GENETIC ANALYSIS OF A STRAIN OF MICE PLATEAUED FOR LITTER SIZE

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ABSTRACT

A strain of mice (S1) was successfully selected for large litter size for 31 generations, increasing the mean by 4.2 young per litter. After generation 31, there was no further progress and it was concluded that a selection plateau had been reached. Realized heritability decreased during the course of the experiment from 0.16 ± 0.06 for the first 15 generations to 0.00 ± 0.03 for generations 30 through 45. — In order to explore the nature of the selection plateau, the following groups were derived from line S1 at generation 34 or 35: Upward selection with inbreeding (SF), random (relaxed) selection (SO), and downward selection (SR). Selections were carried out for 10 or 11 generations. The means of SO and SF were similar to those of S1, ruling out any major effect of natural selection or overdominance. SR decreased, the mean averaging 2.3 young per litter below that of S1 during the last three generations. The fact that SR responded to selection indicates that genetic variance was still present in the plateaued population. The SF sublines were crossed when the inbreeding was 95% and a new line, SX, was formed. SX was maintained for three generations and the difference of +0.7 young per litter above the contemporary generations of S1 was significant. The results from this experiment suggest that the selection plateau in line S1 was caused by reduction of additive genetic variance to a very low level. Some nonadditive genetic variance remained, however, and was attributed to recessive alleles at low frequency. In agreement with results reported by FALCONER (1971), inbreeding with selection followed by crossing of the inbred sublines proved to be effective in overcoming a selection plateau in litter size.

THE limit to artificial selection is theoretically reached when all alleles affecting the trait have become fixed, or when overdominant alleles have reached an equilibrium state. In practice, however, a limit is often reached before all genetic variance has become exhausted (FALCONER 1955; ROBERTS 1966a,b). Depending on the nature of the selection plateau, it is sometimes possible to renew response to selection, and several methods have been proposed to overcome selection limits (see, for example, ROBERTS 1967a,b).

FALCONER (1971) practiced inbreeding with selection followed by crossing of the inbred sublines to overcome a plateau in a line of mice selected for large litter

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size. Al-Murrani and Roberts (1974), on the other hand, failed to improve a line of mice, selected to its limit for body weight, using the same technique and the generality of Falconer's (1971) method has thus not yet been established.

The objectives of the present experiment were to determine the cause of a selection plateau in a line of mice selected for large litter size at birth, and to investigate the effectiveness of inbreeding with selection as a means of overcoming the selection plateau.

The experimental population used to start this study had been selected for 35 generations for large litter size, and an analysis of response to long term selection has been performed in addition to investigation of the selection plateau.

MATERIALS AND METHODS

The animals used in the present experiment are designated as lines C, S1, SF, SO, SR and SX. Lines C and S1 were derived from the same base population, which was formed by crossing four highly inbred strains. The origin of these strains was described by Bradford (1968).

Line C was kept as an unselected control for 45 generations. The line was maintained during the first 35 generations by mating 18 males to two females each. The males were selected by taking one son of each sire, chosen at random, and the females were selected one from every litter whenever possible. From generation 36 to generation 45, the procedure was changed to include 24 mating pairs, one male and one female being sampled from each litter. Mating of selected individuals in line C and in line S1 was at random with (from generation 9 onwards) no attempt to avoid sib or cousin matings.

Line S1 was selected for large litter size, defined as the total number born. The line was maintained the first 35 generations by mating 18 males to two females each, taken at random from the six to 14 largest litters. From generation 36 to generation 45, the selection procedure was the same but the number mated was reduced to 18 pairs.

SF was started in generation 34 from 24 full-sib matings, sampled from S1. The 12 largest litters were selected to form inbred sublines, each of which was maintained by two to seven full-sib matings. Selection for large litter size was applied within lines and each line was propagated from one litter only. After three generations of selection, i.e., at generation 37, three sublines were discontinued and at generation 39, another three sublines were discontinued, because of low fertility (although no line was lost from complete sterility). The remaining six sublines were continued till the experiment was terminated in generation 45.

At generation 35, SO (relaxed selection) and SR (reverse selection) were started from S1. SO was randomly selected and SR was selected for small litter size. Both lines were maintained by 18 mating pairs.

