TRANSPOSABLE ELEMENT-INDUCED RESPONSE TO ARTIFICIAL SELECTION IN *DROSOPHILA MELANOGASTER*

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ABSTRACT

The *P* family of transposable elements in *Drosophila melanogaster* transpose with exceptionally high frequency when males from *P* strains carrying multiple copies of these elements are crossed to females from *M* strains that lack *P* elements, but with substantially lower frequency in the reciprocal cross. Transposition is associated with enhanced mutation rates, caused by insertion and deletion of *P* elements, and chromosome rearrangements. If *P* element mutagenesis creates additional variation for quantitative traits, accelerated response to artificial selection of progeny of *M*♀♀ × *P*♂♂ strain crosses is expected, compared with that from progeny of *P*♀♀ × *M*♂♂ strain crosses.—Divergent artificial selection for number of bristles on the last abdominal tergite was carried out for 16 generations among the progeny of *P*-strain males (Harwich) and *M*-strain females (Canton-S) and also of *M*-strain males (Canton-S) and *P*-strain females (Harwich). Each cross was replicated four times. Average realized heritability of abdominal bristle score for the crosses in which *P* transposition was expected was 0.244 ± 0.017, 1.5 times greater than average heritability estimated from crosses in which transposition was expected to be rare (0.163 ± 0.010). Phenotypic variance of abdominal bristle score increased by a factor of four in lines selected from *M*♀♀ × *P*♂♂ crosses when compared with those selected from *P*♀♀ × *M*♂♂ hybrids. Not all quantitative genetic variation induced by *P* elements is additive. A substantial fraction of nonadditive genetic variation is implicated by chromosomal analysis, which demonstrates deleterious fitness effects of the mutations when homozygous.—Several putative "quantitative" mutations were identified from chromosomes extracted from the selected lines; these will form the basis for further investigation at the molecular level of the genes controlling quantitative inheritance.

TRANSPOSABLE elements comprise approximately one-fifth of the Drosophila genome. At least five major classes of transposable element (*copia*-like, *foldback*, *I*, *F* and *P* sequences), distinguished on the basis of sequence homology, are present as moderately repeated sequences scattered in apparently random genomic locations (RUBIN 1983). These sequences have been labeled "parasitic" or "selfish DNA" (DOOLITTLE and SAPIENZA 1980), because replicative transposition ensures their own survival, but may have deleterious effects on the host. Transposition of elements is liable to cause mutations by altering host DNA; insertion of an element may disrupt a structural locus or alter its regulation, and excision often generates deletions and other chromosomal rearrangements

(BERG, ENGELS and KREBER 1980). Otherwise, the presence of these sequences appears to have no major phenotypic effect, but is it possible that their activities contribute to minor phenotypic differences between individuals by affecting the loci controlling quantitative variation? Investigation of the extent to which mobilization of elements affects quantitative variation is limited by the relatively low rate of movement of elements. Spontaneous rates of transposition, although sufficient to have caused differences between strains of Drosophila in the sites that elements occupy, are not high enough to cause particular mutations on an experimental time scale. However, the *P* family of transposable elements in *D. melanogaster* has several peculiar properties, including enhanced transposition rates in certain well-defined circumstances, which may make it the element of choice for such a study.

The *P* family of transposable elements consists of a large 2.9 kb sequence flanked by 31 base pairs (bp) inverted repeats, and various smaller sequences, each of which can be derived by different internal deletions of the large element (O'HARE and RUBIN 1983). *P* elements are unusual among transposable elements so far discovered in Drosophila in that they are not present in all strains. Strains of *D. melanogaster* that contain these elements (*P* strains) typically have 30–50 copies per haploid genome (the exact number and position varying across strains), while other strains (*M* strains) have no functional *P* elements (BINGHAM, KIDWELL and RUBIN 1982). When *P* males are crossed to *M* females, the F_1 progeny are characterized by a number of abnormalities, which have been embraced by the term "hybrid dysgenesis," including temperature-sensitive sterility, male recombination, high frequency of chromosome rearrangements and increased frequency of lethal and visible (often unstable) mutations (KIDWELL, KIDWELL and SVED 1977). These abnormalities do not occur in crosses of *M* males to *P* females or in intra-*P* and intra-*M* crosses. Early genetic analysis of dysgenic ($M♀♀ \times P♂♂$) and nondysgenic ($P♀♀ \times M♂♂$) crosses (KIDWELL, KIDWELL and SVED 1977), and subsequent molecular analysis of several mutations at the white locus resulting from a dysgenic cross (RUBIN, KIDWELL and BINGHAM 1982), led to the hypothesis that the dysgenic syndrome may be explained in terms of genomic instability of dysgenic hybrids caused by high rates of transposition of *P* (and perhaps other) elements. Because the enhanced transposition of these elements in dysgenic hybrids is a powerful mutagen, this system is an obvious choice for the study of transposable element-induced quantitative variation.

The rationale underlying this investigation is simple. Movement of *P* elements causes mutations, some of which are likely to be at loci controlling quantitative characters. Dysgenic ($M♀♀ \times P♂♂$) and nondysgenic ($P♀♀ \times M♂♂$) hybrids should differ genetically mainly because of *P* element activity in the former cross (however, see DISCUSSION). If one result of *P* element mutagenesis is to create additional genetic variation for a quantitative character, this would be manifest in an accelerated response to artificial selection for that trait in dysgenic, compared with nondysgenic, hybrids, and analysis of this response to selection should lead to the estimation of the amount and nature of *P* element-induced quantitative variation.

MATERIALS AND METHODS

P (Harwich) and *M* (Canton-S) strains were kindly provided by M. G. KIDWELL. Two replicates of nondysgenic ($10P♀♀ \times 10M♂♂$) and dysgenic ($10M♀♀ \times 10P♂♂$) crosses were set up in bottle cultures. The following generation (G0), 50 individuals of each sex were scored for abdominal bristle count on the last abdominal tergite, and the ten highest, as well as the ten lowest, scoring males and females were crossed *en masse* to found nondysgenic and dysgenic high and low selection lines, one pair of lines for each replicate. (The terms "dysgenic" and "nondysgenic" strictly refer only to the F_1 hybrids, not subsequent generations, but will be used throughout as convenient terminology by which to distinguish the initial reciprocal crosses. The problem of the number of generations over which transposition is likely to occur is addressed in the DISCUSSION.) Selection was continued in subsequent generations by choosing the ten most extreme individuals from the 50 scored of each sex, in each line, to be parents of the next generation. An additional two replicates were formed by initially crossing Harwich (*P*) and Canton-S (*M*) sublines that had been inbred by full-sibbing for eight generations; otherwise, the selection procedure was as described above. The first two replicates are subsequently referred to as the "noninbred" crosses, while the second pair of replicates are the "inbred" crosses. The results of the first eight generations of selection of the noninbred crosses have been discussed in a preliminary report (MACKAY 1984); a more detailed analysis of response to 16 generations of artificial selection for both inbred and noninbred replicates is presented here.

At generation 10 of the noninbred crosses, abdominal bristle score of the last two abdominal tergites was recorded on the 50 males and 50 females usually scored each generation, to provide an estimate of the repeatability of bristle score in each line. (Selection of parents was, however, based on the count of the last tergite only.) Also, at generation 10, ten males and ten females were chosen at random from each of the noninbred selection lines to establish lines in which artificial selection was relaxed. These lines were continued for seven generations by randomly choosing ten pairs of parents each generation and recording the abdominal bristle score of 50 males and 50 females as for the selected lines.

