SELECTION FOR DOMINANCE OF HAIRY-WING (*Hw*) IN
*DROSOPHILA MELANOGASTER*¹ I. DOMINANCE AT
DIFFERENT LEVELS OF PHENOTYPE

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FISHER'S theory of the evolution of dominance by natural selection of specific modifier genes (FISHER 1928a, 1928b, 1929, 1930, 1931, 1958; SHEPPARD and FORD 1966) seems to have won fairly general acceptance despite criticism on both mathematical and genetic grounds (WRIGHT 1929a, 1929b, 1934a, 1934b; HALDANE 1930, 1939; MULLER 1932; PLUNKETT 1932; CROSBY 1963; GREGG 1967). General supporting evidence for FISHER's view has come from experiments with cotton (HARLAND 1932, 1934, 1936), the currant moth (FORD 1940), mice (FISHER and HOLT 1944), poultry (FISHER 1935, 1938; DUNN and LANDAUER 1934, 1936), *Drosophila* (LANCEFIELD 1918), and butterflies (CLARKE and SHEPPARD 1960).

FISHER's emphasis was on selection of modifiers of the heterozygote which moved its expression close to the homozygote, and he interpreted the experiments cited above as supporting this viewpoint (FISHER 1958). However, many of the experimental results are inconclusive and some can be interpreted in the opposite way, namely, that selection of modifiers of the homozygote occurred to move its expression close to the heterozygote. The change in the expression of the crest mutant in poultry under domestication (FISHER 1935) is probably the clearest example. From FISHER's data and from descriptions provided by DUNN and JULL (1927), it appears that there is little difference in expression between the crest heterozygote in either the domestic or wild genetic backgrounds and the crest homozygote in the domestic genetic background. But the crest homozygote in wild background has a much more extreme expression, having a larger and more erect crest of feathers and an associated cerebral hernia. Selection under domestication must have modified the expression of the homozygote towards that of the heterozygote.

Relationships of one kind or another between canalization of development and dominance have been postulated by MULLER (1932), GOLDSCHMIDT (1955), and RENDEL (1959a,b, 1962). RENDEL took the view that dominance was a two-step process. The first step ensures that amount of morphogenetic substance or "make" produced by the second dose of an allele will be much less than that produced by the first dose. The second step, the presence of a threshold, ensures that the same phenotype will result from a whole array of values of "make" (i.e., canalization

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of development). However, RENDEL, SHELDON and FINLAY (1965) postulated that canalization of scutellar bristles in *Drosophila melanogaster* is due to regulation of a major gene (sc^+) in the system. An obvious inference from this notion is that dominance and canalization are different aspects of the same process. That is, they have both evolved by selection of a regulator genotype which controls the activity of two doses or one dose of the major gene in such a way as to produce the same phenotype in all or nearly all individuals. Thus there is no obvious difference between $+/+$ and $+/sc$ flies (dominance), except on the probit scale, nearly all $+/+$, $+/sc$, and $+/Y$ flies having four scutellar bristles (canalization). Clearly, this view of regulation of the major gene suggests that dominance is more likely to have occurred by the pathway (heterozygote $\leftarrow$ homozygote) than the opposite, favored by FISHER.

The aim of the series of experiments to be reported here has been to explore these ideas, starting with a mutant, Hairy-wing (Hw) in *Drosophila melanogaster*, which initially shows little or no dominance. Selection was practiced to try to get dominance by these two different pathways, and to see whether canalization occurred at the same time as dominance. This paper describes three lines in which the direction of selection was heterozygote $\rightarrow$ homozygote, and two lines in which selection was for heterozygote $\leftarrow$ homozygote. Correlated responses, other tests of the selection lines, and experiments on dosage effects of the Hw locus will be reported in later papers.

MATERIALS AND METHODS

The Hairy-wing mutant is a single-band duplication lying at the distal end of the X-chromosome and inseparably linked to yellow (γ) (BRIDGES and BREHME 1944). Of the various effects of the mutant, extra bristles along and near the second longitudinal wing vein is the most characteristic and was used as the selection trait (Figure 1). This wing vein is free of bristles in wild-type flies. Hw/Hw flies have numerous bristles; $Hw/+$ and Hw/Y have fewer bristles. Bristles were counted within the dotted area shown in Figure 1 on the right wing viewed from the ventral side.

As the Hw chromosome is marked by the recessive mutant yellow (γ), the different Hairy-wing genotypes can be identified simply on body color. However, it is not possible to distinguish $\gamma Hw/++$ from $++/++$ females in this way. As a proportion of $\gamma Hw/++$ flies has no wing-vein bristles in unselected populations, difficulties of identification do occur. This presented no serious problem, however, because most of the experiments involved crossing $\gamma Hw/++$ females to $\gamma Hw/Y$ males.

A homozygous γHw stock was derived from Stock No. 105, $\gamma Hw/sc^{10-1}$, obtained from the California Institute of Technology. This γHw stock will be referred to as the Hairy-wing stock.

The base population was formed by crossing Oregon R-C wild-type females to Hw males from the Hairy-wing stock in mass cultures, then crossing the F_1 females ($Hw/+$) back to Hw/Y males from the same stock in single-pair matings.