After SF had been selected for seven generations, a four-way cross was made from the six remaining sublines and a new line, SX, was formed. The lines, here designated A through F, were crossed as follows:

\[
\begin{array}{c}
A \quad B \quad C \quad D \quad E \quad F \\
\text{X1} \quad X'2 \quad X3 \quad X'2 \quad X'3 \quad X1
\end{array}
\]

**Line-generation**

- SF-09
- SX-00
- SX-01
- SX-02

SX-02 was produced by random mating of 18 pairs obtained by random selection of equal numbers of individuals from X'1, X'2 and X'3, and SX-03 by random selection and mating of 18 pairs from SX-02. Approximately 30 extra females were mated each generation and were autopsied at about 16 days of gestation and the number of fully developed fetuses was determined. Mean litter size reported for SX-01 to 03 represents the combined mean of the females
producing litters and the autopsied females, since it has been shown previously that losses after day 16 are negligible (Bradford 1969).

All animals were mated when they were between 8 and 10 weeks of age and the males were kept with the females for approximately 10 days. Cages were checked twice daily and the total number born was recorded on the day of birth. Two days after birth the mice were sexed and the litter sizes were adjusted as follows: in lines S1 and C litters of 11 or more were reduced to 10. In lines SF, SR, SO and SX all litters were adjusted to 10 by removing or crossfostering young of the same age. Thus all individuals in all lines (except C) were raised in litters of 10. All animals were weaned, separated and caged by sex when they were 3 weeks old. Water and feed were supplied ad lib., and for the last 25 generations temperature was kept at approximately 23° and the lights were on 14 hours daily.

The intended selection differential was calculated as half the difference between the mean of selected litters and the mean of the population from which they were sampled. The procedure assumes that the effect of the sire is negligible and that litter size is a trait of the dam. The realized selection differential was calculated using only individuals involved in fertile matings.

The heritability was calculated in line C by doubling the regression of daughter on dam, and in S1 from the regression of response on cumulative selection differential, where the response was estimated as the difference between the generation means of S1 and C. Standard error for the realized heritability was computed according to the method of Hill (1972).

Inbreeding in all lines was estimated by the method of coancestry (Cruden 1949).

**RESULTS**

A. Long term response to selection

Intended and realized average selection differentials and pooled standard deviations for lines C and S1 are given in Table 1.

The difference between intended and realized selection differentials estimates part of the natural selection acting against artificial selection. In the present experiment, intended and realized selection differentials were virtually identical for both lines throughout the experiment, indicating that natural selection acting through differential conception rate was not important.

The expected selection differential in line C was zero and the average intended selection differential of 0.12 observed in this line was attributed in part to automatic selection. Automatic selection was avoided insofar as possible by selection from each litter, but due to the fact that some small litters contained only one sex and that occasionally litters of only one individual were born, some selection for large litter size did occur.

The realized selection differentials in line S1 increased between period 1 (generations 1–14) and period 2 (generations 15–29) from 1.24 to 1.50, due appar-

<table>
<thead>
<tr>
<th>Generations</th>
<th>Line</th>
<th>I</th>
<th>C</th>
<th>R</th>
<th>S</th>
<th>I</th>
<th>S</th>
<th>S1</th>
<th>R</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-14</td>
<td></td>
<td>0.13</td>
<td>0.12</td>
<td>2.24</td>
<td></td>
<td>1.25</td>
<td></td>
<td>1.24</td>
<td></td>
<td>2.15</td>
</tr>
<tr>
<td>15-29</td>
<td></td>
<td>0.10</td>
<td>0.11</td>
<td>2.25</td>
<td></td>
<td>1.50</td>
<td></td>
<td>1.50</td>
<td></td>
<td>2.83</td>
</tr>
<tr>
<td>30-44</td>
<td></td>
<td>0.11</td>
<td>0.12</td>
<td>2.19</td>
<td></td>
<td>1.22</td>
<td></td>
<td>1.23</td>
<td></td>
<td>2.70</td>
</tr>
</tbody>
</table>
ently to an increase in phenotypic variance. The decrease in average selection differentials during the last 15 generations to 1.23 is attributed to a reduction of population size, after generation 36.

Direct response to selection for total number born, from generation 1 to generation 45, is shown in Figure 1.

The generation means in line S1 increased almost linearly from generation 1 to generation 31, at which point the line reached its highest mean value of 13.6 ± 0.33. After generation 31 the line showed no further progress, indicating that a selection limit had been reached or approached.

The means in the control line increased during the early part of the experiment and the regression of mean on generation number for the entire period was 0.021 ± 0.007. A small part of this increase may be attributed to automatic selection, but the major reason for the upward trend in the control line is thought to be an environmental trend.