At generation 7 of the noninbred crosses, sternopleural bristle number (the sum of the number of sternopleural bristles on the left and right sides of the flies) was recorded on a sample of 50 males and 50 females from each of the selection lines.

Between generations 10 and 12, individual second and third chromosomes were extracted from each of the noninbred selection lines and were made homozygous by the well-known *Cy/Pm* procedure (for a description of the *Cy* and *Pm* phenotypes and associated chromosomal inversions, see LINDSLEY and GRELL 1968). Since the *Cy/Pm* marker stock generally available is of *M* cytotope, it was necessary to create a *P* cytotype *Cy/Pm* stock, so that crosses of the marked females to males from the selection lines are not dysgenic, and cause further transposition. Chromosomes, *I, III* and *IV* of the Harwich strain were substituted into the *Cy/Pm* stock used to isolate individual second chromosomes by initially crossing Harwich females to *Cy/Pm* males, then backcrossing *Cy/+* and *Pm/+* males separately to the Harwich strain for seven generations. A *P* cytotope *Cy/Pm* stock was reconstituted by reciprocally crossing *Cy/+* and *Pm/+* males and females from the seventh backcross generation, using the *Cy/Pm* progeny of these crosses to establish the *(P)Cy/Pm* strain. To extract second chromosomes from each of the selection lines, individual males were crossed to *(P)Cy/Pm* females. Single *Cy/+* sons from this mating were backcrossed to *(P)Cy/Pm* females, and several male and female *Cy/+* progeny from this cross were mated *inter se* to give a progeny mixture of *Cy/+* heterozygotes and (if viable) *+/+* homozygotes. An average of 17 individual second chromosomes from each of the eight noninbred selection lines were made homozygous, with two replicates of each chromosome line.

An average of 12 individual third chromosomes (replicated twice) from each of the selection lines were made homozygous by a similar procedure, but using the third chromosome marker stock *TM6/mwhe* (for a description of the phenotypes and chromosomal inversions, see LINDSLEY and GRELL 1968). This *P* cytotype stock was kindly provided by A. J. LEIGH BROWN, who synthesized it by an analogous procedure to that described for the *(P) Cy/Pm* strain, but by backcrossing to the π_2 *P* strain. The *P* cytotype of both marker stocks was confirmed by the ability to destabilize sn^w when crossed to sn^w, *M* cytotype, females.

Three measurements were made on each replicate of the second and third chromosome lines: average viability of the *+/+* homozygotes relative to the marker heterozygotes (*Cy/+* or *TM6/+*),

abdominal bristle score and sternopleural bristle score. Viability of +/+ homozygotes relative to marker heterozygotes was estimated from the observed proportion of heterozygotes, r emerging from a cross of two heterozygotes. The expected ratio of heterozygotes to homozygotes, r: $(1 - r)$, is $1/2{:}1/4v$, from which v, the viability, is $2(1 - r)/r$ (SVED 1971). The proportion of heterozygotes, r, was calculated for each chromosome line by pooling the numbers of each genotype emerging from both replicates. Abdominal and sternopleural bristle score was recorded for ten male and ten female +/+ flies for each replicate of each of the chromosome lines.

To determine whether alleles on the X chromosome contributed to the selection response, reciprocal crosses were made at generation 12 among the high and low noninbred dysgenic selection lines. For each replicate separately, ten high-scoring males from the high selection line were crossed *en masse* to ten low-scoring females from the low selection line, and ten low-scoring males from the low line were crossed to ten high-scoring females from the high line. Abdominal bristle score was recorded for 50 male and 50 female progeny of each of those crosses.

The flies were reared on cornmeal-agar-molasses medium, and all cultures were incubated at 20°, a temperature at which gonadal sterility is not appreciable in dysgenic hybrids.

RESULTS

Generation means of the noninbred and inbred, nondysgenic and dysgenic selection lines are depicted graphically in Figures 1–4. Not only is the response to selection for each of the dysgenic replicates, on average, twice that of the nondysgenic replicates, but also the pattern of the response differs. Variation in response among dysgenic replicates is greater than that among nondysgenic replicates. It is also apparent for the noninbred dysgenic crosses that most of the response occurs in the first ten generations of selection for both the high and low selection lines, compared with the nondysgenic crosses, in which the response is more nearly linear. This effect is less marked for the inbred crosses, although the dysgenic low selection lines appear to have reached a similar plateau. For this reason, realized heritabilities of the dysgenic and nondysgenic crosses are compared, based on response to generation 10 (Table 1).

Heritabilities are calculated, in the standard manner, from regression of cumulated divergence in response between high and low lines on cumulated selection differential (FALCONER 1981). Standard errors for these heritabilities, based on variation between replicates, are not presented, because the very nature of the experiment precludes the necessary assumption of homogeneity of variance (HILL 1972). Realized heritability of abdominal bristle score is, on average, 1.5 times greater for the dysgenic than for the nondysgenic selection lines, an outcome that is consistent with the interpretation that a proportion of *P* element-induced variation is additive in nature and can successfully be utilized in response to selection.

Why does the response to selection reach an apparent plateau so quickly for the dysgenic selection lines? Regressions of cumulated divergence in response on cumulated selection differential from generations 11–16 are −0.020 and 0.034 for dysgenic replicates 1 and 2, respectively, neither of which is significantly different from zero. If, as is usually true for Drosophila bristle characters, most of the genetic variation associated with the trait is additive (FALCONER 1981), then the plateau in response to selection might represent the fixation of all useful genetic variation in the high and low dysgenic selection lines. One would then expect a reduction in phenotypic variance of the trait in these lines, reflecting

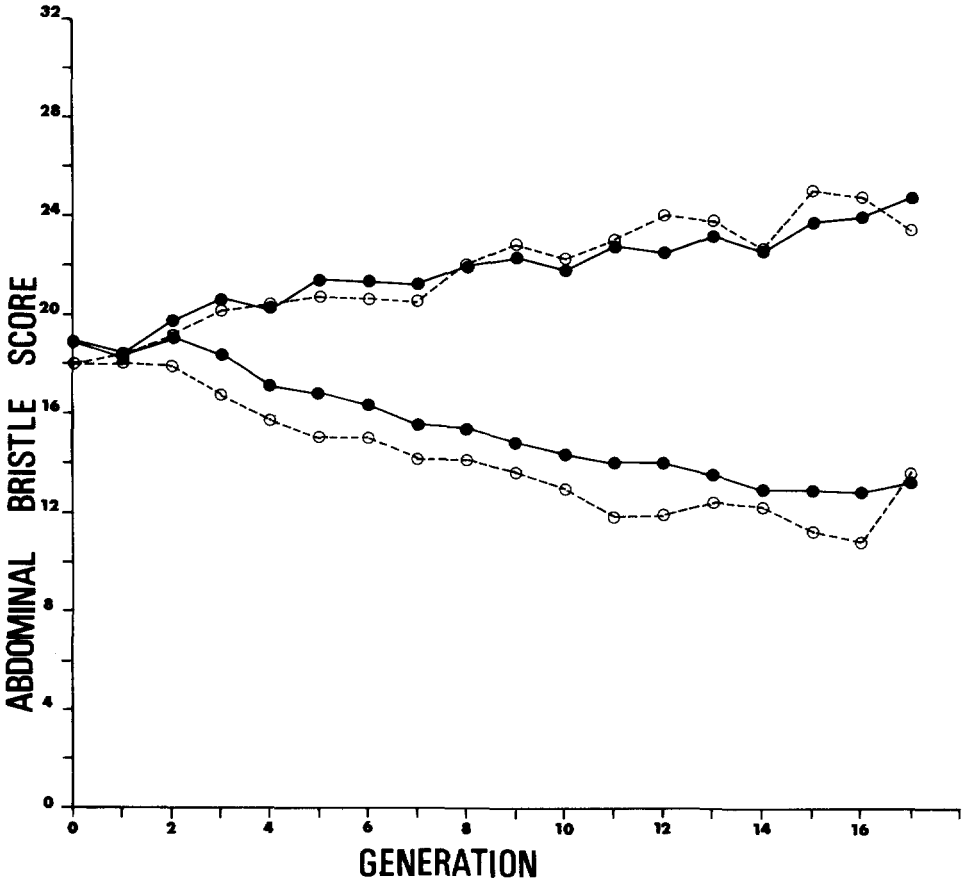

FIGURE 1.—Generation means of abdominal bristle score for the nondysgenic, noninbred selection lines. G0 are the progeny of a cross of ten *M* males and ten *P* females, which were artificially selected for bristle number according to the procedure described in the text. Solid and dashed lines depict the first and second replicates, respectively.