(i) *A line*: Selection in this line was designed to bring the phenotypic expression of the mutant homozygote down to the level of the heterozygote, while holding the latter constant at its unselected level. The first selected generation was produced from the four families in the base population with the smallest difference between the means of Hw/Hw and $Hw/+$. From these selected families, $Hw/+$ females and Hw/Y males with 5 bristles were selected, i.e., at the base population $Hw/+$ level, and were mated in single pairs in a circular mating scheme such that males from the first selected family were mated to females of the second selected family and so on. Thus four distinct *sib-lines* were formed in each generation. This procedure was followed

FIGURE 1.—Wing of *Drosophila melanogaster* showing extra bristles produced by *Hw* flies and the area around the second longitudinal vein within which bristles were counted in these experiments.

for 31 generations. Normally six single-pair matings were set up per sib-line but only the three best of these six cultures used for scoring. One family of the three scored was then selected on the basis of smallest difference between *Hw/Hw* and *Hw/+* and the cycle repeated. Forty *Hw/Hw* and forty *Hw/+* females were scored from each culture in each generation and 20 males of each genotype (*Hw/Y* and *+/Y*) every fifth generation.

A subline (A1) was taken off at generation 15 and another one (A2) at generation 22. In each case the best selected family of that generation was chosen and several single-pair full-sib matings between *Hw/+* and *Hw/Y* made up from it, each sib having 5 bristles. The culture in which the difference between *Hw/Hw* and *Hw/+* progeny was the smallest was selected; full-sib matings were made up from this culture and so on through 17 and 10 generations, respectively.

(ii) *C line*: This line served as a control for line A in that selection was directed towards bringing the expression of the mutant homozygote down to the level of the heterozygote without attempting to hold the latter constant.

The parental generation consisted of the progeny of ten bottle mass matings, five pairs per bottle, between *Hw/+* females and *Hw/Y* males taken at random from the base population used for lines A and B. Twenty *Hw/Hw* females were scored per bottle and the five lowest in each bottle selected. The selected ones were pooled and mated at random to random *+/Y* males, pooled from the same bottles, in mass matings of 5 pairs per culture.

In the next and succeeding alternate generations no selection was possible as there were no *Hw/Hw* flies. Five *Hw/+* females and five *Hw/Y* males were taken at random from each bottle, pooled, and set up in mass cultures of five pairs each. Selection was applied to the *Hw/Hw* progeny of these matings and so on in alternate generations.

(iii) *B line*: Selection in this line was designed to see if the phenotypic expression of the heterozygote could be brought up to the unselected level of the mutant homozygote, without any direct attempt to hold the latter constant. The first selected generation was produced from the same four selected families as were used to begin A line. In the following generations families with the least difference between *Hw/Hw* and *Hw/+* were also selected. From the selected families *Hw/+* females with the highest bristle number were selected and mated in single pairs in a circular mating scheme to random *Hw/Y* males, also from the selected families. The remaining procedures were similar to those in line A.

Four sublines (B1, B2, B3, B4) were taken off line B at generations 5, 5, 16 and 20, respectively. In the first three, the family in that generation with the smallest difference between *Hw/Hw* and *Hw/+* was chosen to start the subline. In B4 the family with the biggest excess of *Hw/+* over *Hw/Hw* bristle number was chosen. This pattern of family selection was followed

in succeeding generations. However, as only one family out of three scored was selected each generation in each subline, full-sib matings were the rule. Selection of individuals from the selected family varied from line to line. In B1, $Hw/+$ females with 20 bristles (the line B population mean at generation 5) were mated singly to random Hw/Y males. In B2 the same procedure was followed for 15 generations until it became impossible due to the increase in the population mean. After that $Hw/+$ females were chosen which had the same bristle number as the mean of that genotype in the previous generation. In B3, $Hw/+$ females with 30 bristles were mated to random Hw/Y males until a similar difficulty was met after 5 generations. The females selected from then on were those with the same bristle score as the mean of the previous generation. In B4, $Hw/+$ females with the highest bristle number were mated to random Hw/Y males.

(iv) *D line*: This line served as a control for line B, heterozygotes being selected for high bristle number as in line B but without any family selection for small difference between homozygote and heterozygote. The parental generation was the same as for line C. The first and following selected generations were produced by mating $Hw/+$ females with highest bristle number to random Hw/Y males in mass cultures. Ten bottle cultures were used per generation, 5 females were selected out of 20 scored in each bottle and in mass matings five pairs per bottle were used.

(v) *E line*: The aim of selection in this line was to bring the phenotypic expression of the heterozygote up to the unselected level of the mutant homozygote while making a direct attempt to hold the latter constant.

A second base population sample was produced in the same way as for lines A and B. The four families with the smallest difference between the means of Hw/Hw and $Hw/+$ were selected. From these only Hw/Hw females with about 20 bristles were used, i.e., the mean level of this base population sample. These females were mated in four mass matings, five pairs per sib-line, to random $+/Y$ males from the appropriate selected family, a circular mating scheme being used as in lines A and B. In the next generation random single-pair matings were made between $Hw/+$ females and Hw/Y males, the circular mating scheme being preserved. These matings produced the next segregating generation in which selections could be made as before. This scheme of alternating generations of mass and single-pair cultures was continued throughout, other procedures being similar to those used in line B.

RESULTS

(i) *A line*: The mean numbers of bristles on and near the second longitudinal wing vein (right wing, ventral aspect) in the base population were 16.13 ± 3.98 for Hw/Hw , 4.71 ± 3.54 for $Hw/+$ and 6.32 ± 3.53 for Hw/Y . The response to selection in Line A is shown in Figure 2. $Hw/+$ and Hw/Y remained relatively constant, but Hw/Hw moved towards them quite rapidly. At the end of selection they were about one bristle apart. Although complete identity of homozygote and heterozygote mean scores was not achieved, it is clear that selection for dominance of Hw at the original level of the heterozygote has been successful. Relaxation of selection over 10 generations possibly led to a little loss of previous selection gain but the situation was essentially stable. The variance of all three genotypes decreased steadily during selection. In generation 31 the standard deviations were Hw/Hw 1.8, $Hw/+$ 1.6, i.e., about half the base population values.

