SELECTION FOR AN INVARIANT CHARACTER, VIBRISSA NUMBER, IN THE HOUSE MOUSE

By R. B. Dun* and A. S. Fraser†

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Summary

The number of secondary vibrissae in the mouse is normally 19. The tabby gene reduces this to about half and causes a marked variability of vibrissa number. Selection on tabby mice for increase and decrease in vibrissa number has been successful. These selection lines were maintained in segregation for + and *Ta* alleles, and this selection, practised solely on tabby mice, has resulted in both an increase and decrease in vibrissa number in normal mice.

I. Introduction

It has been generally accepted that an absence of phenotypic variation has its basis in an absence of genetic variation, i.e. phenotypic invariability implies genetic fixation. Goldschmidt (1935), Landauer (1958) and others, in their researches on the induction of phenocopies, concluded that considerable genetic variation occurs which is only manifested phenotypically in phenocopies, i.e. this genetic variation is only manifested after some environmental stress has markedly affected development. Waddington (1956) extended their observations showing that genetic variation which was only manifested in phenocopies could be selected until it was manifested in the absence of the specific environmental stress.

A further extension of this theme is examined in this paper. In general, mutant genes have a much greater phenotypic variability than their normal alleles. We have taken as a basis for our researches the number of secondary vibrissae in the house mouse, which is remarkably constant in normal mice, but highly variable in the presence of certain mutant genes. Consequently selection for high or low vibrissa number, which is difficult or impossible in normal mice, is quite feasible in mice carrying one of these mutant genes. Such selection if continued long enough can result in differences of vibrissa number in normal mice. We are, in other words, employing the stress of a mutant gene instead of an environmental stress as Waddington did.

II. Material and Methods

The character used in this selection experiment was vibrissa number. This is a composite score formed by addition of the five minor groups of vibrissae found on the head and fore limbs. Figure 1 shows the distribution of these vibrissae. The

*New South Wales Department of Agriculture, Agricultural Experiment Station, Trangie, N.S.W.

†Animal Genetics Section, C.S.I.R.O., University of Sydney.

basic arrangement is 2 supra-orbitals, 1 postorbital, 2 postorals, 3 inter-ramals, and 3 ulnar–carpals, making a total of 19 vibrissae.

Dun (1958) made an extensive survey of the variation of vibrissa number in 3000 normal mice. These were drawn from several inbred lines and random-bred stocks. Variation from the basic number of 19 was rare. The inter-ramal group was the major source of variability having occasionally two rather than the normal three vibrissae. Several discrete variations were found associated with the supra-orbital group. It is important to note that the postorbital vibrissa was present in all the mice examined, and neither more nor less than one vibrissa was found at each postorbital position. Over all the five groups approximately one abnormality per 500 groups was noted. It can be stated that the number of secondary vibrissae is extremely stable, there being little variation in most groups, and no variation of the postorbital vibrissa.

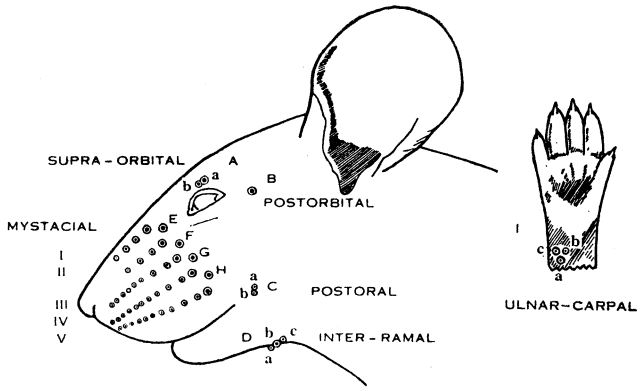

Fig. 1.—Head and distal part of the right fore limb of the mouse showing distribution of vibrissae.

Subsequent to Dun's survey a number of additional mice were scored for vibrissa number. Of 546 Awl01 mice only three showed any variation of vibrissa number, having two instead of three inter-ramal vibrissae. Of 412 CBA mice only one mouse had two instead of three inter-ramals; all other vibrissae were normal. Some 2180 mice from the cross of the DBA line with the CBA and Awl01 lines were scored. In none of these was the postorbital missing. Totalling all the mice examined, over 12,000 postorbital groups have been scored without any variation of the basic number being detected. Clearly, it is safe to state that the number of postorbital vibrissae is an invariant character.

Whereas Waddington (1953) exposed genetic variation to selection by subjecting the animals to an environmental stress during development, we have used the sex-linked semidominant mutant gene tabby (*Ta*) (Falconer 1953) to expose genetic variation in vibrissa number.

The ranges of vibrissa number in normal mice and in *Ta*+ (♀) and *Ta*· (♂) mice are given in Figure 2, which shows the wide range of vibrissa numbers occurring in tabby mice. It was this variation which was utilized in our selection experiment.