the elimination of the genetic component. However, a comparison of phenotypic variance of abdominal bristle score in successive generations of the nondysgenic and dysgenic selection lines, both for noninbred and inbred crosses (Tables 2 and 3), shows that this is not true.

Phenotypic variance of the trait increases in the dysgenic selection lines over the first six generations of selection to a level two to five times that of the nondysgenic lines, and it remains so despite continued selection. This is contrary to the more usual pattern of evolution of phenotypic variance of an additive trait during the course of artificial selection, as exemplified by the nondysgenic selection lines, with little alteration in variance from that of the base population in the early generations. Part of the increase in phenotypic variance of the dysgenic lines may be due to initially rare *P*-induced mutations attaining intermediate frequency as a consequence of selection, but this cannot account for the cessation of response to selection accompanied by such high variance. However,

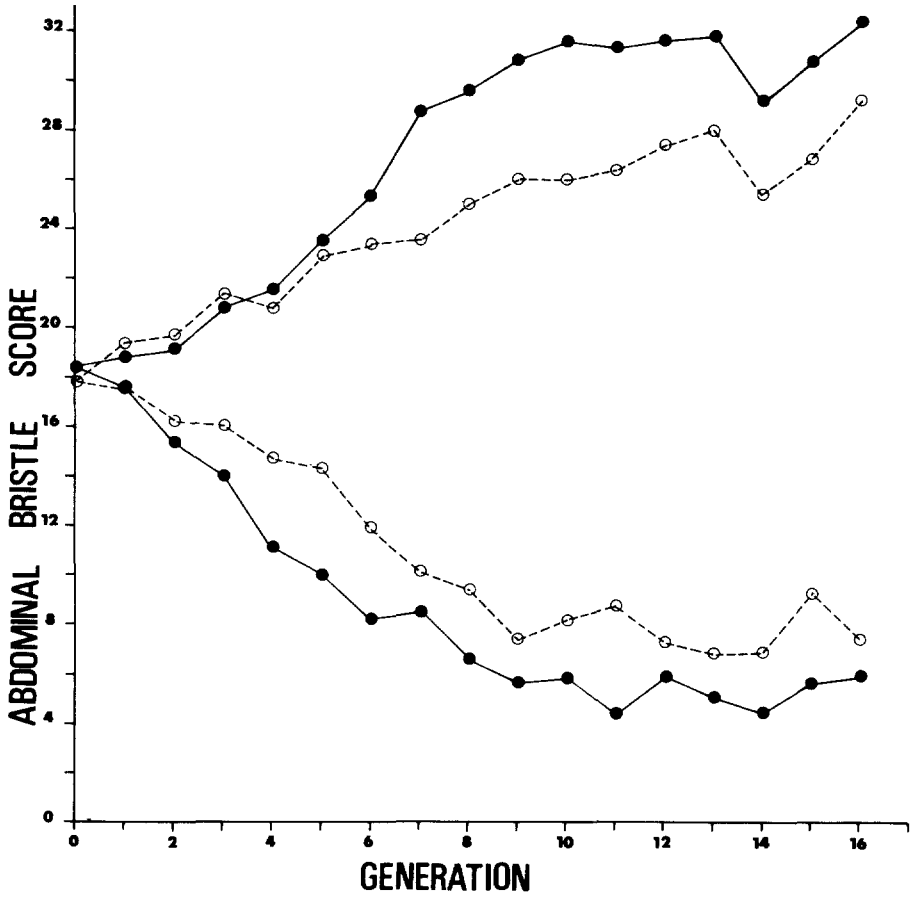

FIGURE 2.—Generation means of abdominal bristle score for the dysgenic, noninbred selection lines. G0 are the progeny of a cross of ten *P* males and ten *M* females, which were artificially selected for bristle number according to the procedure described in the text. Solid and dashed lines depict the first and second replicates, respectively.

if much of the *P* element-induced genetic variation of the dysgenic lines was nonadditive in nature, then the observed results may easily be explained. Nonadditive genetic variance could be generated if some of the *P* element-induced mutations affecting abdominal bristle number also had a detrimental effect on fitness, so that any genetic variance that remains after response to selection has ceased would be due to the segregation of recessive deleterious genes.

Evidence comes from several sources that much of the increased phenotypic variance observed in the dysgenic selection lines is, indeed, due to an increase in nonadditive genetic variation. The first line of evidence is somewhat indirect and comes from a comparison of the relative magnitudes of increase of response to selection, realized heritabilities and phenotypic variances of the dysgenic, compared with nondysgenic, selection lines. The response to selection (R) of the dysgenic lines is, on average, 2.34 times that of their nondysgenic counterparts, and the realized heritability (h^2) is 1.5 times as great. The relationship between