The response to selection in sublines A1 and A2 is shown in Figures 3 and 4. The sublines were similar to line A itself, but the difference between homozygote and heterozygote decreased to less than 0.5 in A1 and became negative in A2. As in line A, both lines were reasonably stable when selection was relaxed. The variance in all three genotypes of lines A1 and A2 decreased as it did in line A.

FIGURE 2.—Response to selection in line A.

FIGURE 3.—Response to selection in subline A1.

FIGURE 4.—Response to selection in subline A₂.

One of the original aims of this series of experiments was to see whether canalization would also result from selection for dominance. In line A the degree of canalization was assessed not only by looking in detail at changes in the variance by probit analysis, but also by testing whether development of the Hairy-wing phenotype had become less sensitive to temperature change.

(a) *Probit analysis*: The sensitivity of bristle development to influences tending to alter bristle number can be measured by estimating the distance in probits subtended by a selected bristle class. To transform a frequency distribution to the probit scale we calculate percent flies with 0; 0.1, & 2; 0.1, 2, & 3; etc. bristles and look for the corresponding probit value in tables of FISHER and YATES (1953). The probit values are the distances from the mean of the population in standard deviations of the 0/1, 1/2, 2/3, etc. bristle cut-off points. By subtraction, the probit distance occupied by each bristle class is obtained. For further details on application of probit analysis to these data, see RENDEL (1962).

Table 1 shows how the probit widths of the bristle classes of Hw/Hw females of line A changed during selection. Values are given only for the classes up to 18 bristles. In the base population the actual number of bristles of this genotype ranged from 5 to 29, about 36% of flies having above 18 bristles; by the 5th generation this value was about 10%, at the 10th generation 0.35%, and at the 15th generation 1%. The probit width of all bristle classes increased during selection but especially of the 5, 6, and 9 bristle classes. The general increase over all classes probably reflects a general reduction in variance, while the additional increase in classes 5, 6, and 7 may indicate canalization beginning at that level of phenotype. However, while the probit values of the $Hw/+$ females and the Hw/Y males increased in the same general way, the increases in the 4–7 bristle classes were not clearly bigger than the rest. These two genotypes, therefore, do not support the above conclusion. Nevertheless, the possibility remains that the general reduction in variance in the three genotypes, reflected by the general increases in probit values, does itself indicate the beginning of some canalization

TABLE 1
*Probit distances occupied by bristle classes of homozygous females (H_w/H_w)
 in various generations of line A*

Bristle Class/ Generation	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Total number scored
0*		0.30	0.23	0.14	0.47	0.18	0.30	0.37	0.26	0.27	0.21	0.25	0.27	0.25	0.24	430
5*					0.56	0.35	0.45	0.37	0.42	0.36	0.37	0.26	0.33	0.22	0.36	368
10*			0.77	0.53	0.36	0.39	0.41	0.46	0.33	0.39	0.53	0.62	0.39			284
15*		0.54	0.37	0.40	0.44	0.39	0.29	0.31	0.43	0.42	0.43	0.42	0.19	0.20	0.37	318
20		0.66	0.43	0.45	0.52	0.43	0.45	0.53	0.42	0.51	0.27	0.43	0.38			328
21		0.58	0.60	0.49	0.58	0.36	0.52	0.28	0.44	0.42	0.41	0.34				336
22	0.48	0.78	0.53	0.42	0.41	0.39	0.41	0.41	0.51	0.33	0.57					332
23	0.73	0.63	0.64	0.48	0.54	0.35	0.40	0.36	0.60	0.17	0.11	0.15	0.24			287
24	0.60	0.66	0.68	0.45	0.43	0.57	0.40	0.43	0.23	0.80						234
25		0.57	0.72	0.68	0.50	0.52	0.42	0.46	0.57	0.25						216
26*	0.40	1.05	0.47	0.39	0.33	0.36	0.58	0.22	0.30	0.26	0.07	0.17	0.28	0.25		194
27		0.60	0.65	0.68	0.43	0.40	0.38	0.42	0.38	0.16	0.27					160
28		0.61	0.77	0.64	0.46	0.47	0.61	0.29	0.25							153
29		0.77	0.67	0.56	0.67	0.59	0.37	0.52								174
30		0.97	0.31	0.72	0.52	0.45	0.49		0.14			0.20	0.30			50
31		0.71	0.65	0.54	0.57	0.48	0.59	0.23	0.16							143
Average of generations 27 to 31		0.73	0.61	0.63	0.53	0.51	0.49	0.37	0.23	0.16	0.27	0.20	0.30			680
Ratio of 27 - 31 : 0		2.43	2.65	4.5	1.13	2.83	1.63	1.00	0.88	0.39	1.29	0.80	1.11			

* Probit values not calculated for bristle classes beyond 18 bristles.

of development. Probit analysis in lines A1 and A2 showed trends similar to line A.