These data summarize the widest possible ranges of vibrissa number in normal mice, including all stocks and lines, and are shown separately for the various inbred lines and the TA stock in Table 1. The TA stock is a crossbred stock in which the tabby gene is kept segregating. In these TA stocks the + segregants show less

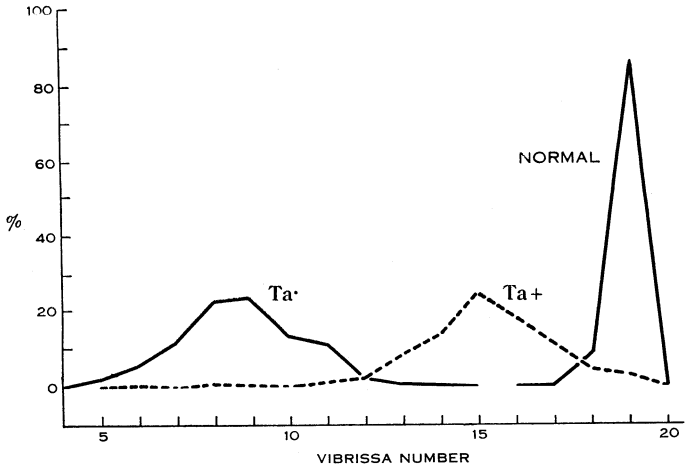

Fig. 2.—Range of vibrissa number in normal mice compared with the range in $Ta+$ females and $Ta\cdot$ males.

phenotypic variation than in the whole survey of non-TA stocks. It is clear that the variability of vibrissa number is marked in tabby mice and almost non-existent in + mice. It seems reasonable to claim that any genetic variation determining vibrissa number in tabby mice also occurs in + mice. If it can be shown that + mice respond

TABLE 1

FREQUENCIES OF NUMBERS OF VIBRISSAE IN INBRED LINES, AND IN THE NORMAL MICE OF THE TA STOCK

Stock	Supra-orbitals			Post-orbitals		Postorals				Inter-ramals					Ulnar–Carpals			
	2	1	0	1	0	3	2	1	0	4	3	2	1	0	3	2	1	0
Aw101	459	1	–	460	–	–	459	–	–	–	230	–	–	–	460	–	–	–
CBA	496	–	–	496	–	–	496	–	–	–	245	3	–	–	496	–	–	–
C_3H	403	–	–	408	–	–	407	–	–	2	194	8	–	–	407	1	–	–
C_{57}	324	–	–	324	–	–	324	–	–	2	137	22	1	–	324	–	–	–
DBA	308	–	–	308	–	1	307	–	–	–	98	56	–	–	308	–	–	–
A	231	1	–	232	–	–	231	–	–	6	47	62	1	–	223	9	–	–
TA(+)	238	–	–	238	–	–	238	–	–	–	108	10	1	–	90	–	–	–

to selection based on the variation of tabby mice this point will be proved. It is a fair inference that, as the TA stocks were built up from backcrosses and intercrosses of the other stocks listed in Table 1, background variation present in + animals of the TA stocks came from the other + stocks and is present in them.

(*a*) *The Selection Stock*

A basic selection stock, the ST stock, was formed by crossing mice from the following lines:

(1) HF
(2) MH
(3) TA
} Tabby stocks

(4) CBA
(5) Aw101
} Inbred lines

HF and MH were stocks developed for histological work, which were established from the original tabby stock (the TA stock). The latter was obtained from the Institute of Animal Genetics, Edinburgh. Both the CBA and Aw101 stocks were frequently used in the formation of the HF and MH stocks.

TABLE 2

PERCENTAGE REPRESENTATION OF FIVE STRAINS OF MICE IN THE FOUNDATION STOCK ST AND IN THE SELECTION LINES HST AND LST AT GENERATIONS 1 AND 4

Selection Lines	Strains of Mice				
	HF	MH	TA	Aw101	CBA
ST	28·6	21·4	19·0	16·7	14·3
HST, generation 1	8·9	42·9	1·8	44·6	1·8
LST, generation 1	16·1	19·6	41·1	3·6	19·6
HST, generation 4	4·2	47·6	0	47·6	0·6
LST, generation 4	19·4	19·4	36·6	0	24·6

In the initial matings to form the ST stock, 21 *Ta*+ females from the three tabby stocks were mated with normal males: 8 from the HF, MH, and TA stocks and 13 from the Aw101 and CBA stocks. These matings produced *Ta*+ females which were selected for high and low vibrissa number to establish the two selection lines: HST (high selection) and LST (low selection). These *Ta*+ females were mated to + males which had been selected on the performance of their *Ta*+ sisters. The result was a mixture of mouse strains in the initial phase of the experiment. Table 2 shows the percentage representation of each stock in the pedigrees of the foundation ST stock, and in the HST and LST selection lines at generations 1 and 4.

The Aw101 and MH stocks were predominant in the foundation of the HST selection line, whereas the TA and CBA stocks were predominant in the foundation of the LST selection line. This asymmetry in genetic constitution of the two lines means that no especial significance can be attributed to any asymmetry of response to selection.

Sib-matings were avoided throughout the experiment. With a population size of 10 males and 30 females one would expect a loss of 1·7 per cent. of the initial

heterozygosity per generation. The actual loss was nearly double this: the doubling results from the use of sib-testing in the selection of normal males which reduces the effective number of males.

(*b*) *The Method of Selection*

Mice were initially selected by a combination of mass selection of *Ta*+ females and sib-testing of + males. It was impossible to select + males on their own phenotype, since they showed no, or very little, variation—certainly insufficient to allow useful selection.