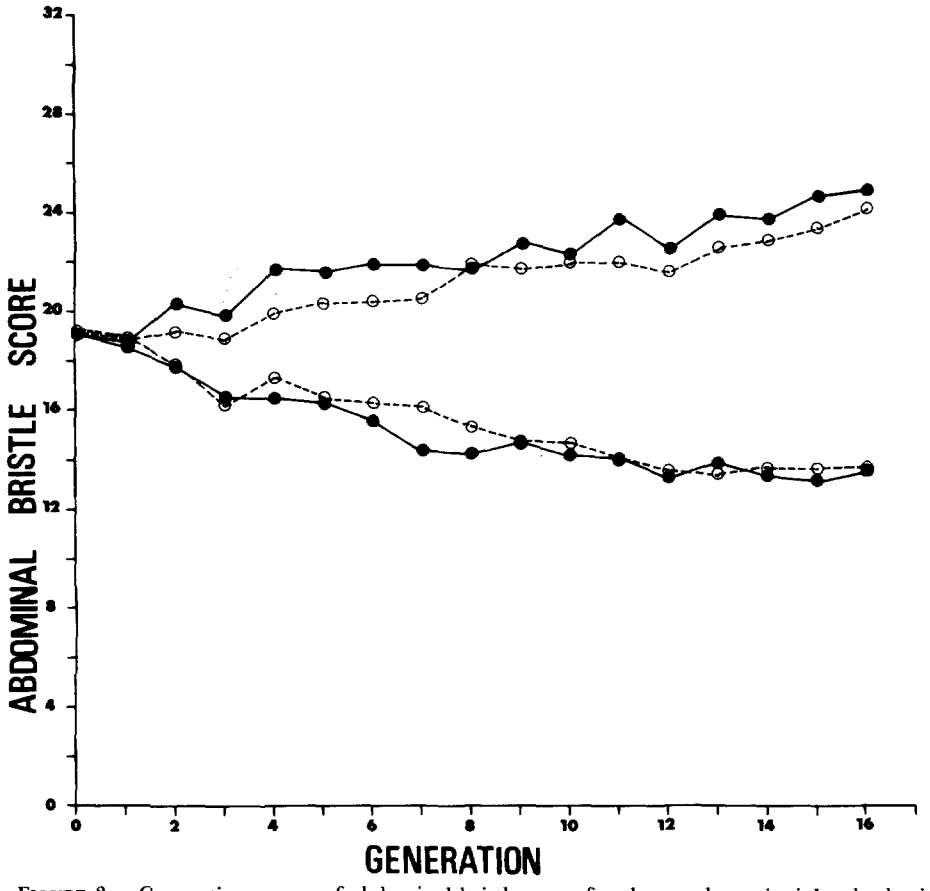

FIGURE 3.—Generation means of abdominal bristle score for the nondysgenic, inbred selection lines. G0 are the progeny of a cross of ten *M* males and ten *P* females, which were artificially selected for bristle number according to the procedure described in the text. Solid and dashed lines depict the first and second replicates, respectively.

these quantities is the well-known expression $R = i\,h^2\sigma_p$ (FALCONER 1981), where i (the intensity of selection) is the same in dysgenic and nondysgenic lines, and σ_p is the square root of the phenotypic variance. If all the increase in phenotypic variance of the dysgenic lines was due to an increase in the additive component, one would therefore predict σ_p would be a factor of 1.56 greater in the dysgenic lines, corresponding to an increase in phenotypic variance of 2.34. Since the increase in the phenotypic variance is, on average, by a factor of four, the deduction must be that a significant proportion of this increase must be due to an increase in either nonadditive genetic (dominance + epistatic) variation, or environmental sensitivity, or both.

The second line of evidence for the existence of substantial nonadditive genetic variance in the dysgenic selection lines comes from a comparison of realized heritability and repeatability estimates at generation 10 of the noninbred crosses (Table 4).

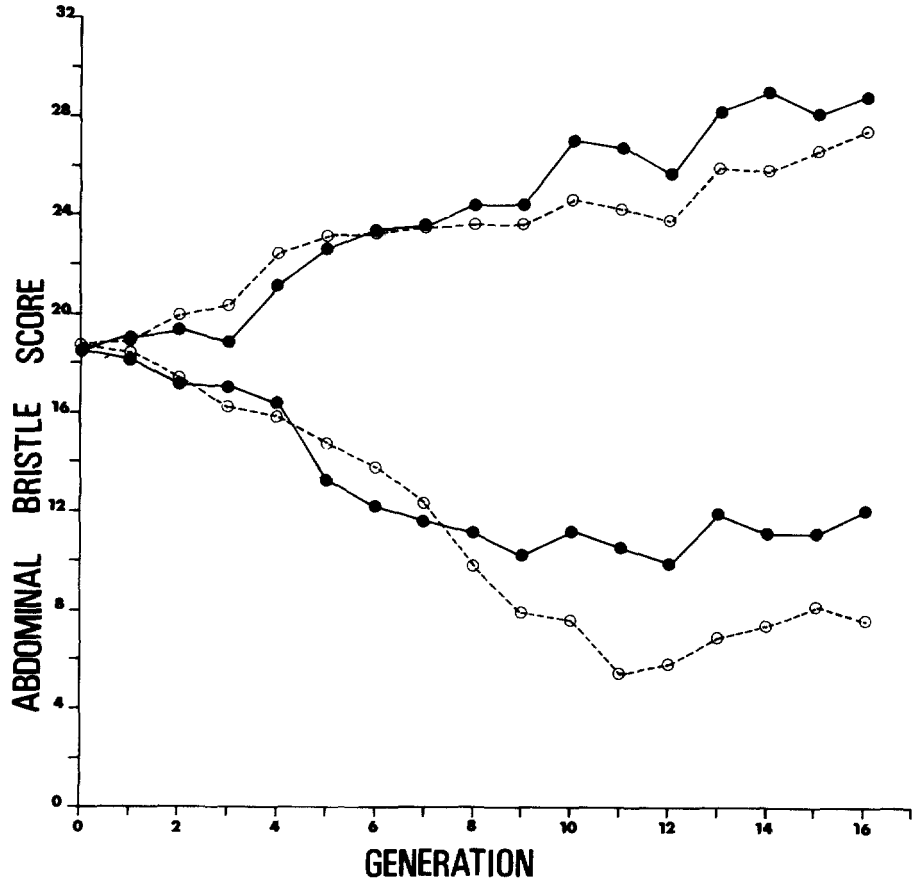

FIGURE 4.—Generation means of abdominal bristle score for the dysgenic, inbred selection lines. G0 are the progeny of a cross of ten *P* males and ten *M* females, which were artificially selected for bristle number according to the procedure described in the text. Solid and dashed lines depict the first and second replicates, respectively.

TABLE 1

Realized heritabilities of abdominal bristle score, to generation 10 (calculated as described in the text)

Lines	Replicate	Nondysgenic lines	Dysgenic lines
Noninbred	1	0.167	0.280
	2	0.190	0.214
Inbred	1	0.152	0.216
	2	0.142	0.264

Realized heritability is the ratio of additive to total phenotypic variance. Repeatability, measured as the correlation of abdominal bristle score on two successive segments, is the ratio of additive genetic variance + nonadditive genetic variance + environmental variance to total phenotypic variance, assuming

TABLE 2

Phenotypic variance of abdominal bristle score in successive generations for the noninbred dysgenic and nondysgenic selection lines

	Nondysgenic crosses ($P♀♀ \times M♂♂$)				Dysgenic crosses ($M♀♀ \times P♂♂$)			
	Replicate 1		Replicate 2		Replicate 1		Replicate 2	
Generation	High	Low	High	Low	High	Low	High	Low
0	3.67	3.67	2.53	2.53	3.72	3.72	6.87	6.87
1	4.65	2.85	4.02	3.68	4.05	6.50	4.82	3.88
2	4.87	3.60	3.47	3.29	6.42	9.58	4.54	5.79
3	3.06	3.64	3.02	3.50	5.74	12.34	5.86	4.34
4	3.45	3.52	3.25	3.19	9.97	19.97	5.24	12.72
5	5.03	3.97	3.45	4.04	10.89	15.26	8.41	14.27
6	2.93	3.19	3.80	3.22	16.68	17.69	7.84	20.81
7	4.18	4.27	5.50	4.51	23.07	19.83	8.90	22.76
8	4.59	3.45	3.93	3.82	16.98	15.43	10.14	20.24
9	4.52	3.45	6.53	3.53	20.24	16.36	9.05	17.02
10	4.12	3.79	3.21	8.90	13.40	15.41	12.22	17.92
11	2.90	3.66	4.04	5.97	12.74	13.18	12.40	14.48
12	3.24	3.28	4.75	6.35	15.88	15.59	15.33	19.23
13	5.07	2.53	5.18	6.89	13.16	12.99	10.84	14.93
14	3.68	3.66	3.65	6.54	12.70	10.56	15.65	18.00
15	3.46	4.20	4.29	8.75	13.36	17.04	16.05	17.09
16	2.81	3.03	3.04	7.95	17.48	15.77		14.62
		3.77						

TABLE 3

Phenotypic variance of abdominal bristle score in successive generations for the inbred dysgenic and nondysgenic selection lines

