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Long-term selection for a quantitative character in large replicate populations of *Drosophila melanogaster*

II. Lethals and visible mutants with large effects

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SUMMARY

Lethal frequencies on the second and third chromosomes were estimated three times in six replicate lines of *Drosophila melanogaster* selected for increased abdominal bristle number, at G 14–16, G 37–44 and G 79. Ten lethals were detected at a frequency of about 5% or higher at G 14–16, of which only one recurred in subsequent tests. Another ten lethals which had not been detected previously were found at G 37–44, and the 5 most frequent ones recurred at G 79. In the last test, 15 presumably new lethals were detected, of which at least 4 appeared well established. In addition, six reversions (from *sc* to sc^+), a new mutant at the scute locus and *sca* were discovered. The effects on the selected character of some lethals and visible mutants were large and variable, but not always sufficient to explain the observed frequencies. The major lethals detected at G 37–44 and G 79 for the first time were most probably 'mutations' (in the broad sense) which occurred during selection. The likely origins of such 'mutations' were discussed, with a suggestion that the known mutation rate for recessive lethals would not be incompatible with the observed frequency of occurrence of the 'mutations'.

1. INTRODUCTION

In experimental quantitative genetics, it has been argued that much of the genetic difference between two extreme populations may be explained by a relatively small number of genes with sizable effects (e.g. Thoday, Gibson & Spickett, 1964; Robertson, 1966). A special class of such genes would be lethals that have been found at high frequency in many selection lines of *Drosophila* (Reeve & Robertson, 1953; Clayton & Robertson, 1957; Frankham, Jones & Barker, 1968; Hollingdale, 1971; Madalena & Robertson, 1975).

This paper describes lethal tests made at intervals on the selection lines reported in the preceding paper (Yoo, 1979*a*).

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2. MATERIALS AND METHODS

The first lethal test was carried out around generation (G) 15 using a sample of 50 males taken before selection from each of the six replicate lines (Rathie, 1976). His results are reproduced in this paper. More than 100 males were sampled around G 41 for the second test, and 50 males in G 79 for the third test. Table 1 gives details of the number of second and third chromosomes successfully tested for lethals in each line.

Table 1. *The number of second and third chromosomes (N) tested for lethals in each generation (G)*

	G 14–16*		G 37–44		G 79	
Line	G	N	G	N	G	N
Ua	14	44	42	130	79	50
Ub	14	47	43	102	79	50
CRa	15	46	39	120	79	50
CRb	15	42	41	112	79	49
CCa	16	47	44	114	79	50
CCb	16	48	37 39	34 64	79	50

* From Rathie (1976).

Lethals on the second and third chromosomes were tested using the stock [In (2LR) SM1, *Cy*; In (3LR) Ubx^{130}]/T(2; 3) ap^{Xa} (Lindsley & Grell, 1968). This tester stock was found to be satisfactory in suppressing crossing-over in the present experiment. All chromosomes whose homozygote viability was less than 20 % of the *Cy* or *Ubx* heterozygote were maintained as balanced stocks for later testing of identity among lethals (allelism test). However, those showing consistently high viability (approximately 10 % or higher) in later tests were excluded unless associated with easily detectable morphological expression. The G 14–16 test was performed similarly but incomplete lethals were not considered as they were absent or very rare (Rathie, 1976).

Lethals from any one line were grouped into subsets of no more than 10 each, and allelic relationship within subsets was first determined by half-diallel crossing. Lethal stocks representing allelic groups in each subset were then intercrossed to infer the relationship among allelic groups from different subsets. Representative lethals from different selection lines were later intercrossed for between-line allelism tests. Finally, lethals with a frequency of about 5 % or higher were kept for a further allelism test with lethals to be extracted in later generations.

To estimate the effect on abdominal bristle number of some lethals, a random sample of flies from the appropriate line was scored for the character and progeny-tested with a sufficient number of offspring (80 or more per parent). Only when the lethal heterozygote was morphologically distinguishable from the wild-type, the two genotypes of both sexes taken at random were scored for abdominal bristle number.

No more than 3 pairs of parents were allowed per vial (2·5 × 7·6 cm) for the lethal and allelism tests. The effects on abdominal bristle number were measured in bottles (142 ml) with 10 pairs of parents mated for three days. Flies were cultured on a dead yeast fortified medium at 25 ± 0·5 °C and 65–70 % relative humidity.