There were 12 pairs of selected mice mated in generation 1, 18 in generation 2. At this stage dissatisfaction was felt with the results which were being obtained. Accordingly females were subsequently allowed to have two litters: the first to provide animals for selection, the second to provide additional data. In addition the mating scheme shown below was adopted:

	Females		Males	
(1)	*Ta*+	×	+·	Parents
	Ta+, ++		*Ta*·, +·	Progeny
(2)	++	×	*Ta*·	Parents
	Ta+		+·	Progeny
(3)	*Ta*+	×	+·	Parents

and so on. This mating scheme is self-continuing and has the marked advantage of producing + mice every generation.

TABLE 3

HERITABILITIES AND STANDARD ERRORS OF VIBRISSA NUMBER

Genotype Scored	Sires h^2(S)	Component Degrees of Freedom	Dams h^2(D)	Component Degrees of Freedom	$h^2\left(\frac{S+D}{2}\right)$
Tabby females (*Ta*+)	0·05±0·11	11	0·78±0·33	22	0·42
Tabby males (*Ta*·)	0·44±0·24	11	0·70±0·33	22	0·57

Initially these + mice showed no useful degree of variation. At later generations, when + mice occurred with aberrant numbers of vibrissae, such mice were only accepted as parents where this was indicated from the vibrissa number of their tabby sibs, i.e. in the whole experiment no selection has been practised directly on phenotypes of + mice.

It can be seen from Table 1 that there is some variation of the frequency of inter-ramals in normal mice. Consequently a second selection experiment was initiated in which selection pressure was set to cause both increase and decrease of the frequency of inter-ramals (the two selection lines are termed HIR and LIR

respectively). The aim of this experiment was to demonstrate that selection on inter-ramals in normal mice could not produce the same changes of total number of vibrissae that were found in the tabby selection experiment.

(c) *Heritability of Vibrissae Number*

The heritability of vibrissae number in normal mice can be taken as effectively zero. In *Ta*+ and *Ta*· mice, the heritability was first estimated by analysis

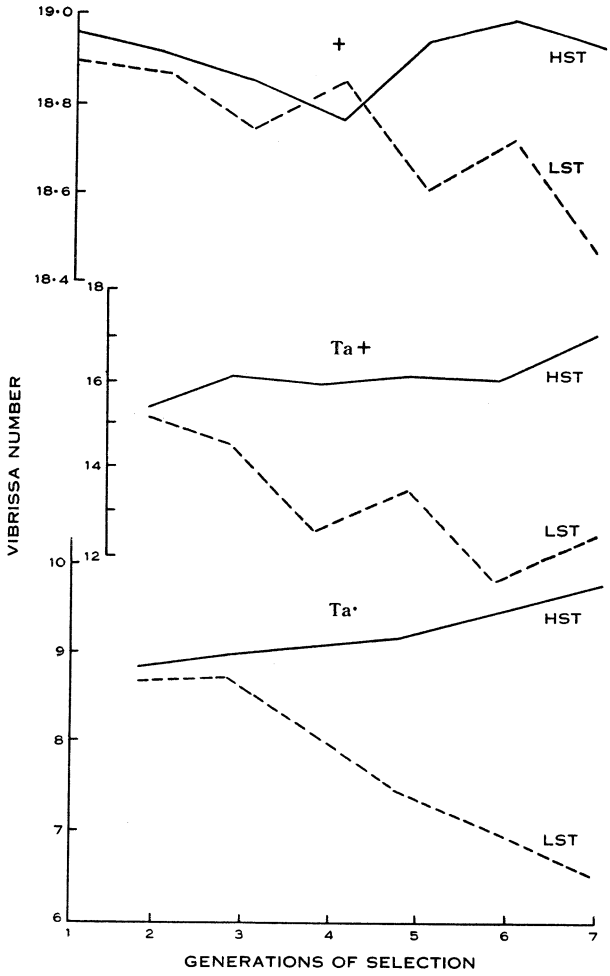

Fig. 3.—Mean vibrissa number at the three levels of expression plotted against generation for the tabby selection experiment: each level of expression is shown plotted against a different scale to emphasize the differences between HST and LST.

of the components of variance for full and half-sibs. The standard errors of the estimates were calculated using the method of intraclass correlations (Fisher 1946). Results are set out in Table 3.

TABLE 4

CHANGES IN THE MEAN AND VARIANCE OF VIBRISSA NUMBER IN *Ta*+ AND *Ta*· MICE DURING SEVEN GENERATIONS OF SELECTION

Parameter	Selection Line	Basic Selection Stock (ST)	Generation 1	2	3	4	5	6	7
Ta+ mice									
Number of mice	HST	76	50	128	39	99	45	125	50
	LST		40	99	48	109	38	112	46
Mean	HST	8·90	9·92	15·27	16·00	15·79	16·00	16·02	17·02
	LST		8·90	15·06	14·46	12·61	13·63	11·42	12·48
Variance	HST	1·372	2·786	3·759	2·263	3·680	4·318	4·040	2·225
	LST		2·349	3·980	4·083	6·080	3·374	5·670	5·233
Coefficient of variation (%)	HST	13·2	16·8	12·7	9·4	12·2	13·0	12·5	8·8
	LST		17·2	13·3	14·0	19·6	13·5	20·8	18·3
Ta· mice									
Number of mice	HST			132	34		41		37
	LST			124	29		34		34
Mean	HST			8·81	9·00		9·29		9·81
	LST			8·62	8·72		7·35		6·59
Variance	HST			2·770	4·570		3·676		2·992
	LST			2·550	1·890		1·447		0·915
Coefficient of variation (%)	HST			19·0	23·8		20·7		17·6
	LST			18·6	15·8		16·3		14·5