(b) *Effect of temperature:* Line A was compared at generations 30 (Test 1)

TABLE 2
*Temperature effects on the mean bristle number in the unselected Hairy-wing line,
 A line, and subline A1 (Test 1)*

LINES	GENOTYPES	TEMPERATURE						DIFFERENCES (low - medium - high temperature)			
		18°C		25°C		30°C		18° - 25°	25° - 30°	18° - 30°	
		n	m + s	n	m + s	n	m + s				
Unselected Hairy-wing base line	$\overline{Hw}/\overline{Hw}$	27	15.52 ± 2.47	162	12.65 ± 2.70	178	5.66 ± 2.76	2.87	6.99	9.86	
	$\overline{Hw}/\overline{Y}$	140	15.23 ± 2.55	151	8.34 ± 3.87	185	0.0	6.89	8.34	15.23	
A line	$\overline{Hw}/\overline{Hw}$	6	8.00 ± 0.63	145	7.01 ± 1.95	120	5.54 ± 1.64	0.99	1.47	2.46	
	$\overline{Hw}/+$	122	8.42 ± 1.92	150	7.18 ± 1.94	120	0.03	1.24	7.15	8.39	
	$\overline{Hw}/\overline{Y}$	124	8.71 ± 1.97	139	6.73 ± 1.96	100	0.03	1.98	6.70	8.68	
Subline A1	$\overline{Hw}/\overline{Hw}$	-	-	40	5.75 ± 1.19	58	5.26 ± 1.38	-	0.49	-	
	$\overline{Hw}/+$	45	8.07 ± 1.97	42	7.17 ± 2.03	67	0.0	0.90	7.17	8.07	
	$\overline{Hw}/\overline{Y}$	16	6.69 ± 1.73	27	6.37 ± 1.33	53	0.0	0.32	6.37	6.69	

s = standard deviation

m = mean bristle number

n = number scored

and 35 (Test 2), and A1 at generations 16 (Test 1) and 21 (Test 2), with the unselected base line. In both tests and in each line, five mass cultures with 5 pairs of parents were raised and scored at each of three temperatures (18°, 25°, and

TABLE 3
*Temperature effects on mean bristle number in the unselected Hairy-wing base line,
 A line, and subline A1 (Test 2)*

LINES	GENOTYPES	TEMPERATURE						DIFFERENCES (low - medium - high temperature)		
		18°C			25°C			30°C		
		n	m ± s	n	m ± s	n	m ± s	n	m ± s	
Unselected Hairy-wing base line	Hw/Hw	45	19.27 ± 4.03	100	16.87 ± 4.80					
	Hw/+	100	16.03 ± 3.39	100	3.59 ± 3.23	90	2.47 ± 2.17			16.80
	Hw/Y ⁻	100	18.33 ± 4.82	100	8.95 ± 6.39	90	0.0	2.40	14.40	16.03
A line	Hw/Hw	34	8.38 ± 1.70	90	6.86 ± 1.86					
	Hw/+	100	9.02 ± 1.88	80	4.41 ± 1.51	46	5.00 ± 1.41	1.52	1.86	3.38
	Hw/Y ⁻	100	9.88 ± 2.20	70	5.39 ± 1.60	50	0.0	4.61	4.41	9.02
Subline A1	Hw/Hw	36	6.97 ± 1.52	100	6.14 ± 1.58					
	Hw/+	55	7.89 ± 1.60	100	5.10 ± 1.79	40	3.20 ± 1.12	0.83	2.94	3.77
	Hw/Y ⁻	47	8.83 ± 2.03	100	5.07 ± 1.44	51	0.0	2.79	5.10	7.89
						60	0.0	3.76	5.07	8.83

n = number scored m = mean bristle number s = standard deviation

30°C), except that 20 cultures per line were used for the 18°C treatment in the second test.

Tables 2 and 3 give the results of these tests. In general all the lines have fewer

bristles at 30°C and more bristles at 18°C than at 25°C. The selected lines were less affected by temperature than the unselected base line. In *Hw/Hw* females the difference between 18° and 30° was only 3–4 bristles in the selected lines compared with 10–17 bristles in the unselected. In *Hw/+* females and *Hw/Y* males the difference due to temperature between selected and unselected was less because at 30°C all these genotypes were reduced virtually to zero bristles. One explanation of this is that it is simply a scale effect masking the real difference between selected and unselected at 30°C. Whether this is so or not, it seems reasonable to conclude that the selection practiced in the A lines was effective in stabilizing development to some extent against changes in the environment.

(ii) *C line*: The selection response of line C is shown in Figure 5. The number of bristles in the three genotypes decreased rapidly to reach zero by generations 11 and 12, the response of *Hw/Hw* being much bigger than *Hw/+* and *Hw/Y* after generation 6. Examination of the original data shows that by generation 5, *Hw/Hw* flies without bristles began to appear and to be selected. From then on the frequency of *Hw/Hw* without bristles increased rapidly and the mean fell dramatically. Selection was relaxed completely at the 15th generation.

The probit scale is more informative about changes in the mean when the mean bristle number approaches zero. Changes in the mean on the probit scale are shown in Table 4. The means of the three genotypes came very close together

FIGURE 5.—Response to selection in line C.

TABLE 4

Change in the mean on the probit scale of the genotypes in C line
 Values given are distances in standard deviations from the 0, 1 bristle threshold

Generation	<i>Hw/Hw</i>	<i>Hw/+</i>	Difference <i>Hw/Hw</i> — <i>Hw/+</i>	<i>Hw/Y</i>
5	+2.33 σ	+0.44 σ	1.89 σ	+1.20 σ
6	+2.33	+0.23	1.90	...
7	+0.95	—0.06	1.01	...
8	+0.21	—0.35	0.56	...
9	+0.10	—0.27	0.37	...
10	—0.93	—1.18	0.25	—0.84
11	—1.55	...	...	...

on the probit scale as well as on the arithmetic scale. That is, the similarity of means was not simply a scale effect as all classes approached zero bristles, but a real approximation of the homozygote to the heterozygote as they both passed behind the zero threshold. Formally this means that in line C dominance was achieved at the level of zero bristles. The three genotypes remained at this level through 10 generations of relaxation of selection.