3. RESULTS

(i) *Lethal frequencies*

The total frequencies of individual lethals (genes or combinations of genes) are given in Table 2, separately for the second and third chromosomes. As the lethal frequency was not estimated in the base population, estimates given by Frankham *et al.* (1968) for complete lethals in the wild-type Canberra strain, from which the base population originated (Rathie, 1969), are included in the footnote for comparison.

Table 2. *The total frequencies of individual lethals on the second chromosome and of those on the third chromosome* (%)*

	Second chromosome			Third chromosome		
Line	G 14–16	G 37–44	G 79	G 14–16	G 37–44	G 79
			Complete lethals			
Ua	2·3	10·8	12·0	6·8	8·5	14·0
Ub	14·9	44·1	48·0	17·0	6·9	48·0
CRa	17·4	2·5	22·0	10·9	4·2	58·0
CRb	2·4	0·0	0·0	9·5	25·9	51·0
CCa	25·5	10·5	16·0	10·6	2·6	26·0
CCb	4·2	1·0	6·0	8·3	20·4	40·0
Mean	11·1	11·5	17·3	10·5	11·4	39·5
			Incomplete lethals			
Ua	—	0·0	0·0	—	0·0	0·0
Ub	—	1·0	4·0	—	3·9	0·0
CRa	—	25·8	28·0	—	0·0	0·0
CRb	—	0·0	26·5	—	21·7	34·7
CCa	—	26·3	30·0	—	0·9	2·0
CCb	—	0·0	0·0	—	1·0	24·0
Mean	—	8·9	14·8	—	4·6	10·1

* In the wild-type Canberra strain, the frequency of complete lethals was estimated to be 9·5 % and 14·5 % for the second and third chromosome respectively (Frankham *et al.* 1968). These may be taken as lethal frequencies before selection was started.

Table 2 gives an impression that the overall lethal frequency did not increase until very late (G 79) in the selection. However, it should be noted that most of the lethals occurring more than once in G 14–16 had been replaced by new lethals occurring at high frequency by G 37–44 (see below). The contribution of one or a few major lethals to the total frequency was even more obvious in G 79, and for this reason, the between-line differences would be better discussed in terms of individual lethals.

The procedures of the allelism test generally appeared quite adequate for determination of different allelic groups in tests at G 14–16 and G 37–44. But it was sometimes difficult to interpret the results of diallel crossing among incomplete lethals in the G 79 test due to sporadically high viability in some combinations (CCb) or the improvement of viability in subsequent matings (CRb). These incomplete lethals could not be studied any further.

Table 3. *The frequencies of individual complete and incomplete lethals on the second chromosome* (%)

Line	Code	G 14–16	G 37–44	G 79
Ua	II1	—	6·2	0·0
	II2	—	—	10·0
Ub	II1	8·5	0·0	0·0
	II2	—	35·3	40·0
	II3	—	—	6·0
CRa	II1	6·5	0·0	0·0
	II2	8·7	0·0	0·0
	II3*	—	25·8	28·0
	II4	—	—	22·0
CCa	II1	21·3	7·9	16·0
	II2*	—	26·3	30·3

* CRaII3 and CCaII2 are allelic incomplete lethals.

Tables 3 and 4 list the frequencies of individual lethals, complete and incomplete, on the second and third chromosomes respectively. Only the lethals initially observed at a frequency of about 5% or higher are presented. When two lethals from different selection lines were 'allelic', they were still given separate codes, as they were not identified as real alleles at the same locus and their effects on bristle number, when measured, were only with reference to genetic backgrounds related to the selection lines of their origin. When two relatively common lethals occur together on the same chromosome, the frequency of one or the other is likely to be underestimated. This seems to be the case for the third chromosomes of CRb sampled at G 37–44 as the complete lethal chromosomes were not all tested for the presence of incomplete lethals. Therefore, the frequency of incomplete lethals was based on those chromosomes free of the complete lethals.

One third chromosome lethal from the base population (Base III1) was maintained and tested for recurrence in the selection lines. The frequency of this lethal, the highest of all, approached 2% in the base (Frankham *et al.* 1968), but it has never been discovered in the selection lines. Among the 10 lethals which occurred more than once in G 14–16, only one recurred in G 37–44. Ten lethals were first detected in the G 37–44 test at a frequency of 5% or higher, and the five most frequent lethals recurred at similar or higher frequency in G 79. Fifteen lethals were first detected in the G 79 test each more than twice, of which at least four appeared well established.