Using the parent–offspring regression, the heritability of total vibrissae number was $0 \cdot 36 \pm 0 \cdot 24$. Unfortunately the errors of these estimates were high, but the agreement between estimates from the two methods suggests that the heritability lies in the range 0·3–0·5. It is sufficiently high to suggest that mass selection would be effective.

III. Results

(*a*) *Effects of Selection*

The tabby selection experiment has three levels of expression: (1) the + level; (2) the *Ta*+ level; and (3) the *Ta*· level. The mean values at each generation for all three levels are shown in Figure 6, which since only a single scale is used allows comparison of the effects of selection between the three levels. The data are also plotted in Figure 3 on scales which are different for the three levels in order to show more clearly the rather small changes which have occurred at the + level.

Selection has been successful in both directions in both *Ta*+ and *Ta*· mice. At the *Ta*+ level the lines have separated by approximately 3 standard deviations by generation 7. The change in LST has been at twice the rate of the change in HST, the regression coefficients being $-0 \cdot 60 \pm 1 \cdot 32$ and $0 \cdot 25 \pm 0 \cdot 34$ respectively. The response to selection at the *Ta*· level closely parallels that of the *Ta*+ level.

It is interesting to note that there is a tendency in both the HST and LST lines for vibrissa number to increase in generations 3, 5, and 7, while the reverse applies in generations 4 and 6. It is likely that these fluctuations are in some way associated with the mating scheme, and it is probable that a maternal effect is involved. This is being investigated.

The variance of vibrissa number is affected by selection. The means, variances, and coefficients of variation of the two tabby levels are given in Table 4. At the *Ta*+ level there is a tendency for the variance to decrease in the high line and increase in the low line; conversely, at the *Ta*· level there is a tendency for the variance to increase in the high line and decrease in the low line. These changes of variance can be explained by the existence of an upper limit to the phenotypic expression of genetic variation at 19 vibrissae, and a lower barrier at 5–6 vibrissae. At the *Ta*+ level the high selection is moving the distribution against the upper barrier, and at the *Ta*· level the low selection is moving the distribution against the lower barrier. The changes of variance are not sufficiently large to justify this model being accepted unequivocally and further selection has, as one of its aims, the investigation of these changes of variance.

Detailed presentation of the effects of selection on the separate groups of vibrissae are given in Dun (1959*a*). The groups which show the maximum response to selection are those which are affected by tabby such that the number of vibrissae is well removed from either the upper or lower barriers to phenotypic expression. For example, the number of supra-orbital bristles in *Ta*+ mice is close to the upper limit of 4, and selection in a high direction had little success, whereas it was possible to depress the supra-orbital score fairly markedly in the low line. The reverse of this situation is seen with the inter-ramal group. In unselected *Ta*+ mice, the number of

inter-ramals is near the lower limit of one vibrissa. Consequently selection downwards has been ineffective compared to selection for an increased number of inter-ramals.

Changes in the expression of the + genotypes are based on male scores which were made every generation, and female scores which were made on all generations except 4 and 6 when no + females were born. The + genotypes of the high- and low-selection lines have become clearly separated on vibrissa number: they differ by almost half a vibrissa. At generation 4, LST was temporarily higher than HST. This was entirely due to changes in the inter-ramal group: the HST having a larger number with 2 instead of 3. Mice with two inter-ramals are found from time to time in unselected stocks and to avoid the possibility that chance variations in this will mask changes in other groups in the early stages of selection, the remaining groups have been shown separately in Figure 4. In this figure the percentages of mice which had unusually high or low vibrissa numbers are shown for each generation, excluding the inter-ramal group.

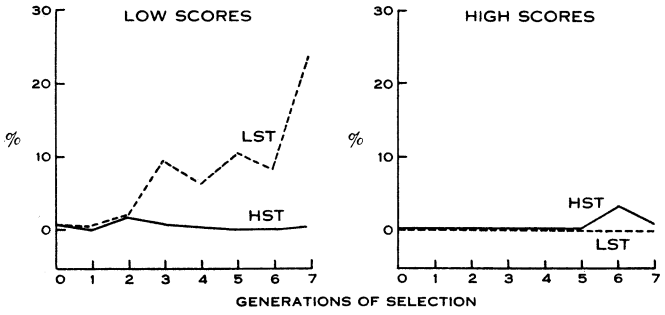

Fig. 4.—Incidence of normal mice having either abnormally low or abnormally high vibrissa number during the course of the selection experiment.