	Nondysgenic crosses ($P♀♀ \times M♂♂$)				Dysgenic crosses ($M♀♀ \times P♂♂$)			
	Replicate 1		Replicate 2		Replicate 1		Replicate 2	
Generation	High	Low	High	Low	High	Low	High	Low
0	2.63	2.63	2.47	2.47	3.02	3.02	3.34	3.34
1	5.87	4.21	4.84	4.49	3.10	3.87	4.50	3.60
2	4.04	3.78	3.62	3.93	5.07	3.79	6.19	3.92
3	3.73	4.94	3.51	4.15	6.31	3.71	4.45	3.76
4	5.15	4.03	3.41	4.59	5.65	7.88	5.95	3.71
5	3.69	3.48	3.97	4.06	6.36	13.47	5.19	4.52
6	3.94	3.62	4.92	4.67	6.57	18.10	5.68	6.12
7	3.21	3.19	4.18	3.86	8.25	10.93	5.02	11.70
8	3.65	3.26	4.45	3.49	6.67	11.67	5.83	17.36
9	3.09	2.57	3.93	2.89	8.16	14.36	6.32	16.03
10	3.48	2.23	3.91	2.49	10.38	11.96	6.08	10.62
11	5.67	2.30	4.70	2.90	13.90	13.29	8.07	11.20
12	4.77	5.41	3.20	2.91	6.93	14.47	6.29	9.99
13	3.96	3.61	3.98	2.63	16.23	14.59	6.08	16.49
14	3.86	3.15	4.71	3.75	7.61	8.40	7.13	8.21
15	3.78	3.41	5.08	4.70	9.43	9.00	6.35	14.19
16	3.11	2.79	5.15	3.22	10.11	8.90	4.55	16.64

TABLE 4

Comparison of repeatability (± SE) of abdominal bristle score at generation 10 of the noninbred selection lines and realized heritabilities, calculated from regression of cumulated response on cumulated selection differential up to generation 10, and between generations 10 and 11

Selection lines	Repeatability (G10)	Heritability (G10–11)	Heritability (G0–10)
Nondysgenic			
Replicate 1, high	0.410 (0.092)	0.363	0.134
Replicate 1, low	0.216 (0.099)	0.163	0.203
Replicate 2, high	0.240 (0.098)	0.321	0.164
Replicate 2, low	0.115 (0.100)	0.241	0.215
Dysgenic			
Replicate 1, high	0.532 (0.086)	0.000	0.331
Replicate 1, low	0.600 (0.081)	0.289	0.237
Replicate 2, high	0.647 (0.077)	0.050	0.208
Replicate 2, low	0.400 (0.093)	0.000	0.215

a genetic correlation of score on successive abdominal segments of one and no environmental correlation (REEVE and ROBERTSON 1954). If repeatabilities are greater than realized heritabilities, this must be due to inflation by nonadditive genetic variance and/or environmental variance. Repeatabilities estimated at generation 10 should be compared to heritabilities estimated from response to selection at that generation. Repeatabilities exceed realized heritabilities by more than a factor of six for the dysgenic lines, but are nearly equivalent among the nondysgenic lines. Since heritabilities estimated from a single generation response to selection are notoriously inaccurate, realized heritabilities calculated over generations 0–10 are also given. Comparison of repeatabilities with realized heritabilities calculated in this manner gives the same qualitative results; repeatabilities substantially exceed heritability estimates in the dysgenic lines, but not the nondysgenic lines.

A third argument for the presence of nonadditive genetic variance caused by deleterious effects of *P*-induced mutations is more direct and does not confound nonadditive genetic and environmental variance. If some *P*-induced mutations affecting bristle number have a deleterious effect on fitness through impaired viability or fertility in the homozygote, but have an effect on the bristle trait so that heterozygotes would be selected, then ultimately an equilibrium will be reached caused by a balance between natural and artificial selection. Heterozygotes will be chosen as parents by artificial selection, but the mutant homozygotes will be rejected each generation by natural selection, so that variance is maintained in the population at an apparent selection limit. If one stops artificial selection and allows the animals to breed at random, then only natural selection will operate, and the population mean will return toward that of the base population: the mean of lines selected for high score will decrease, and that of lines selected for low score will increase. If, however, there is no natural selection operating on the character, the mean of the population will remain at the selected level on relaxation of artificial selection. Tables 5 and 6 compare the response

TABLE 5

Means ($\bar{X}$) and variances (V) of abdominal bristle score for the nondysgenic selection lines, following relaxation of selection at generation 10

	Replicate 1				Replicate 2			
	High		Low		High		Low	
Generation	$\bar{X}$	V	$\bar{X}$	V	$\bar{X}$	V	$\bar{X}$	V
R0 (G10)	21.79	4.12	14.29	2.66	22.24	3.21	12.86	8.90
R1	21.83	5.23	15.13	4.11	21.89	2.85	13.34	8.29
R2	22.51	3.37	15.06	2.96	21.98	4.39	13.41	4.39
R3	22.39	3.84	15.21	4.12	21.78	5.07	13.21	4.32
R4	22.38	3.51	14.45	2.62	21.30	4.09	13.64	4.31
R5	21.17	5.16	14.21	2.79	21.07	4.29	13.69	4.18
R6	22.78	4.35	14.62	4.82	21.76	4.24	12.99	8.67
R7	23.24	3.47	14.85	5.10	22.64	5.16	13.88	8.61
b[a]	0.129 NS		−0.023 NS		−0.013 NS		0.079 NS	

[a] None of the regression coefficients (b) of mean bristle score on generation of relaxation are significantly different from zero (NS).

TABLE 6

Means ($\bar{X}$) and variances (V) of abdominal bristle score for the dysgenic selection lines following relaxation of selection at generation 10

	Replicate 1				Replicate 2			
	High		Low		High		Low	
Generation	$\bar{X}$	V	$\bar{X}$	V	$\bar{X}$	V	$\bar{X}$	V
R0 (G10)	31.61	13.40	5.76	15.41	26.01	12.22	8.09	17.92
R1	29.45	10.86	5.37	14.55	25.20	11.72	8.37	22.07
R2	27.43	5.60	7.36	16.25	23.01	9.02	8.23	14.56
R3	26.95	7.76	7.60	16.80	23.92	7.84	9.49	18.23
R4	26.31	7.63	7.24	15.81	23.59	7.00	10.55	15.56
R5	24.80	4.55	8.22	17.26	22.47	6.67	9.02	14.36
R6	25.81	7.69	7.31	15.88	22.67	6.35	10.42	15.03
R7	25.98	5.53	8.19	18.91	22.87	7.97	10.36	15.12
b[a]	−0.787*		0.344*		−0.436*		0.352*	

[a] All of the regression coefficients (b) of mean bristle score on generation of relaxation are significantly different from zero. * $P < 0.025$.

TABLE 7

Comparison of numbers of homozygous lethal chromosomes extracted from nondysgenic and dysgenic selection lines (replicates pooled)

Selection lines	Chromosome *II*			Chromosome *III*		
	L	*N*	*P*	*L*	*N*	*P*
Nondysgenic						
High	5	36	0.139	3	24	0.125
Low	4	38	0.105	6	21	0.286
Dysgenic						
High	7	29	0.241	13	28	0.464
Low	8	35	0.229	10	24	0.417

L = the number of homozygous lethal chromosomes; N = the total number of chromosomes extracted; P (L/N) = the proportion of lethal chromosomes.

of nondysgenic and dysgenic lines to relaxed selection at generation 10. The means of all nondysgenic lines remained at the value they had attained by generation 10, whereas the means of all dysgenic lines behaved as if the selected values were associated with deleterious effects on fitness. The phenotypic variance of abdominal bristle score decreases markedly when selection is suspended for the high selected dysgenic lines, as would be expected if natural selection is eliminating deleterious alleles. Surprisingly, this is not so for the low selected dysgenic lines; perhaps variation is maintained in these lines by a balanced lethal system, or genes with low effect but highly variable expression have been fixed.