CRaII3 had a homozygote viability of 5·3% relative to the *Cy* heterozygote in

the lethal test at G 39, but the viability increased in subsequent generations while it was maintained balanced by *Cy*, attaining to a normal level after some 20 generations. In addition, a small proportion (4 %) of 'allelic' crosses in the allelism test irregularly showed high viability. This lethal was probably loosely linked to CRaII4. CCaII2 was allelic with and in viability very similar to CRaII3. The viability of these two lethals was dependent on the genetic background of non-homologous chromosomes.

Table 4. *The frequencies of individual complete and incomplete lethals on the third chromosome* (%)

Line	Code	G 14–16	G 37–44	G 79
Ua	III1	—	—	6·0
Ub	III1*	4·3	0·0	(not tested)
	III2	—	—	6·0
	III3	—	—	8·0
	III4	—	—	32·0
CRa	III1	—	—	8·0
	III2	—	—	8·0
	III3	—	—	12·0
	III4	—	—	24·0
CRb	III1	7·1	0·0	0·0
	III2	—	7·1	0·0
	III3‡	—	15·7	34·7
	III4	—	4·8	0·0
	III5	—	12·5	0·0
	III6	—	6·3	0·0
	III7†	—	—	51·0
CCa	III1	4·3	0·0	(not tested)
	III2	4·3	0·0	(not tested)
	III3	—	—	6·0
	III4	—	—	16·0
CCb	III1*	4·2	0·0	(not tested)
	III2	4·2	0·0	(not tested)
	III3†	—	18·4	26·0
	III4	—	—	10·0
Base	III1	(not discovered in the selection lines)		

*, † Allelic relationships between lethals from different lines.
‡ Incomplete lethal.

The CRbIII3 homozygote had a relatively high viability (15·0 %), but could be distinguished morphologically (wings held out at about 30° from midline). An effective balanced lethal system appears to have been established between this lethal and CRbIII7 by G 79 probably due to close linkage, as the proportion of chromosomes having the two lethals (2·0 %) was far smaller than the expected (17·7 %). Thus, the frequency increased from 15·7 % in G 41 to 34·7 % in G 79.

In addition to the lethal tests in Table 1, a small-scale test was performed for CRb in G 51, as this line had just shown a large accelerated response. The lethal CRbIII7 was first found in this test at a frequency of 33·3 % among 30 females

with more than 31 bristles, when the generation mean was 27. By G 79, the frequency had increased to the maximum possible, probably through the balanced lethal system with CRbIII3.

(ii) *Effects of lethals on abdominal bristle number*

The effect of lethals on abdominal bristle number was estimated for a few high frequency lethals (Table 5). In all cases, the lethals had demonstrable effects at least in males when measured in the genetic background of their respective selection lines. However, the frequencies of UbII2 and CCaII1 cannot be explained

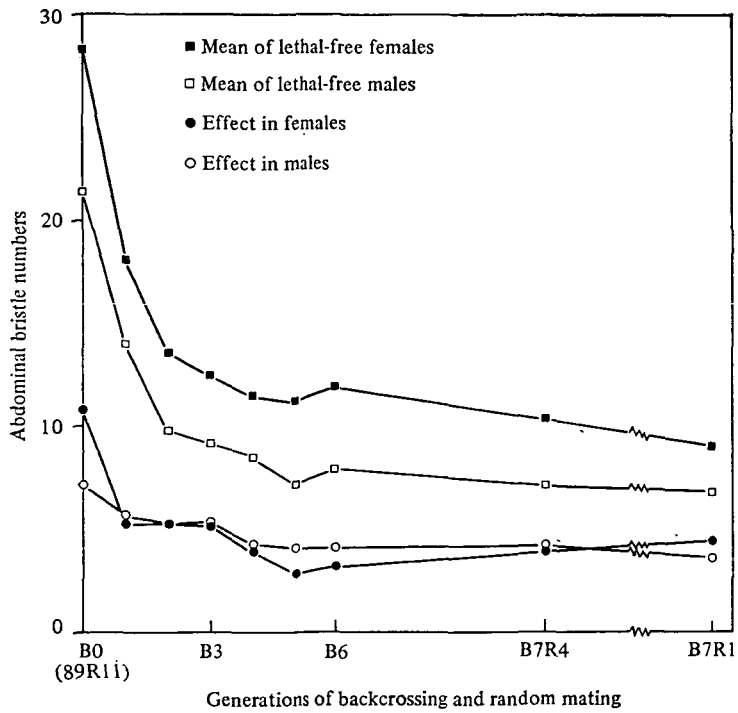

Fig. 1. The effects on abdominal bristle number of the lethal CRbIII7 in successive backcrosses to the base population.

solely by their effects on bristle number, as the observed effects were much less than those expected from their frequencies on the assumption of equal reproductive fitness for both the lethal carriers and non-carriers (Latter & Robertson, 1962; Hollingdale, 1971). In the case of UbII2, the available data suggest that the lethal heterozygote had some reproductive advantage which was either not large enough in itself to maintain the lethal under relaxed selection or dependent on genetic background.