It is apparent that commencing at generation 4 there has been a progressive increase in the number of + mice in the low line which have a lower number of vibrissae than is normally found in unselected stocks. Conversely, commencing at generation 6, the first mice with extra vibrissae occurred in + mice from the high line.

The specific vibrissae involved in these changes are of some interest and each group will now be dealt with in turn. The supra-orbitals showed little change to generation 5, when five normal mice were recorded from the low line with supra-orbital *b* missing. This in itself was unusual as extensive examinations of normal mice had shown that it was a rare occurrence to find one such mouse. Two of these mice also lacked a postorbital vibrissa. This is a convincing demonstration that the normally uniform development of vibrissae had been upset. In generation 6, three mice with an extra supra-orbital vibrissa were found in the high line.

The postorbital group is of particular interest because, as already mentioned, it has been found to consist of one vibrissa in over 12,000 groups examined. The first change at this site occurred in the low line in generation 5 (see above). Two further cases were seen in the low line at generation 6 and one of these also lacked a supra-orbital *b*.

Although occasional mice lacked a postorbital vibrissa (three in the high line, and 10 in the low line), it is not certain that a change in normal variation of this group has yet occurred. Changes in the course of development of the inter-ramals were also less easily established because of the natural occurrence of inter-ramal groups with both 2 and 3 vibrissae. However, several unusual scores were recorded which follow the pattern established by the less variable groups. In generation 3 of the low line, two mice were recorded with only one inter-ramal vibrissa, and in the high-selection line, one mouse in each of generations 6 and 7 had four.

The group in which the selection lines differed most was the ulnar–carpal group. In generation 7 of the low line, no less than 29 groups had two instead of three ulnar–carpals, vibrissa *b* not developing.

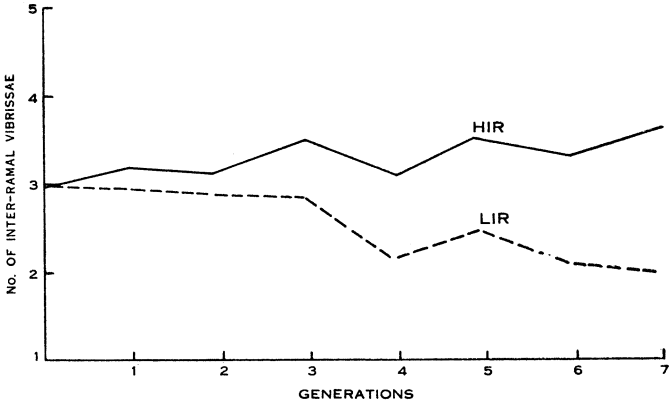

Fig. 5.—Seven generations of selection for and against number of inter-ramal vibrissae.

These data establish our primary thesis: namely, that genetic variation which is either only slightly, or not at all, expressed in + mice is expressed in tabby mice and can be selected at the tabby levels to such extremes that it is manifested in + mice, i.e. in the absence of the tabby gene. However, although variation of vibrissa number is remarkably low, the inter-ramal group does vary, and it can be argued that our selection has been on this group, producing correlated responses on the other groups. To check this point, a selection experiment was initiated based on + mice in which selection was practised for the number of inter-ramals. Figure 5 shows the mean numbers of inter-ramals at the seven generations of selection. By generation 7 the high line had 1·5 more inter-ramal vibrissae than the low line. The point of interest is that there were virtually no associated changes in other groups. The only unusual scores are shown in Table 5.

This shows that occasionally mice have been observed with vibrissae missing at the supra-orbital, postoral, and ulnar–carpal sites. The incidence of missing vibrissae was 1 in 1618 groups for supra-orbitals, 0 for postorbitals, 1 in 809 groups for postorals, and 1 in 324 groups for ulnar–carpals. These rates are similar to those found in unselected + mice, and it is extremely unlikely that they indicate any change in frequency due to the selection on the inter-ramals.

(*b*) *Correlated Responses in the Tabby Selection Experiment*

Although selection has been applied only on the secondary groups of vibrissae it is of interest to determine whether correlated changes have been produced in the

TABLE 5

CHANGES IN OTHER GROUPS OF VIBRISSAE FOLLOWING SELECTION FOR HIGH AND LOW INTER-RAMAL NUMBER

+ mice

Selection Line	Groups of Vibrissae			
	Supra-orbital	Postorbital	Postoral	Ulnar–Carpal
High line	One mouse in generation 1 with *b* missing (unilateral)	Invariably present	One mouse in generation 3 with *b* missing (unilateral) One mouse in generation 4 as above	Three mice in generation 1 with *b* missing (unilateral)
Low line	Invariably present	Invariably present	Invariably present	Two mice in generation 4 with *b* missing (unilateral)

primary group of vibrissae, i.e. the mystacial group. In general, the results show that mystacial vibrissae have, as yet, been little affected by selection. There is very little difference between + mice in the two selection lines.

