reciprocal inter-P and -M strain crosses. The search for answers to these and related questions provides interesting avenues for further study.

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