The lethals CCbIII3 and CRbIII7 which are allelic, have a visible effect on wing vein (similar to *Delta*), but this morphological effect did not come into notice until selection had been relaxed for some generations. The effect of CRbIII7 estimated

Table 5. *The effects on abdominal bristle number of some high-frequency lethals.*

Lethal	Sex	Generation	Carrier		Non-carrier		Difference ± S.E.	Difference in σ_P*
			No.	Mean	No.	Mean		
CCaII1†	Male	23	54	17·00	47	16·11	0·89	
	Female	22	38	21·85	40	21·54	0·31	
UbII2	Male	53	31	20·16	24	19·42	0·74 ± 0·61	0·31
		55	53	20·26	30	19·30	0·96 ± 0·59	0·36
		Pooled					0·87 ± 0·43	0·34
CRaII3	Male	53	103	24·14	63	19·62	4·52 ± 0·41	1·62
CCbIII3	Male	48	122	20·88	28	16·54	4·34 ± 0·33	3·10
		54	55	22·91	18	18·89	4·02 ± 0·42	3·35
		Pooled					4·22 ± 0·26	3·19
		100R1	50	29·68	50	23·34	6·34 ± 0·54	2·43
	Female	100R1	50	43·18	50	33·24	9·94 ± 0·65	2·96
CRbIII7	Male	89R10B7R15‡	50	10·42	50	6·84	3·58 ± 0·32	2·79
		89R11§	81	28·64	114	21·44	7·20 ± 0·32	3·76
		100R1	50	32·72	50	23·76	8·96 ± 0·66	3·82
	Female	89R10B7R15‡	50	13·42	50	9·04	4·38 ± 0·41	2·38
		89R11§	93	39·02	131	28·28	10·75 ± 0·37	4·78
		100R1	50	45·26	50	31·92	13·34 ± 0·79	3·60

* σ_P of the wild-type homozygote in current generations.

† Estimated by Rathie (1976). Differences are significant only in males ($P < 0·05$).

‡ 89R10B7R15 denotes 89 generations of selection for increased abdominal bristle number, followed by 10 generations of random mating, 7 of backcrossing to the base population, and 15 of random mating.

§ Pooled estimates over the three consecutive generations around G 89R11.

after 11 generations of relaxed selection (G 89R11) was extremely large (even greater than the mean bristle number of the base population), and so the effect was assessed in different genetic backgrounds introduced through continuous backcrossing to the base population (Fig. 1). The final estimates after 7 generations of backcrossing followed by 15 generations of random mating (89R10B7R15) are given in Table 5. As CCbIII3 had already been lost, a sample of flies was taken from the original selection line (CCb), which had been maintained elsewhere under mild selection (Dr B. L. Sheldon, pers. comm.). The estimates in G 100R1 were obtained from the progeny of this sample cultured in this laboratory. Similar estimates were also obtained for CRbIII7 at the same time.

The effects of CRaII3, CCbIII3 and CRbIII7 were large enough for their frequencies to be explained by the heterozygote advantage endowed by artificial selection. But it should be pointed out that the magnitude of the effects of CCbIII3 and CRbIII7 was highly dependent on the level of genetic background (Fig. 1). The dependency may be largely removed by expressing the effects in terms of phenotypic standard deviation (Table 5).

(iii) *Visible mutants*

As the *sc* Canberra strain, from which the selection lines originated, had been deliberately marked with sex-linked recessive y^2 and *sc* to facilitate bristle counting (Rathie, 1969), reverse mutations (back to wild-type) were eliminated during selection. In the whole period, we found six apparent reversions of *sc* independently of each other, each together with y^2 (this makes the possibility of contamination unlikely). Five of them were later compared to sc^+ for scutellar bristle number and found to have essentially the same effect. In all, the number of flies scored during the whole period was approximately 210750 in each sex, giving a spontaneous reverse mutation rate of $7{\cdot}9 \times 10^{-6}$ per X chromosome.