TABLE 6

SCORES FOR INTENSITY OF COAT STRIPING IN *Ta*+ MICE AT GENERATIONS 2 AND 7 OF THE TABBY SELECTION EXPERIMENT

Generation	Group	Number of Mice	Mean Tabby Score	Standard Error
2	HST	37	4·02	0·29
	LST	27	4·78	0·32
7	HST	36	3·42	0·27
	LST	36	5·03	0·32

Although we have considered the effect of the tabby gene on the secondary groups of vibrissae, this gene is usually scored from its effect on the coat. In *Ta*+ mice there is a marked striping of the colour of the coat. In *TaTa* and *Ta*· mice the structure of the coat is markedly changed, mimicking the structure of the coat of

crinkled mice. It is of interest to determine whether selection on one aspect of the tabby phenotype (the number of vibrissae) produces correlated effects on another aspect, the coloration of the coat in *Ta*+ mice. A set of photographs of *Ta*+ females were taken and graded visually on a nine-point scale. Coats scored 1 were indistinguishable from normal, while coats scored 9 were indistinguishable from hemizygous tabby males. Mice were scored in generations 2 and 7, and the mean scores are given in Table 6.

It is evident that a change in dominance of the tabby gene is accompanying the alterations of vibrissa number. This is to be expected as Dun (1959*b*) has shown that there is a negative correlation between vibrissa number and tabby score. *Ta*+ females in the high line are tending to a low score, i.e. tabby is becoming recessive. In the low line, selection is changing tabby towards full dominance.

TABLE 7

BODY WEIGHTS AND TAIL LENGTHS OF MICE AT GENERATION 7 OF THE TABBY SELECTION EXPERIMENT

Genotype	Selection Line	Body Weight (g)		Tail Length (cm)
		28 Days	56 Days	
++ (♀)	HST	15·13±0·25	21·31±0·29	9·42±0·05
	LST	15·27±0·30	19·31±0·30	9·26±0·06
Ta+ (♀)	HST	14·14±0·33	21·59±0·29	9·25±0·05
	LST	14·61±0·35	18·84±0·33	9·21±0·05
+· (♂)	HST	15·03±0·28	25·26±0·33	9·52±0·05
	LST	15·70±0·30	22·44±0·32	9·51±0·05
Ta· (♂)	HST	12·77±0·32	22·73±0·40	8·66±0·07
	LST	11·75±0·47	17·50±0·84	8·25±0·08

At generation 7, all mice born in the selection lines were weighed at 28 and 56 days of age. Tail lengths were also measured at 56 days. The results are summarized in Table 7.

It is interesting to note that the *Ta* gene depresses growth more markedly in the low- than in the high-selection line. + males are 11·3 per cent. heavier than *Ta*· males in the HST line whereas they are 28·3 per cent. heavier in the LST line. At 56 days HST mice of all genotypes are significantly heavier and have longer tails than their LST analogues. This difference is due to a greater rate of weight increase in the post-weaning period.

Two measurements of fertility were recorded each generation: total number of mice per litter, and number of days between commencement of mating and the ensuing parturition. The results are shown in Table 8, giving the average difference between HST and LST females. A positive difference indicates higher figures for the high-selection lines.

HST females have consistently produced larger litters than LST females, the difference reaching significance in generations 3, 4, and 5. The number of days to parturition does not show a general trend in favour of either line. In order to examine the possibility that vibrissa number of *Ta*+ mice was related to fertility (as suggested by the larger litter size in HST), correlations were estimated. Only one correlation reaches significance, but there is a general trend for *Ta*+ mice of high vibrissa number to produce larger litters in a shorter time.

These effects on reproductive fitness may be fortuitous, rather than direct effects of selection on vibrissa number. As an illustration, the frequencies of certain colour genes have changed in the selection lines. Since several colour genes have

TABLE 8

DIFFERENCES IN LITTER SIZE AND DAYS BETWEEN MATING AND PARTURITION BETWEEN HST AND LST FEMALES MATED IN EACH GENERATION OF THE SELECTION EXPERIMENT

Difference in:	Generation						
	1	2	3	4	5	6	7
Litter size	+0·79	+0·35	+0·77*	+0·80*	+1·10*	+0·53	+0·87
Standard error	0·62	0·58	0·38	0·40	0·45	0·42	0·53
Time to parturition (days)	−0·57	−3·39	+0·80	+2·13*	−2·27	+1·10	+0·37
Standard error	1·52	3·97	0·80	0·97	1·26	1·30	1·35
Degrees of freedom	24	30	55	57	56	58	53

*Significant at the 5 per cent. level.

been shown in other researches to have effects on body size and reproductive fitness, it is possible that the difference of these characters between the selection lines are concomitants of the different frequencies of the colour genes. The different frequencies of colour genes may be fortuitous but it is possible that these genes have effects on vibrissa number, and that the differences of their frequencies between the selection lines are concomitants of the selection on vibrissa number. No effect of these genes on vibrissa number could be detected, but the data were not extensive, and do not exclude this possibility.

IV. DISCUSSION

Our results can be summarized as showing:

(1) A low variance of vibrissa number in unselected + mice. This could be due to (i) a lack of genetic variation, (ii) constancy of the aspects of the environment which affect vibrissa number, or (iii) canalization of the development of vibrissa such that both genetic and environmental variation are ineffective.