Direct evidence for reduced fitness of the dysgenic, compared with nondysgenic lines, is from estimates of second and third chromosome homozygous viabilities. Twice as many chromosomes extracted from the dysgenic lines were lethal ($v = 0$) when homozygous; this comparison is valid for both chromosomes and both directions of selection (Table 7). If these homozygous lethal chromosomes cause extreme values of the character when heterozygous, this would create nonadditive genetic variation for the trait and a selection limit. Average homozygous viabilities and abdominal bristle scores of the nonlethal chromosomal homozygotes are given in Table 8. For chromosome *II*, there is little difference in average homozygous viability of chromosomes extracted from nondysgenic and dysgenic selection lines, with the exception of chromosomes from the low selection line of the first dysgenic replicate; these have exceptionally poor viability. However, third chromosomes isolated from the dysgenic selection lines have average viabilities reduced to one-half of those of the nondysgenic lines.

It appears that response to selection for all lines may be attributed to loci on both second and third chromosomes, because average abdominal bristle score of second and third chromosome homozygotes from the high selection lines exceeds that of the low selection lines. (However, background variation from the other major autosome was not controlled in these chromosome extraction lines; therefore, the homozygous line means are confounded because 6.25% of the individuals in each line are expected to be homozygous for the autosome not specifically extracted.) Divergence of average homozygous abdominal bristle score between

TABLE 8

Average viabilities ($\bar{V}$) and abdominal bristle scores ($\bar{A}$) of second and third chromosomal homozygotes extracted from the noninbred nondysgenic and dysgenic selection lines

Selection lines	Chromosome *II*			Chromosome *III*		
	N	$\bar{V}$	$\bar{A}$	N	$\bar{V}$	$\bar{A}$
Nondysgenic						
Replicate 1, high	18	0.667	18.862	12	0.547	18.890
		(0.063)	(0.195)		(0.091)	(0.213)
Replicate 1, low	19	0.637	14.828	10	0.397	16.603
		(0.103)	(0.267)		(0.073)	(0.162)
Replicate 2, high	18	0.595	18.742	12	0.384	19.150
		(0.086)	(0.193)		(0.068)	(0.469)
Replicate 2, low	19	0.447	15.154	11	0.434	14.862
		(0.113)	(0.527)		(0.119)	(0.470)
Dysgenic						
Replicate 1, high	12	0.718	20.267	16	0.112	20.283
		(0.131)	(0.230)		(0.057)	(0.740)
Replicate 1, low	17	0.219	9.334	13	0.151	15.613
		(0.061)	(2.052)		(0.063)	(0.582)
Replicate 2, high	17	0.579	20.398	12	0.328	21.119
		(0.111)	(0.212)		(0.055)	(0.525)
Replicate 2, low	18	0.703	15.213	11	0.227	16.142
		(0.076)	(0.522)		(0.052)	(0.248)

Standard errors (in parentheses) are calculated from variances between chromosome line means. N chromosomes were extracted from each selection line.

the high and low dysgenic selection lines is greater than that of the nondysgenic lines for both second and third chromosomes. For chromosome *II* this difference in divergence is approximately four bristles, for chromosome *III* it is 1.5 bristles. Most of the increase in divergence of response for chromosome *II* is due to five chromosomes extracted from the first low dysgenic replicate, with an average score of two abdominal bristles (on all tergites); for chromosome *III* the additional divergence of homozygous bristle score of the dysgenic lines comes from chromosomes isolated from both high replicates that have an average score of 23 bristles.

The allele on the semilethal, extremely low-scoring, second chromosome extracted from a low dysgenic selection line maps to the right arm of chromosome *II* at approximate position 2-90, and complementation tests indicate it is an allele of the smooth locus (2-91.5, LINDSLEY and GRELL 1968) (A. ROBERTSON, personal communication). The difference in response of the dysgenic and nondysgenic crosses to selection for decreased abdominal bristle number cannot, however, be explained entirely in terms of the segregation of alleles at the smooth locus in the dysgenic lines. The semilethal smooth allele discovered is recessive and female sterile and cannot be maintained as a homozygote; furthermore, a population segregating only for wild-type and mutant smooth alleles would have a bimodal distribution of bristle phenotypes, not the nearly uniform distribution observed. Similarly, the difference in response of the dysgenic and nondysgenic crosses to selection for increased abdominal bristle number cannot be explained in terms of the segregation in the dysgenic lines of a single allele at a third chromosome locus that increases bristle number to 23 when homozygous, as the effect is neither sufficiently extreme nor associated with a reduction of fitness. (Population means at the limit of the high dysgenic selection lines are 31 and 26 bristles for the first and second replicates, respectively, with standard deviations of 3.7.) However, approximately one-half of the third chromosomes extracted from the dysgenic high lines were homozygous lethal, so it is plausible that a locus (or loci) on this chromosome is partly responsible for increased dysgenic abdominal bristle score through a large heterozygous effect on the character.

To determine whether loci on the *X* chromosome contributed to the additional response of the dysgenic hybrids to selection for abdominal bristle score, reciprocal crosses were made in generation 12 between males and females from the high and low noninbred dysgenic selection lines, for each replicate separately. If an *X*-linked allele (or alleles) affect the trait, the average bristle score of the male progeny is expected to be similar to that of the female parents, while the average score of the female progeny will equal the midparent value, if the alleles are additive. If the alleles affecting the trait are on autosomes, male and female progeny are expected to have similar mean values of the trait. In this analysis the known sex dimorphism in bristle score must be taken into account. Females generally have more bristles on each tergite than do males; therefore, to estimate the amount of dimorphism in the dysgenic selection lines, the sex difference in bristle score was calculated for generations 9 through 13, for high and low lines separately. The female-male difference in single segment score averaged over both replicates for these five generations was 3.34 ± 0.26 for the high lines and

TABLE 9

Reciprocal crosses of the noninbred high and low dysgenic selection lines at generation 12

	Mean abdominal bristle score			
	Parents		Offspring	
Replicate	♀♀	♂♂	♀♀	♂♂
1	2.4	31.1	23.40 (0.359)	15.06 (0.593)
	33.5	2.0	22.44 (0.419)	22.36 (0.380)
2	4.8	26.9	23.30 (0.340)	13.34 (0.688)
	31.8	1.8	23.94 (0.388)	20.98 (0.348)

Shown are the average abdominal bristle scores of the ten male and ten female parents and of 50 of their male and female progeny (± standard errors).

was 1.47 ± 0.25 for the low lines. To attribute any difference in male and female bristle score in the progeny of the reciprocal crosses to *X*-linked inheritance, this must be significantly greater than the 3.34 bristle difference expected from dimorphism, to be conservative.

Average abdominal bristle scores of male and female parents and their progeny are given in Table 9. Males and females resulting from a cross of high-scoring females to low-scoring males have similar average bristle scores. The difference between female and male score averaged over both replicates is only 1.52; therefore, it appears that alleles causing increased bristle score are largely autosomal and that any *X*-linked alleles causing low values of the trait are recessive. Male progeny resulting from crosses of low-scoring females to high-scoring males have mean scores 9.15 bristles less than their sisters (averaged over both replicates). This difference is significantly greater than that expected from ordinary dimorphism; therefore, it appears alleles causing low values of the trait are present on the *X* chromosome. Males from this cross do not have average bristle scores as low as the female parents because of the high alleles descending from the male parents.