Heritability for litter size was estimated for lines C and S1 for three periods: generations 1 through 15, 16 through 30 and 31 through 45. The estimates are listed in Table 2.

<table>
<thead>
<tr>
<th>Generations</th>
<th>Line C</th>
<th>Line S1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-15</td>
<td>0.32 ± 0.10</td>
<td>0.16 ± 0.06</td>
</tr>
<tr>
<td>16-30</td>
<td>0.22 ± 0.10</td>
<td>0.05 ± 0.04</td>
</tr>
<tr>
<td>31-45</td>
<td>0.24 ± 0.11</td>
<td>0.00 ± 0.03</td>
</tr>
</tbody>
</table>

Figure 1.—Response to selection for large litter size. C-control, S1-selected.
The realized heritability estimate in S1 showed a marked decline from the first period, $0.16 \pm 0.06$, to the third period, $0.00 \pm 0.03$, reflecting the cessation of response to selection, as indicated in Figure 1.

The heritabilities computed from daughter-dam regression in line C decreased, but not significantly, from $0.32 \pm 0.10$ in period 1 to $0.22 \pm 0.10$ and $0.24 \pm 0.11$ in periods 2 and 3, but was consistently higher than the realized heritability in line S1.

The relative number of individuals born dead increased in line S1 during the course of the experiment, as is shown in Figure 2. The regression of mean on generation number was $0.019 \pm 0.016$ for line C and $0.215 \pm 0.024$ for line S1, while the pooled intraline, intrageneration correlation between litter size and percent born dead was $-0.18$.

The base population, from which C and S1 were derived, was formed from a cross of four highly inbred lines and inbreeding at this point was thus zero. In generation 1, i.e., the progeny of matings among the four-way cross individuals, $1/4$ of the loci were expected to be homozygous for alleles identical by descent which, by definition, corresponded to $25\%$ inbreeding. By generation 45 the inbreeding, relative to this base, amounted to $45\%$ and $80\%$ for lines C and S1, respectively. The higher inbreeding in S1, relative to C, resulted from the fact that only six to 14 litters were selected each generation in line S1, while all litters were sampled for replacements in line C.

The effect of inbreeding on litter size was estimated from the base population
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TABLE 3
Relative effect of inbreeding of dams (F₁) and their offspring (F₂) on litter size (LS) in the base population (B) and in generations 1 and 2 of line C

<table>
<thead>
<tr>
<th>Generation</th>
<th>F₁</th>
<th>F₂</th>
<th>LS</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>0</td>
<td>0</td>
<td>9.33 ± 0.36</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0.25</td>
<td>8.26 ± 0.32</td>
</tr>
<tr>
<td>2</td>
<td>0.25</td>
<td>0.25</td>
<td>7.31 ± 0.31</td>
</tr>
</tbody>
</table>

and the first two generations in line C and is shown in Table 3. Litter size decreased by 0.43 young for 10% increase of inbreeding in the litter itself and by 0.38 young for 10% increase of inbreeding in the dams.

The effect of inbreeding on percent born dead was estimated from the intra-generation regression in both lines. The regression coefficients for percent born dead on inbreeding of the litter were −0.04 ± 0.08 and −0.20 ± 0.12 for lines C and S1, respectively, neither of which is significantly different from zero. The regressions of percent born dead on inbreeding of the dams were 0.10 ± 0.08 and 0.27 ± 0.13 for lines C and S1. The two regressions are not significantly different from each other and the pooled estimate was 0.18 ± 0.08.

B. Selection plateau

Intended and realized selection differentials for lines S1, SO, SR, SF and SX are listed in Table 4.

The absolute value of the average realized selection differentials for lines S1 and SR were 1.12 and 1.00, indicating that selection intensities for large and for small litter size were about equal.

Line SO was randomly selected and the average intended selection differential in this line amounted to −0.05, which is similar to its expected value of 0.00.