The sensitivity of line C flies to temperatures of 18°C and 30°C was tested at the 4th relaxed generation, in conjunction with the temperature test of line A reported above (Table 3). The mean bristle numbers of *Hw/Hw* in line C were 0.67 ± 0.99 at 18°, 0.006 at 25°, and zero at 30°C. The effect of low temperature on line C homozygotes measured on the probit scale was greater than in line A and the unselected base line (Table 5). This gives no indication of canalization beginning at the 0–1 bristle level in line C (unlike line A where some canalization probably occurred at 5–6 bristles). However, *Hw/+* and *Hw/Y* had no bristles at all at the three different temperatures. Their closeness to *Hw/Hw* on the probit scale at 25°C (Table 4) and the relatively large increase in bristle number of unselected *Hw/+* and *Hw/Y* at 18°C (Tables 2 and 3) suggest that these two C line genotypes were less responsive to 18°C treatment than their unselected counterparts. This is an indication of some stability in the face of temperature change having developed in line C, but the evidence is too scanty for any weight to be put on it.

TABLE 5

Probit values at selected bristle cut-off points in Hw homozygotes of A line, C line and unselected base line at 25°C and 18°C

	A line at 5, 6 bristle cut-off point	C line at 0, 1 bristle cut-off point	Unselected base line at 14, 15 bristle cut-off point
18°C	3.11	5.25	3.78
25°C	4.08	7.48	4.59
Difference between 18°C and 25°C	0.97	2.23	0.81

FIGURE 6.—Response to selection in line B.

(iii) *B line*: The selection response in line B is shown in Figure 6. The mean bristle number of the 3 genotypes increased rapidly, but faster in $Hw/+$ and Hw/Y than in Hw/Hw . $Hw/+$ quickly reached about the same level as Hw/Hw , i.e., a situation of dominance of Hw . Hw/Y ran parallel to $Hw/+$, the ratio of the score of one to the other remaining much the same throughout (approximately 1.2). A plateau was reached between generations 25 and 35. In addition the hemizygous wild-type males ($+/Y$), which had no bristles on the wing vein initially, began to develop some as selection proceeded. By generation 10 a few wild-type males showed one or more bristles and their frequency continued to increase slightly from then on. Wild-type females were not scored in this line.

Figure 7 illustrates the marked increase in bristle number in this line. The Hw/Hw often had irregular, branching, and plexate veins but the $Hw/+$ and Hw/Y mostly showed a more regular pattern of extra bristles situated along a normal wing vein.

In all three mutant genotypes the standard deviation increased steadily as the mean increased. Maximum values were 7.96 for Hw/Hw at generation 15, 7.88

FIGURE 7.—Wing of a *Hw/Hw* fly from line B showing the increase in number of wing bristles in this line.

for *Hw/+* at generation 22, and 6.53 for *Hw/Y* at generation 15. However, as the rate of response slowed and the plateau was reached, the standard deviation declined again to about 5.0–5.5 in the three genotypes. Neither the mean bristle numbers nor the standard deviations were affected much by relaxing selection for 12 generations (Figure 6). The high degree of dominance achieved by selection was thus retained when the selection pressure was removed.

The selection response in line B1, which was derived from line B at generation

FIGURE 8.—Response to selection in subline B1.

FIGURE 9.—Response to selection in subline B2.

5 and in which the aim was to hold the heterozygote mean at 20 bristles, is shown in Figure 8. The difference between *Hw/Hw* and *Hw/+* narrowed to less than one bristle in the first generation and stayed about this level for seven generations. However, ten generations of rather erratic fluctuation and very low fertility followed before the line was finally lost. In spite of the selection of *Hw/+* females with only 20 bristles the female means drifted to about 24 bristles. The hemizygous male score increased to retain its proportionality to *Hw/+* females. The standard deviations fluctuated just below the starting levels as at generation 5 of B line, i.e., 3–5 for *Hw/Hw* and *Hw/+* and 4–5 for *Hw/Y*.

Line B2, with the same aim as B1, responded quite differently as shown in Figure 9. While the *Hw/+* mean was held around 20–23 bristles (generations 1–13), the difference between this genotype and *Hw/Hw* actually increased rather than decreased. This trend was suddenly reversed in generations 14 and 15, the *Hw/+* mean increasing sharply while *Hw/Hw* remained at about 27 bristles. The two genotypes then stayed close together mostly at 27–29 bristles, except for large, low fluctuations in *Hw/+* at generations 20, 24, and 29. As in previous lines, *Hw/Y* males followed the pattern of the *Hw/+* females. The relaxed line showed lower means and an increase in the difference between *Hw/Hw* and the *Hw/+* compared with the general levels of the last 15 generations of the selection line. The standard deviations of the three genotypes during selection and relaxation were similar to line B1, i.e., lower than generation 5 of line B.

The selection response in line B3, derived from generation 16 of B line and aimed at holding the heterozygote mean at 30 bristles, is shown in Figure 10. The means of both *Hw/Hw* and *Hw/+* increased rapidly to a ceiling around 40 bristles, similar to B line. The difference between them ranged from 0 to 4 bristles with *Hw/+* usually higher than *Hw/Hw*. At the same time the *Hw/Y* males increased to a plateau of about 50 bristles, maintaining a ratio of about 1.2

FIGURE 10.—Response to selection in subline B3.

to the $Hw/+$. The original procedure of selecting $Hw/+$ with 30 bristles could not be maintained after generation 4. The standard deviations of the three genotypes decreased rapidly from their original level of 6.5–7.5 to about 3.5–4.5. Relaxation of selection did not alter the degree of dominance or the variance, but may have led to a slight reduction in the means after 10 generations (Figure 10).