Table 10 documents the association of sternopleural and abdominal bristle scores in the selected lines. These two bristle characters are usually genetically uncorrelated in *D. melanogaster* (CLAYTON *et al.* 1957). One cannot estimate genetic correlations from these data, as it is necessary to have information from a reciprocal selection experiment in which sternopleural bristles are directly selected and the correlated response in abdominal bristle score is observed. Nevertheless, it is interesting that the correlation of scores of the two bristle traits is not the same for the nondysgenic lines ($r = 0.26 \pm 0.68$) and the dysgenic lines ($r = 0.98 \pm 0.10$). Examination of the correlation between abdominal and sternopleural bristle score in the second and third chromosome homozygotes indicates that at least one of the effects causing this increased correlation can be assigned to the third chromosome of the dysgenic high lines. The correlation between homozygous abdominal and sternopleural bristle score is not significantly different from zero in third chromosomes extracted from low or high nondysgenic selection lines or from low dysgenic lines; however, this correlation

TABLE 10

Association of mean abdominal and sternopleural bristle score at generation 7 of the noninbred selection lines

Selection lines	Mean bristle score	
	Abdominal	Sternopleural
Nondysgenic		
Replicate 1, high	21.16	20.21
Replicate 1, low	15.50	22.08
Replicate 2, high	20.53	22.47
Replicate 2, low	14.14	19.67
Dysgenic		
Replicate 1, high	28.70	24.40
Replicate 1, low	8.51	18.95
Replicate 2, high	23.46	24.27
Replicate 2, low	10.13	20.07

is 0.9 among third chromosomes isolated from dysgenic high lines. In particular, those chromosomes that have average homozygous abdominal bristle scores of 23 also have extremely high-average sternopleural bristle scores of 26.7. By comparison, third chromosomes extracted from those lines that have less extreme abdominal scores also have sternopleural scores averaging 18.5. Further analysis will resolve whether the association between high abdominal and sternopleural scores is caused by a single allele with a pleiotropic effect on both bristle traits or by two independent third chromosome alleles.

DISCUSSION

It appears that a significant amount of new mutational variation affecting the quantitative trait, abdominal bristle number, can be generated by the activity of transposable elements mobilized during hybrid dysgenesis. Although much of this new variation was deleterious, judging by the overall reduction in viability of chromosomes extracted from the selection lines, sufficient new additive variation was generated to account for an accelerated response to artificial selection in dysgenic, compared with nondysgenic, hybrids. It is instructive to compare the amount of variation arising from dysgenesis with that created by more conventional mutagens. CLAYTON and ROBERTSON (1955, 1964) and HOLLINGDALE and BARKER (1971) have investigated the effect of *X*-irradiation on the induction of selectable variation in abdominal bristle number of *D. melanogaster*. Comparison of response to divergent artificial selection of control and irradiated populations consistently gave estimates of an increase in response of the treated populations over approximately 20 generations of irradiation of about 1.5 bristles (single segment). The increase in response of the dysgenic populations averages 10.8 bristles (divergence) greater than the mean response of the nondysgenic lines in only ten generations; clearly, dysgenesis is a more powerful mutation than the dose of X rays used by CLAYTON and ROBERTSON

TABLE 11

Realized heritability (h^2), phenotypic variance (V_P) and additive genetic variance (V_A) estimated from the first ten generations of selection

Selection lines	Replicate	h^2	V_P	V_A
Nondysgenic, noninbred	1	0.167	3.867	0.646
	2	0.190	4.093	0.778
Nondysgenic, inbred	1	0.152	3.758	0.571
	2	0.142	3.968	0.563
Dysgenic, noninbred	1	0.280	13.791	3.861
	2	0.214	10.839	2.319
Dysgenic, inbred	1	0.216	8.313	1.796
	2	0.264	6.828	1.802

h^2 is calculated from divergence in response by regression of cumulated response on cumulated selection differential, V_P from average variance of high and low lines pooled over generations 1–10, and V_A by $h^2 V_P$.

(1800 r/generation; 1964) and HOLLINGDALE and BARKER (1000 r/generation; 1971).

How much additive mutational variation has been induced by dysgenesis? The amount of additive genetic variance present in a base population before selection can be estimated by the product of the realized heritability and the phenotypic variance. Additive genetic variance estimates are presented in Table 11 for each of the eight pairs of selection lines. The additive genetic variance for the dysgenic populations (average over all pairs of lines of 2.445) has two components: (1) variance in the original hybrids caused by segregation of alleles present in the Harwich and Canton-S stocks and (2) new variation accruing from dysgenesis. The first component is estimated by the observed genetic variation from the nondysgenic populations of 0.640 (averaged over all pairs of lines), and the second component, the new variation, thereby obtained by difference to be 1.8. This calculation underestimates the new mutational variation from dysgenesis, because some mutations will have been lost by sampling and because the dysgenic responses were not linear. CLAYTON and ROBERTSON (1964) calculated the amount of new variation caused by *X*-irradiation in their experiments, in which selection was for the sum of the scores on the two posterior tergites, to be 1.1×10^{-5}/r/generation, which is equivalent to new variation for single segment score of 2.4×10^{-6}/r/generation. It would therefore take a cumulative dose of 750,000 r of X rays to produce an equivalent amount of new variation to that caused by dysgenesis. It is doubtful that the animals would survive such treatment.

What is the nature of this new variation? Dysgenesis causes mutations by insertion and deletion of *P* elements, as well as by chromosome rearrangements, all of which could potentially contribute to variation for abdominal bristle number. The absolute number of mutational events may be very large. Transposition is likely to occur for several generations after an initial $M♀♀ \times P♂♂$ cross, as it may take up to ten generations to establish the *P* cytotype necessary for relative stability of the elements (KIDWELL, NOVY and FEELEY 1981; KIYASU and KIDWELL 1984). There is also evidence, as yet circumstantial, that *P* element

transposition mobilizes other families of transposable elements in concert. Two of seven white mutations resulting from a dysgenic cross were insertions of *copia*, which does not normally transpose at high rates (RUBIN, KIDWELL and BINGHAM 1982), and derivatives of an unstable cut mutation arising from hybrid dysgenesis and caused by an insertion of *mdg* 4 are associated with multiple transpositions of *P, FB, copia*, and *copia*-like elements (GERASIMOVA, MIZROKHI and GEORGIEV 1984). More basic work is necessary on the biology of transposition associated with dysgenesis and, in particular, the determination of rates and patterns of transposition. Without this information one can only deduce that the potential for mutation in this system is exceptional, given the various mechanisms by which *P* (and perhaps other) elements cause mutations, the number of generations over which transposition may occur and the effective population size.

Because substantial transposable element-induced variation has been detected for the quantitative character, abdominal bristle number, further analysis of the selection lines may lead to the identification and molecular characterization of genes controlling quantitative inheritance. BINGHAM, LEVIS and RUBIN (1981) have proposed a novel method of studying any genetically defined locus at the molecular level, providing that a mutation of the gene of interest is caused by insertion of a transposable element, which itself has been cloned. The inserted element plus flanking sequences corresponding to the wild type can then be recovered from a clone library by homology to the transposable element sequence. Element sequences can be subsequently removed from this clone by restriction endonuclease digestion to create a probe containing the fragment of wild-type sequence, which can itself be used to recover the unmutated gene of interest. This strategy has been applied successfully to the cloning and sequencing of the white locus of *D. melanogaster*, by using a white mutant caused by insertion of the *copia* transposable element (BINGHAM, LEVIS and RUBIN 1981). Such a molecular "fishing" experiment is not restricted to Mendelian phenotypes and could, in principle, be extended to mutant alleles at loci controlling quantitative traits.