When the *sc* allele was checked in later generations (Yoo, 1974), a new mutant (sc^n) that increased abdominal but decreased scutellar bristle number was found in CCa. The frequency of this mutant appeared to be around 0·8 in G 77, and rapidly approached fixation due to its favourable effect on abdominal bristle number. Differences between *sc* and sc^n (Table 6) were measured in the CCa genetic background (Yoo, 1974).

At one stage of the selection programme (G 57), CRa was split into two populations, which were subsequently selected in much the same way. The mutant scabrous (*sca*) occurred in one population probably around G 70, but never in the other which was maintained under selection as the usual CRa line to G 87. The gene frequency rapidly increased from about 0·46 in G 72 to fixation in G 78. This mutant was later identified as allelic with *sca* of Jones, Frankham & Barker (1968). The effects of *sca* in single and double doses were estimated to be $4{\cdot}55 \pm 0{\cdot}93$ and $5{\cdot}08 \pm 0{\cdot}95$ bristles in females (mean and σ_p were then approximately 31 and 3·1 for the wild-type homozygote), and a significant excess of the heterozygotes was noticed.

Table 6. *The effects on abdominal and scutellar bristle number of the scute mutant* (sc^n) *in CCa*

	Abdominals ± S.E.*	Scutellars†
Female		
(1) Mean of *sc*/*sc*	30·93 ± 0·17	2·16
(2) (sc^n/sc^n)–(*sc*/*sc*)	6·41 ± 0·26	−2·14
(3) (sc^n/*sc*)–(*sc*/*sc*)	4·69 ± 0·32	−0·71
(4) Degree of dom. = (3)/(2)	0·73 ± 0·06	0·33
Male		
(5) Mean of *sc*/*Y*	25·10 ± 0·12	1·72
(6) (sc^n/*Y*)–(*sc*/*Y*)	2·58 ± 0·18	−1·70

* (1), (2), (5) and (6) are based on data collected in 6 generations during the period between G 86R4 and G 86R35. (3) is based on data only in 3 generations during the same period.

† Data collected in G 86R21. Approximately 120 flies were scored for each genotype mean.

4. DISCUSSION

(i) *The effect of lethals on selection response*

Lethals have been shown to be a significant part of the genetic characteristics of long-term selection lines (Madalena & Robertson, 1975; references therein), although their relationship to response pattern was not always expounded.

When a lethal is selected for because of its pleiotropic effect on bristle number or of close linkage to a gene with such an effect, we would expect to observe a rapid response to selection, abrupt increase but no subsequent decrease of variance, tendency to positive skewness with leptokurtosis at the beginning and probably the opposite at equilibrium, and immediate and rapid loss of additional genetic gain obtained upon relaxed selection. We know from the lethal tests approximately when some of the lethals first appeared and were selected for, and in many cases, these expected changes were observable around that time.

UbII2 and UbIII4 seem to have been responsible for a part of the accelerated response around G 20 and the rise around G 62 in Ub, respectively. The rapid response of CRa around G 37 may be related to CRaII3, and the two consecutive waves of accelerated response around G 63 and 73 to CRaII4 and CRaIII4. In CCa, the rapid response around G 20 was probably due to CCaII2 and one of the two stepwise responses around G 57 and 65 perhaps due to CCaIII4; the last accelerated response around G 76 was not due to a lethal, but due to a mutation at the scute locus. CCb had only one apparent accelerated response around G 34 most likely due to CCbIII3. The first rapid response of CRb around G 50 was caused by CRbIII7, which later formed an incomplete balanced lethal system with CRbIII3 presumably around G60, giving rise to the steady response, decrease of variance, leptokurtosis and negative skewness; the second jump around G 74 appeared to be caused by a gene or a combination of genes with a pleiotropic effect similar to *sca* (scabrous).

As a whole, the lethals were responsible for the majority of the accelerated

responses and on that score, made substantial contributions to the total amount of response as well as to the pattern and replicate variation of response.

On the other hand, when artificial selection favours a lethal, a good deal of selection pressure will be required simply to maintain it at equilibrium. The consequent attenuation of selection intensity for the rest of genome, which accumulates over generations, may lessen the genetic progress otherwise possible. This also means that the total amount of effective selection applied might have been different among the above lines – an indirect effect of the lethals on replicate variation in response, which partly explains why replicate variation was larger after than before the final relaxation of selection (Yoo, 1979*a*).