Figure 11 shows the selection response in line B4. The aim in this line, derived from generation 20 of line B, was to select for an increase in the excess of $Hw/+$ over Hw/Hw bristle number, which first occurred in that generation. The difference increased to about 6–7 bristles by generations 6 and 7, and later increased still further but varied between 4 and 12 bristles. Hw/Hw remained fairly steady around 41 bristles, but $Hw/+$ increased to about 50 bristles. The increase in Hw/Y males was less than proportionate to the increase in $Hw/+$, unlike lines B, B1, B2 and B3. The standard deviations varied between 3.5 and 5.5 for Hw/Hw , 3.6 and 7.2 for $Hw/+$, 5 and 6.2 for Hw/Y without showing any clear trends. Relaxation of selection (Figure 11) led to (i) loss of the negative difference in 5 generations, (ii) a large decrease in the means of $Hw/+$ and Hw/Y and a small decrease in Hw/Hw , (iii) recovery of the ratio of 1.2 for Hw/Y to $Hw/+$, and (iv) a slight reduction in the standard deviation of Hw/Hw , but a slight increase in $Hw/+$ and Hw/Y .

(iv) *D line*: The response to selection in line D is shown in Figure 12. The general trends of the response, including the pattern of extra bristles, were surprisingly similar to those in line B (Figure 6 and Section (iii) above) in spite of

FIGURE 11.—Response to selection in subline B4.

the very different selection procedures. The main difference from line B was that an excess of $Hw/+$ over Hw/Hw , beginning at Generation 19, persisted until selection ceased at generation 40. In addition selection was continued for 5 generations longer than in line B and yielded a further response of about 5 bristles in each of the three Hw genotypes.

Wing vein bristles were first recorded in wild-type males at generation 25, when their mean score was 0.15. At generation 40 their mean had increased to 0.62 bristles. Wild-type (+/+) females were also produced from matings of $Hw/+$ females and +/Y males at generation 40. Their mean bristle number was 1.33 ± 1.62 with a range from zero to 6 bristles.

The standard deviations in line D increased similarly to line B, peak values of 6.6 for Hw/Hw at generation 6, 6.4 for $Hw/+$ at generations 9 and 11, and 6.3 for Hw/Y at generation 10 being reached earlier than in line B. They declined only slightly after that, varying between 4.6 and 5.7 for Hw/Hw and between 5.0 and 6.0 for $Hw/+$ and Hw/Y at the end of selection.

Ten generations of relaxation of selection (Figure 12) had no effect on the relationship between the scores of the three Hw genotypes, but the means of the females may have declined slightly.

At generation 32 when the response to selection for high $Hw/+$ appeared to have reached a ceiling, we decided to begin selecting in a derived line (line F) for high bristle score in +/Y males. This line was maintained in ten cultures per

FIGURE 12.—Response to selection in line D.

generation, each with 5 random $Hw/+$ female parents and 5 selected $+/Y$ male parents. Each generation 20 $+/Y$ were scored per culture, the top 5 being selected and pooled with those from the other cultures. Every fifth generation the other genotypes, Hw/Hw , $Hw/+$, Hw/Y , $+/+$ were scored, except that Hw/Hw was missed in generation 5.

The response to selection in line F is shown in Figure 13. Four or five generations of minor response were followed by a steady and large response for 15 generations in $+/Y$ males, $Hw/+$ females, and Hw/Y males but not in Hw/Hw females. Thus the close approximation of heterozygote to homozygote (dominance) achieved in D line was reduced by the selection on $+/Y$ males. The standard deviation remained steady at 6–7 for Hw/Hw but increased to about 9 for $Hw/+$ and Hw/Y . The standard deviation of $+/+$ females also increased, from about 3 at generation 5 to about 9 at generation 20, and of $+/Y$ males from 2.6 at generation 5 to 6–7 in the last few generations.

(v) *E line*: This line was started later than the other main lines (i.e., at about generation 20 of lines A and B) and from a different sampling of the base popu-

FIGURE 13.—Response to selection in line F.

FIGURE 14.—Response to selection in line E.

lation. The mean bristle numbers of the Hairy-wing genotypes in the E-line base population were higher than in the base population sample from which lines A, B, C, and D were started, i.e., Hw/Hw was about 20 bristles, $Hw/+$ about 9 bristles, and Hw/Y about 11 bristles. While the increase was probably due mainly to culture or sampling effects, some part was clearly due to the E-line experiment being scored by a different observer.

The response to selection in line E is shown in Figure 14. The difference between heterozygotes and homozygotes was reduced to about 4 bristles after 5 generations of selection. It increased again to as much as 8 bristles between generations 6 and 11, fluctuated considerably around 3 to 5 bristles in the following period before reaching a low of 1.5 bristles at generation 23. This was followed immediately by a further widening of the difference to as much as 8 bristles, then a return to about 2 bristles at generation 33, and finally an increase followed by a decrease in the difference in the last two generations. All of the time the homozygote mean remained in the region of 20–26 bristles. The attempt to hold this genotype constant was reasonably successful, though some factor clearly prevented the fixation of the high degree of dominance (homozygote equals heterozygote) achieved periodically. The mean of the hemizygous males increased proportionately more than the heterozygotes, unlike the other selection lines. The ratio of Hw/Y to $Hw/+$ was consistently above 1.2 and had a peak value of 1.47 at generation 21. The mean of Hw/Y was above that of the homozygous females for most of the second half of the experiment.