The selection differentials for SF, shown in Table 4, represent the average

TABLE 4
Intended (I) and realized (R) selection differentials

<table>
<thead>
<tr>
<th>Generation (of line S1)</th>
<th>S1</th>
<th>R</th>
<th>SO</th>
<th>R</th>
<th>Line</th>
<th>SR</th>
<th>I</th>
<th>R</th>
<th>I</th>
<th>SF</th>
<th>R</th>
<th>I</th>
<th>SX</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>1.45</td>
<td>1.44</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>1.46</td>
<td>1.46</td>
<td>---</td>
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<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>35</td>
<td>1.74</td>
<td>1.79</td>
<td>0.17</td>
<td>0.28</td>
<td>−1.55</td>
<td>−1.46</td>
<td>.55</td>
<td>.50</td>
<td>---</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>36</td>
<td>1.04</td>
<td>1.10</td>
<td>−0.38</td>
<td>−0.29</td>
<td>−0.43</td>
<td>−0.40</td>
<td>1.20</td>
<td>1.07</td>
<td>---</td>
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<tr>
<td>37</td>
<td>1.24</td>
<td>1.32</td>
<td>−0.50</td>
<td>−0.46</td>
<td>−1.32</td>
<td>−1.39</td>
<td>0.85</td>
<td>0.77</td>
<td>---</td>
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</tr>
<tr>
<td>38</td>
<td>0.81</td>
<td>0.84</td>
<td>0.71</td>
<td>0.74</td>
<td>−1.11</td>
<td>−1.02</td>
<td>1.42</td>
<td>1.29</td>
<td>---</td>
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<td></td>
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<tr>
<td>39</td>
<td>1.49</td>
<td>1.44</td>
<td>0.17</td>
<td>0.21</td>
<td>−0.75</td>
<td>−0.76</td>
<td>0.36</td>
<td>0.36</td>
<td>---</td>
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<tr>
<td>40</td>
<td>0.80</td>
<td>0.78</td>
<td>−0.02</td>
<td>0.06</td>
<td>−1.12</td>
<td>−1.17</td>
<td>0.77</td>
<td>0.69</td>
<td>---</td>
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</tr>
<tr>
<td>41</td>
<td>1.16</td>
<td>1.14</td>
<td>−0.34</td>
<td>−0.29</td>
<td>−0.20</td>
<td>−0.37</td>
<td>0.60</td>
<td>0.51</td>
<td>0.41</td>
<td>0.41</td>
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<tr>
<td>42</td>
<td>0.80</td>
<td>0.82</td>
<td>−0.14</td>
<td>−0.17</td>
<td>−1.17</td>
<td>−1.17</td>
<td>0.73</td>
<td>0.66</td>
<td>0.07</td>
<td>0.04</td>
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<tr>
<td>43</td>
<td>0.87</td>
<td>0.86</td>
<td>−0.48</td>
<td>−0.53</td>
<td>−1.55</td>
<td>−1.47</td>
<td>0.92</td>
<td>0.74</td>
<td>0.02</td>
<td>0.00</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>0.73</td>
<td>0.76</td>
<td>0.28</td>
<td>0.24</td>
<td>−0.80</td>
<td>−0.74</td>
<td>0.30</td>
<td>0.33</td>
<td>0.02</td>
<td>0.04</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>1.10</td>
<td>1.12</td>
<td>−0.05</td>
<td>−0.02</td>
<td>−1.00</td>
<td>−1.00</td>
<td>0.83</td>
<td>0.76</td>
<td>0.13</td>
<td>0.12</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
within-line plus between-line (generation 36 and 38) values. Both intended and realized selection differentials show a slight but nonsignificant downward trend in this population, which may be attributed to a decrease in phenotypic variation. Line SX was randomly selected and the average intended selection differential of 0.13 is attributed to chance alone.

In all lines, the realized and intended selection differentials are similar, indicating that natural selection, acting through conception rate, is not important.

Direct response to selection for litter size in lines S1, SO, SR, SF and SX, from generations 34 through 45, is graphically illustrated in Figure 3 and the unweighted means of the last three generations are given in Table 5 together with the pooled standard deviations.

The generation means in S1 fluctuated somewhat, but showed no directional trend, and the average over the last three generations of 12.6 ± 0.34 is the same as the mean in generation 34, 12.6 ± 0.62.

Mean litter size in line SO increased during the first two generations (36 and 37), but from generation 38 onwards it was similar to S1. The generation means in line SR were similar to those of line S1 for the first four generations. At generation 40, however, SR started to diverge from S1 and the regressions of means on generation numbers for generations 35 to 45 were −0.01 ± 0.08 and −0.29 ± 0.08 for S1 and SR, respectively.