(2) A high variance of vibrissa number in *Ta* mice which could be due to (i) an increased sensitivity to environmental variation caused by the *Ta* gene, (ii)

variation of a genetic system specifically acting only in the presence of *Ta*, i.e. specific modifiers, or (iii) variation of a genetic system whose effects are "canalized" and therefore not expressed phenotypically in + mice but which are expressed in *Ta* mice, because the *Ta* gene reduces or removes the canalization. That there is an increased sensitivity to environmental effects has been shown by Hardy and Fraser (unpublished data) who both found marked maternal effects of the genotype of the dam on the vibrissa number of her *Ta* progeny.

(3) A marked effect of selection on the number of vibrissae in *Ta* mice showing that the variation of vibrissa number in such mice is, to some degree, genetically determined. This is confirmation of the estimate of heritability found in a random-mated population, i.e. 30–50 per cent. It can be argued that the *Ta* is a *mutator*, but since the variation occurs only in vibrissa number this is very unlikely.

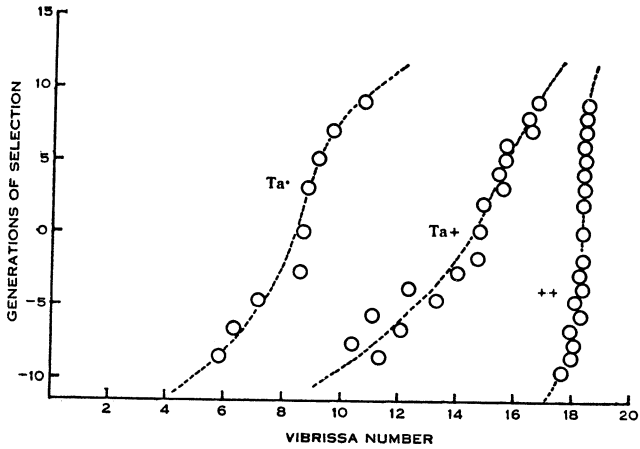

Fig. 6.—Mean vibrissa number is shown plotted against generations of selection for the ++, *Ta*+, and *Ta*· genotypes. This figure should be compared with that given by Dun and Fraser (1958).

(4) That concomitant changes in the other aspects of the tabby phenotype occurred with the changes of vibrissa number. The genetic system affected by selection can be described as one of "dominance modification". There are strong indications that *Ta*+ mice with a high vibrissa number (i.e. approaching normal) produce larger litters in a shorter time. Consequently, the genetic system affects vibrissa number, dominance, and reproductive fitness.

(5) That selection for changes of vibrissa number in *Ta* mice causes concomitant changes in the vibrissa number of + mice, i.e. the genetic system determining variation of vibrissa number in *Ta* mice can, if selected to a sufficient extreme, produce effects on vibrissa number in + mice. This shows that the "dominance modifiers" of *Ta* affect the expression of the + allele, and, consequently, are not specific modifiers of the *Ta* gene. It can be argued that selection on vibrissa number of + mice, in the absence of the *Ta* gene, could affect the dominance of the *Ta* gene. Clearly such an argument has relevance to criticisms of Fisher's theory of dominance, but it is not possible to generalize from this one example of incidental dominance.

Dun and Fraser (1958), in a preliminary note on these results, expressed their conclusions in a diagram, which is shown in a modified form in Figure 6. This is based on the *Ta* locus determining the relationship of the basic genetic system, termed the "vibrissa number system", to the developed number of vibrissae. This relationship is, on this model, a sigmoid function, whose slope and mean are affected by the *Ta* gene. The concept of canalization is, essentially, described by a sigmoid relationship of genotype to phenotype. We concluded that selection shifts a genetic system which determines the mean number of vibrissae.

Rendel (1959), in a similar selection experiment involving the scute gene and the number of scutellar bristles in *Drosophila*, has found an essentially similar system. The standard number of such bristles is 4, and variation is rare. The scute gene causes a reduction to 1–2, and a marked increase of variation around this mean. Selection for increased scutellar number in populations segregating for scute produces changes in the scute flies and this selection, when sufficiently advanced, is correlated with changes in the scutellar number of + sibs. The selection has proceeded further than ours since scute flies with the same number of scutellar bristles as + flies have been produced. As the average number of bristles in scute flies approached "standard" (i.e. 4), there was a marked reduction of variability. Conversely, a marked increase of variability occurred in + flies as their average scutellar number exceeded 4.

Rendel concludes that there is a canalization of scutellar number at 4, i.e. the relationship of phenotype to genotype is sigmoid with a marked inflexion zone at 4 bristles. The results are very similar to ours but Rendel does not consider that the scute gene affects the canalization. On the basis of the model which he proposes, the scute gene is postulated to affect the degree of expression of the "scutellar number" genes directly; not by modifying the sigmoid function relating the basic genetic system to the phenotype. His model is illustrated in Figure 7.