Hence, the lethals seem to have made both positive and negative contributions to the total response. The only line (Ua) that was free of major lethals, was also the lowest in total response, perhaps suggesting that the nett effect of the lethals was positive on the whole.

When a selection line carries two or more lethals at high equilibrium frequency, the effective selection pressure can be very much reduced, unless an efficient balanced lethal system has been established as in CRb. In most of the lines, this appeared to be one of the major factors responsible for the slow or lack of response at the last stage of selection, despite the intense selection and abundant residual genetic variability (Yoo, 1979*b*).

(ii) *The source of lethals*

Although lethals have been detected in many *Drosophila* selection experiments, positive evidence on their origin is scanty, and most of the discussion has been rather circumstantial. Here we suggest that most of the lethals described in this paper originated as new 'mutations' during selection, i.e. they were not derived as such from the base population. This suggestion applies particularly to the high-frequency lethals which were first detected in G 37–44 and G 79, as with such large effects on the selected character and lethality, they would hardly persist for about 15 or 39 generations without being detected.

What would be the origin of such 'mutations'? Assuming the spontaneous mutation rate for recessive lethals to be 0·005 per chromosome per generation for the second (Crow & Temin, 1964) and similarly for the third chromosome, about 5000 lethals are expected to have occurred in the six lines during selection. A small fraction, say 0·5%, of them would be sufficient to account for most of the lethals at high frequency. In addition to point mutations, unequal crossing-over (Frankham, Briscoe & Nurthen, 1978), intragenic crossing-over (Watt, 1972) and small deletions (e.g. *Delta*) could be an important source of the lethals and other genetic variation generated during selection.

Although *sca* has been observed in several selection lines for abdominal bristle number (reviewed by Hollingdale, 1971), its origin has not yet been satisfactorily explained. That *sca* appeared in the line split off CRa in G 57 but not in CRa itself, suggests 'mutation' as a reasonable explanation at least for the present *sca*. Dr R. Frankham (pers. comm.) also found two new 'mutational' cases of *sca* in his selec-

tion lines. Thus, the more recent evidence, together with Robertson's (1978) theoretical results, favours 'mutation' for the origin of *sca*. The occurrence of many reversions and a new mutation at the scute locus further strengthens the argument for mutational origin of some lethals with large effects.

Kojima (1969) suggested mutation as an explanation for the long-continued selection responses in mice (Comstock, 1973), but there seems to be a general tendency to under-rate the role of mutation in long-term selection, probably because the experiments specifically designed to resolve the question have produced conflicting results (Scossiroli & Scossiroli, 1959; Clayton & Robertson, 1964; Hollingdale & Barker, 1971*a*, *b*). The role of 'mutations' in the broad sense in artificial selection needs to be re-examined in the light of more recent experimental (Frankham *et al.* 1978) and theoretical (Lande, 1976) work.

An alternative source could be recombinant or synthetic lethals, which are fairly common in natural populations of *Drosophila* (Wallace *et al.* 1953; Dobzhansky & Spassky, 1960). To explain the present lethals in this way, it may have to be assumed that the recombination took place between two very closely linked loci, each segregating for a relatively frequent allele in repulsion phase against the other, and that the double heterozygote had a considerably larger effect on the selected character in coupling phase than in repulsion phase, i.e. a strong position effect. There is no evidence to suggest how often such assumptions can be met, although it must be quite rare.

Waddington (1957) implied 'evolving' major genes as the origin of the lethals found by Clayton & Robertson (1957). A similar interpretation seems to be plausible for the incomplete lethal CRaII3 (and the allelic CCaII2), which showed variable homozygote viability dependent on the genetic background of non-homologous chromosomes. In other words, this lethal perhaps had not been a recessive lethal in the base population, but with artificial selection the homozygote viability might have been decreased to the extent to be regarded as lethal. We have little evidence to suggest that any other lethals evolved similarly from minor genes. It should be noted, however, that such minor genes, if present, had certainly been sampled in each line, but the lethals were mostly non-allelic; that a threshold model is required on their bristle number effects to explain the accelerated responses due to these lethals; and that if the threshold is assumed to refer to the level of bristle number, it was extremely variable among the lethals.

In conclusion, this investigation shows that most of the lethals which caused accelerated responses to selection were first detected after a number of generations of selection. This suggests that these lethals were 'mutations' in the broad sense, and did not originate as such from the base population.

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