The variance of all three genotypes increased sharply in the first ten generations, remained high for ten to fifteen generations and declined to base population level again in the last five to ten generations. The highest levels of the standard deviations were 5.8 for Hw/Hw at generations 2 and 6, 6.5 for $Hw/+$ at generation 9, and 8.3 for Hw/Y at generation 8. The pattern of change in the variance bore no obvious relationship to the response pattern in Figure 14.

DISCUSSION

Perhaps the most interesting feature of these results is the wide array of levels of phenotype at which dominance has been achieved by selection. By dominance we mean the equivalence or approximation of the mean phenotypes of heterozygote and homozygote. The peculiar features of the hemizygote results will be discussed later. Thus, we have produced populations in which Hw is completely or almost completely dominant over its wild allele around the levels of 0, 5–7, 20–22, 23, 23–28, 38–41, 40–44, 44–47, 40–50, and 48–55 bristles. Dominance was obtained in all the selection lines and sublines, and retained in most of them when selection was relaxed. However, dominance was in no case accompanied by the uniformity of expression usually associated with dominance of wild-type genes.

If we look at the different selection lines in terms of the types of gene action and interaction apparently involved, we can say that in the A lines negative or minus (suppressor, repressor) modifiers specific for two doses of Hw have been selected. In lines B, B4, and D the main dominance response was probably due to positive or plus (enhancer) modifiers specific for one dose of Hw , superimposed

on the effect of selection of general plus modifiers raising the bristle number of all genotypes in the lines, including $+/Y$ and $+/+$. The sublines B1, B2, and B3, however, because of the selection for constant $Hw/+$, could have also accumulated negative modifiers specific for the homozygote, similar to the A lines, but, of course, at much higher levels of bristle number. Similarly line C would have involved negative modifiers specific for the homozygote, superimposed on the effect of general negative modifiers reducing the bristle number of all genotypes. In line E the response could have been due to plus modifiers specific for a single dose of Hw or a combination of this, general plus modifiers, and minus modifiers specific for two doses of Hw . Line F, starting from the situation already obtaining in line D, would have accumulated plus modifiers specific for the $+$ allele rather than for Hw , the response being in $+/Y$, $+/+$, and $Hw/+$ but not in Hw/Hw . Again the peculiar nature of the Hw/Y response does not fit this view, and will be discussed later.

On this view of the selection responses, dominance is modified by at least the two different pathways referred to in the introduction, i.e., selection of modifiers moving the expression of the heterozygote towards that of the homozygote, as emphasized by FISHER, and selection of modifiers moving the phenotype of the homozygote towards that of the heterozygote. The latter was favored by the present authors following RENDEL, SHELDON and FINLAY's (1965) model of canalization through control of a major gene in the developmental system. That is, dominance and canalization could be considered to have been evolved by selection of a regulator genotype which confines the activity of two doses of the gene to approximately the level of one dose. However, none of the selection lines supports this idea. Even the A lines achieved only a very minor degree of canalization, while reaching almost complete dominance, so they did not select simply regulator genes controlling the phenotype at the 5-6 bristle level. None of the other lines showed any indication of canalization, which reinforces the conclusion from the A lines that the dominance modifiers are different in type and function from the regulators envisaged by the canalization model. Canalization must therefore be discarded as an important factor in the evolution of dominance, though dominance is not ruled out as an important step in the evolution of canalization. Indeed, contrary to our own earlier view and to MULLER's (1932), constancy of phenotype in the face of genetic and environmental variation is probably the result of at least two selection steps, dominance and canalization. Dominance roughly equalizes the activity of one and two doses of the gene, whether by a repression mechanism on the homozygote or an enhancement mechanism on the heterozygote. Canalization superimposes the tight control needed to give almost absolute constancy of phenotype, and this is achieved by regulator genes, different from the dominance modifiers, controlling the output of the major gene in such a way as to buffer development at a particular level of phenotype against variation in both minor gene background and environment. The question remains as to whether the different pathways and the different types of gene action and interaction by which dominance has been achieved in this experiment give any further indication of the basic genetic mechanisms

involved. Where negative modifiers specific for the homozygote have been postulated, they can obviously be regarded as having a controlling or regulating function, though not in the tight-control or canalization sense. They could switch on and switch off gene activity at the locus in such a way that the output of two doses of the gene is kept down to about the same as one dose, and therefore fall within the ambit of the JACOB-MONOD and derived models of gene regulation (JACOB and MONOD 1961; JACOB, ULLMAN and MONOD 1964; BECKWITH 1967). Where positive modifiers specific for the heterozygote are postulated, it is more difficult to see the type of mechanism that might be operating. It is possible, of course, that the interpretation given for lines B and D is wrong and that repressor genes for the homozygote are involved here too, the heterozygote having attained that level by selection of general plus modifiers. However, this appears untenable since selection in line D was simply for the highest heterozygotes, allowing no direct scope for selection against higher expression of the homozygote.

RENDEL (1968, 1969) has suggested that the dominance modifiers, whether in our terms specific repressors of the homozygote or specific enhancers of the heterozygote, act by controlling the number and type of replicas (slave genes, CALLAN 1967) made by the dominant gene and its allele. He further suggests that canalization regulators act by controlling the activity of the replicas. However, it is not clear to the authors that the dominance aspect of this hypothesis can accommodate all the results of the experiments reported here.