Neither sets of data contain any features which allow discrimination between the two models, i.e. it is equally valid to consider that the tabby and scute genes act directly on the basic *vibrissa number* and *scutellar number* genetic systems, or that they act on the sigmoid relationship of genotype to phenotype. Accurate analyses of the distributions of the characters at various mean numbers of vibrissae or bristles could distinguish between the alternatives for specific types of canalization, but it is probably more useful to compare the developmental tracks affected by the basic genetic systems and the major mutants. The complexity of the systems with which we are dealing is such that both methods should be followed, since neither is likely to be completely conclusive. An extremely interesting feature of Rendel's data is pertinent to this problem. This is the occurrence of scute flies with 4 bristles in which one of the bristle sites was empty. Such flies indicate that the "canalization zone" of 4 bristles is not equally stable across its range since such flies are only observed at the low end of the 4 zone. + flies segregating from the selection experiment do not show any such abnormalities indicating that the lower stabilization (canalization) is not a feature of the middle and high end of the 4 zone, or is manifested in ways which were not scored. It would be of interest to have measurements of the size of bristles in populations located at the edges of the 4 zone, since these might indicate the degree of stability at the edges.

The genetic system determining the number of vibrissae differs markedly in expression between the three genotypes. At the + level the vibrissa number genotype produces very little variation; in the "heritability" terminology, the mode of action of this genotype is almost completely epistatic. At the *Ta* levels, two differences are apparent: firstly, that there is a decrease in the average effect of this genotype, and, secondly, a shift in the mode of action from being almost completely epistatic to its being predominantly additive.

We can describe the *Ta* gene as an "epistasis modifier". We then have a "dominance modifier" system effecting the tabby locus, which is itself an epistasis modifier of the dominance modifier system. Clearly such terminology is becoming too complicated and involved to describe situations like this.

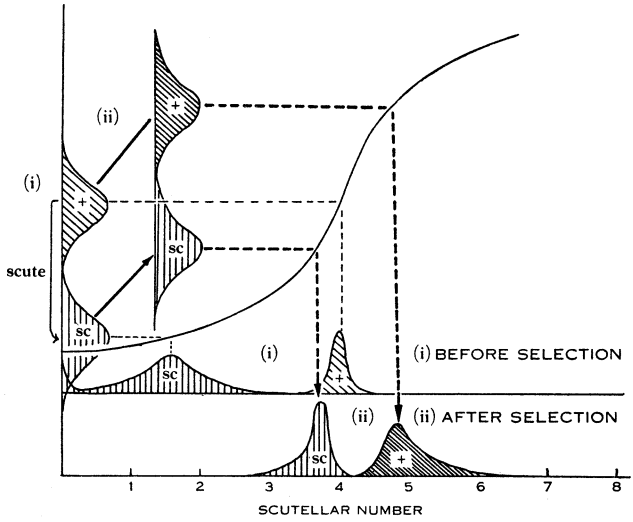

Fig. 7.—Schematic representation of the results and interpretation of Rendel's (1959) selection experiment. Scute is postulated not to affect the sigmoid relationship of genotype/phenotype as has been proposed for the tabby gene, but rather to directly reduce the potency of the basic "scutellar number" genes. The genetic distributions are shown vertically; the phenotypic distributions horizontally.

Consider the genetics of a population which would be produced by crossing our high and low lines. In such a population segregation would occur at the tabby locus, and variation of the vibrissa number system would be marked. The range of vibrissa number would be from 4–5 to 21–22, and in the absence of any secondary effects of the tabby gene it would be difficult to identify the existence of segregation at that locus. Estimates of the "additive" and "epistatic" variance, if based on average values over the whole distribution, would, firstly, give incorrect values of these parameters, and, secondly, give no measure of the complexity of the system. If, however, these parameters were estimated on an assortatively mated population and heritability etc. were determined at several ranges of the phenotype then the complexity of the system would become apparent, and valid predictions could be made of the effects of selection.

An important feature of these experiments is the demonstration of genetic variability in the absence of phenotypic variability. Waddington (1953, 1956), Bateman (1956), Rendel (1959), and our own experiment have all demonstrated this, and it is pertinent to question the assumption that lack of phenotypic variability generation after generation is a demonstration of homozygosis. Although the number of demonstrations of such genetic variability is small, it may be much more widespread than is at present considered possible. It is therefore necessary to consider why such heterozygosity exists. Some results of Fraser (1959), although preliminary, are of interest. It was shown in Monte Carlo simulations of the effects of selection against variability that such selection would form an epistatic system determining a sigmoid relationship of genotype to phenotype, if sufficient genetic variability existed. Even in the absence of genes capable of giving rise to such a system, selection did not produce any marked degree of homozygosity except in small populations.

Although these results require considerable amplification, it is possible to argue from them that the heterozygosity demonstrated in the selection experiments of Waddington, Bateman, Rendel, and Dun and Fraser is a relic. Selection could have acted first on a polygenic system so that this was centred around the desired phenotype. Selection against variability, if the number of loci involved is large, would be ineffective unless directed at other genetic systems capable of determining a sigmoid genotype to phenotype relationship, i.e. canalization. On this hypothesis heterozygosity is a consequence of the inability of optimizing selection to produce homozygosis when acting on a polygenic system rather than a direct determinant of decreased phenotypic variability as proposed by Lerner (1954). Since optimizing selection would favour complex epistatic interactions, the final result would be a genetically variable system with a marked degree of epistasis, in which inbreeding could be expected to result in extreme deviants. Similarly many of the phenomena taken by Lerner (1954) to indicate that homeostasis has a heterozygous basis could be a result of the ineffectiveness of selection in causing genetic fixation and its tendency to determine increased epistasis.

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