How successful is *P* element mutagenesis likely to be as a method for recovery of insertional mutations at loci controlling particular quantitative traits, so that genes controlling quantitative inheritance can be analyzed at the molecular level? This depends on several factors. First, it is necessary that the relevant mutations are caused by insertion of elements, not by deletion or rearrangements. Second, success of the scheme depends on the sites of insertion of the elements being scattered at random throughout the genome, so that insertions can eventually occur at any given site. A preliminary survey of *X*-chromosome sites occupied by *copia*-like elements in a natural population (MONTGOMERY and LANGLEY 1983) indicates that most sites are indeed unique, but there is also evidence that not all loci are equally susceptible to insertions of *P* elements and that there may be particular "hotspots" of insertion (*e.g.*, the singed and white loci) (O'HARE and RUBIN 1983; SIMMONS *et al.* 1984). The individuals from all four replicates of the low dysgenic selection lines are phenotypically very similar, and not only because they have reduced numbers of bristles. The distribution patterns of the bristles, as well as various abnormalities of segmentation and pigmentation, are

common to all replicates, as if the same mutations have occurred in each. The high dysgenic selection lines that show the greatest response in bristle number also share other phenotypic similarities. Crosses between the replicates of the selection lines followed by further selection, as well as analysis of the distribution of *P* and other elements in each line by *in situ* hybridization, will resolve whether or not the same transposition events have repeatedly occurred.

Finally, the insertion must have an effect large enough to be recognizable phenotypically. The identification of quantitative mutations relies on the extraction of chromosomes from the dysgenic and nondysgenic selection lines and on scoring their homozygous and heterozygous phenotype. Any chromosome isolated from a dysgenic line that has a mean score outside the range of values observed for chromosomes of nondysgenic lines is a candidate for further study, but insertions causing small phenotypic changes may be missed. It is hoped that the smooth second chromosomes from the low dysgenic selection lines, the third chromosomes with extreme abdominal and sternopleural phenotypes extracted from the high dysgenic selection lines and the homozygous lethal third chromosomes isolated from the same high lines will provide interesting material for the investigation at the molecular level of genes controlling quantitative inheritance. The procedure of identifying putative polygenes via major morphological mutations may at first seem contradictory, for any gene of large effect is, by definition, not a polygene. In this regard it is important to distinguish the effects of mutant from wild-type alleles. It is feasible that variation at a typical locus affecting a quantitative trait primarily consists of many different wild-type alleles, in the sense that substitution of one for the other results in only a minor alteration of phenotype. However, rare mutations may occur at such a locus that confer such an extreme phenotype that the locus becomes recognizable by virtue of Mendelian segregation of the allele with large effect. The smooth locus is only one of 145 known major genes affecting number, shape, size and pattern of bristles and hairs on all parts of a fly (BRYANT and MURNIK 1980), most of which have pleiotropic effects on several bristle characters and fitness. Wild-type allelic variation even at subset of these loci would be sufficient to account for variation in bristle number observed in natural populations. It may even be that most "polygenes" have already been identified by major morphological mutations.

The use of artificial selection for a quantitative trait among the progeny of dysgenic and nondysgenic crosses has several limitations as a general technique for identifying mutations affecting that trait, and this should be taken into account in the design of future experiments. The detection of *P* element-induced quantitative mutations depends on increased response to selection or phenotypic variation of the dysgenic hybrids, compared with nondysgenic hybrids. If there is much additive genetic variation segregating in the cross of the *P* and *M* strains, the response to selection from the naturally occurring variation may be so large that any additional response accruing from new mutational variation may not be separable statistically from random variation between replicate lines. Fortuitously, the realized heritability of abdominal bristle score resulting from the cross of Harwich females to Canton-S males was sufficiently low that additional transposable element-induced variation in the reciprocal cross was detected by

this method. The use of inbred *P* and *M* strains may therefore be appropriate in this regard, since segregation on the F_2 is limited to differences in alleles fixed in the two strains; this is likely to give rise to less genetic variation for the character than would be present in crosses of two noninbred strains. Little difference was observed in response to selection between crosses of inbred and noninbred Harwich and Canton-S strains, presumably because the original stocks were largely homozygous. Canton-S is a standard laboratory inbred strain of long standing, and the Harwich strain descended from the progeny of only two inseminated females (KIDWELL, KIDWELL and SVED 1977).

In addition, the use of the nondysgenic cross as a control is imperfect, because transposition can occur in these hybrids. Attainment of *P* cytotype in the progeny of a *P*♀♀ × *M*♂♂ cross will not necessarily be immediate, although it is expected to be more rapid than in the reciprocal cross (KIDWELL, NOVY, and FEELEY 1981; KIYASU and KIDWELL 1984). Nevertheless, transposition may occur in the first few generations of a nondysgenic cross. Furthermore, transposition of *P* elements appears to be more frequent than other classes of mobile elements, even when "stabilized" by the *P* cytotype. PRESTON and ENGELS (1984) have estimated the rate of gain and loss of sites on the *X* chromosome of a strong *P* strain to be, respectively, 0.29 and 0.0015 per chromosome per generation. Even such a low frequency of transposition may give rise to an appreciable number of mutational events, because opportunities for transposition must be multiplied by the population size of the selection lines. Evidence that transposition may have occurred in the nondysgenic selection lines comes from the homozygous viabilities of extracted second and third chromosomes. Rather more lethal chromosomes were recovered than was expected, given that the Canton-S and Harwich strains were fairly homozygous, and viability of nonlethal chromosomes was poor. Complementation testing of homozygous lethal second and third chromosomes extracted from the parental strains with the lethal chromosomes isolated from the selection lines should resolve whether the lethals from the selection lines were present initially or were caused by dysgenesis.

Another complication regarding the use of the reciprocal, nondysgenic cross of *P*♀♀ × *M*♂♂ as a control for the dysgenic, *M*♀♀ × *P*♂♂, cross is that the two sets of hybrids are not exactly genetically identical. Hybrids resulting from the nondysgenic cross have two *P X*-chromosomes and one *M X*-chromosome, while hybrids from the dysgenic cross have two *M X*-chromosomes and one *P X*-chromosome, and the *Y* chromosomes are of different origin. Interpretation of reciprocal cross differences in response to selection in terms of differences in *P* element-induced "quantitative" mutations is therefore confounded by the nondysgenic and dysgenic hybrid difference in *X* chromosome complement. For this experiment, three lines of evidence indicate that alleles on the *X* chromosomes of the parental strains were not largely responsible for the observed difference in response to selection of the two hybrid crosses. The mean bristle scores of the reciprocal F_1 hybrids were not significantly different from each other or from the midparent value of the parental strains; artificial selection for abdominal bristle number within the parental Harwich and Canton-S strains gave little response (A. ROBERTSON, personal communication), and, more directly, second

and third chromosomes extracted from the dysgenic selection lines have effects on the character that are not observed for chromosomes isolated from the nondysgenic lines.

A final drawback to using the technique of artificial selection to concentrate insertional mutations affecting the selected trait is that the analysis of the response to selection of the dysgenic hybrids in terms of mutations only affecting the selected trait is confounded by the probable presence of other insertions affecting other characters. It is possible that the apparent selection limit observed may not be caused by pleiotropic effects of an insertion into a bristle locus (or loci), but may be caused by other closely linked insertions with deleterious effects on fitness.

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