On this hypothesis, in our unselected base population *Hw/Hw* flies would have been producing more replicas of *Hw* than *Hw/+* and *Hw/Y*. Replicas of the + allele would have been produced in *Hw/+* but contributed nothing to the phenotype. In lines A, A1, A2, and C the selected genotype which stopped *Hw/Hw* making replicas of *Hw* at the same number as unselected *Hw/+* would presumably be activated by or responsive to the number of *Hw* replicas such that replication at the locus would cease when that number was reached. If the *Hw/Hw* response in lines B and D is accounted for completely by general plus modifiers of bristle number (i.e., an increase of some 30 bristles), the dominance modifiers can be considered to have increased the capacity of *Hw/+* to make replicas of *Hw* up to about the number in unselected *Hw/Hw*. A similar view can be taken of line E if the lack of response in *Hw/Hw* indicates no change in the background of general modifiers. As indicated above in a less specific sense, it is more difficult to see a possible mechanism for this enhancer activity. One possibility would be repression of replication of the + allele in *Hw/+* and correspondingly increased replication of the *Hw* allele, but this tends to be ruled out by the similar response of *Hw/Y* where there is no + allele. Line F raises a further difficulty. The response in *+/+* and *+/Y* is seen in *Hw/+* and *Hw/Y* but not in *Hw/Hw*, so it should not be due simply to general plus modifiers. Disregarding *Hw/Y* for the moment, neither should it be due to increased replication of the + allele, since the bristle-making potential of + is insignificant compared to *Hw*. If the response in F line requires an explanation not involving gene replicas, then it is likely the other selection lines do also. Nevertheless, we cannot rule out the possibility that the apparently insignificant bristle-making

potential of the + allele is itself the result of control over production of + replicas in the unselected population. Clearly more information is needed, but for the present, RENDEL's suggestion would appear to be the best working hypothesis available.

The remaining major feature of our results not yet discussed is the special relationship shown between the hemizygote and the heterozygote. In all the selection lines the hemizygote response ran parallel to that of the heterozygote, with the ratio of the scores remaining about the unselected level of 1.2 regardless of what happened to the homozygote. To describe it in this way, however, is not to ignore the fact that in the high lines *Hw/Y* often had about 10 bristles more than *Hw/+*, i.e., as big a bristle difference as occurred between *Hw/+* and *Hw/Hw* in the base population. A possible explanation is that the initial unselected relationship between them is due to specific modifiers in the X-chromosome active only in the single-X individual (similar to STERN's and MULLER's views of dosage compensators for sex-linked genes). These remain and have their effect at whatever level *Hw/+* is fixed. In view of the increased bristle difference, however, it is more likely that the selected specific enhancers of the heterozygote simply have a greater effect in the hemizygote. Absence of competition from the + allele in *Hw/Y* may be the reason, if a gene replica model is operating. Neither of these explanations brings us much closer to an understanding of the basic mechanism.

Perhaps a final comment should be made on the type of mutant (*Hw*) we have been dealing with, since it may affect the reader's interpretation of our results. MULLER (1932) classified *Hw* as a neomorph and its wild-type allele *Hw*⁺ as an amorph. However, DEMEREC and HOOVER (1939), on the basis of results for individuals with various numbers and arrangements of salivary band 1B1-2, which is duplicated in *Hw*, maintained that *Hw* is a hypermorph and that *Hw*⁺ has a weak but definite effect. Our results for +/+ and +/Y in lines B, D, and F also raised doubts about the amorph label for *Hw*⁺. From results of some gene dosage experiments involving extra doses of *Hw* or *Hw*⁺ in unselected and selected backgrounds we have concluded that *Hw* behaves indeed as a hypermorph and *Hw*⁺ as a hypomorph, since the latter always has a measurable effect. These results will be reported in a later paper.

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SUMMARY

Results are presented for five selection lines and seven sublines derived from them at various stages of selection. The character being studied was the number of bristles along the second longitudinal wing vein. In three lines family selection was practiced for the minimum difference between *Hw/Hw* and *Hw/+*. In the first line (A) individual selection of *Hw/+* and *Hw/Y* flies with 5 bristles was

superimposed on the family selection to try to hold the mean level of *Hw*/+ and *Hw*/*Y* at that of the base population. In the second line (B), individual *Hw*/+ flies with the highest scores were selected from the selected families, i.e., initially those closest to *Hw*/*Hw*. No direct attempt was made to hold *Hw*/*Hw* at the unselected level. In the third line (E) individual *Hw*/*Hw* flies with about 20 bristles were selected from the selected families, i.e., to try to hold the mean level of *Hw*/*Hw* at that of the base population. The other two main lines were mass selection lines, one selected for lowest scores of *Hw*/*Hw* (C), and the other for highest scores of *Hw*/+ (D).—Dominance of varying degrees was obtained in all the selection lines and sublines, and about a range of different levels, namely 0, 6, 21, 23, 25, 39, 42, 45, and 51 bristles. That is, the mean score of *Hw*/+ was equal to or approximated the mean score of *Hw*/*Hw*. However, the uniformity of phenotype normally associated with wild-type dominance did not occur. It is concluded that dominance can be obtained either by selection of modifiers moving the expression of the heterozygote towards that of the homozygote, as emphasized by FISHER, or by selection of modifiers moving the phenotype of the homozygote towards that of the heterozygote, which was preferred by the present authors on the basis of RENDEL, SHELDON and FINLAY's (1965) model of canalization through control of a major gene in the developmental system. Constancy of phenotype in the face of genetic and environmental variation is seen as resulting from at least two selection or evolutionary steps (i) dominance, which roughly equalizes the activity of one and two doses of the major gene, and (ii) canalization, which superimposes a tight control over the product of the major gene by regulators other than the dominance modifiers.

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