Figure 3.—Direct response to selection for litter size. Continued upward selection (S1); relaxed selection (SO); upward selection with inbreeding (SF); cross of inbred lines (SX), X generation 42: F₁ litters, X, generation 43: F₂ dams; downward selection (SR).
TABLE 5

Unweighted means (\(\bar{X}\)) and pooled intrageneration standard deviations (S) for litter size for generations 43 through 45

<table>
<thead>
<tr>
<th></th>
<th>SI</th>
<th>SO</th>
<th>Lines SR</th>
<th>SF</th>
<th>SX</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\bar{X})</td>
<td>12.6 ± 0.34</td>
<td>12.3 ± 0.41</td>
<td>10.3 ± 0.41</td>
<td>11.8 ± 0.24</td>
<td>13.3 ± 0.33</td>
</tr>
<tr>
<td>S</td>
<td>2.40</td>
<td>2.81</td>
<td>2.91</td>
<td>1.93*</td>
<td>2.35</td>
</tr>
</tbody>
</table>

* Pooled within families.

Response to selection with inbreeding is shown for individual full-sib families in Figure 4, and the unweighted mean of these lines, designated SF, is shown in Figure 3. The generation means of the full-sib families fluctuated a great deal and no trend among the lines was observed. The mean of the full-sib families of the SF population was similar to S1 in most generations and there was no apparent tendency for the two populations to diverge. The inbreeding, when SF was started in generation 34, was 73% and by generation 45 it had increased to 98%.

The mean of the first cross litters produced by crossing the inbred lines (SX-00; generation 42 in Figure 3) was similar to the contemporary SF mean: 12.1 ± 0.60 vs. 12.4 ± 0.26. When the crossbred dams gave birth in generation 43, however, a substantial increase in litter size was realized and the mean of 14.2 ± 0.29 was significantly larger than that in the contemporary S1 and SF groups, 12.7 ± 0.59.

![Graph showing response to selection with inbreeding for large litter size](image-url)
and $12.3 \pm 0.45$, respectively. In generation 44, SX showed a slight decrease, but the line had consistently larger litter size than S1 and SF until the experiment was terminated in generation 45.

**DISCUSSION**

The response to selection for large litter size obtained in line S1 is characteristic of that of a quantitative trait. The mean increased asymptotically and reached an apparent selection plateau, in this case after about 31 generations.

A number of selection experiments for litter size in mice have been reported in the literature, but in only one study has the line been carried to a plateau (Falconer 1971). Falconer obtained a total response of 2.1 young per litter in his up-selected line, which is about half of that found in the present study. The difference in total response between the two experiments can be explained partly by the fact that Falconer defined litter size as the number born alive, while in this study litter size was estimated as the total number born, dead and alive. If the present data are adjusted for number born dead, total response would amount to about 3.9, which is still considerably larger than that obtained by Falconer. Several factors may contribute to this difference in response, such as different environments and different base populations. In addition, Falconer mated his animals at about 6 weeks of age, whereas mating age was about 9 weeks in the present study, and he applied within-family selection rather than mass selection. The relative importance of these various factors is of interest, but the available data unfortunately do not allow identification of the specific cause or causes of the difference.

The decrease in realized heritability during the course of the experiment was expected, and mainly reflected a gradual exhaustion of the additive genetic variance due to inbreeding and selection. The value for heritability of 0.16, estimated over the first 15 generations, is similar to that reported by Falconer (1960b). Falconer obtained a realized heritability of 0.08 after 20 generations of within-litter selection. If this value is converted to that of individual heritability it becomes 0.15. WOMACK and BOGART (1968) estimated the realized heritability to be 0.05 and 0.13 in two lines of mice selected for large litter size for five generations. Allowing for fluctuations due to sampling error, the four estimates are in reasonable agreement and support the conclusion that litter size is a trait with a low heritability. The heritability based on daughter-dam regression in line C of 0.32 was about twice the realized heritability in line S1 for the first 15 generations. Part of this difference can probably be attributed to chance alone, but compared to realized heritability estimates, doubled regression of offspring on dam overestimates heritability by including fractions of covariances between direct and maternal gene effects, variance from interactions between loci with additive effects, and variance in maternal influence from average gene effects (Dickerson 1969). The covariance between direct and maternal effect can be negative, as was the case in Falconer's (1965) study, but since the litters were partially standardized in the present experiment, the effect is probably small.

Selection for one character almost always leads to changes in others. In the present study, the frequency of individuals born dead increased in line S1 during
the course of the study. It appears, however, that this increase was not caused by selection for large litter size, but resulted from an increase in inbreeding of the dams. This is in agreement with observations by Krzanowska (1960) and McCarthy (1967). In the present experiment the number born dead is biased upwards in the sense that it also includes individuals which were born alive, but died before the litters were examined. Although no records were kept, it was often observed that dead individuals were still encapsulated in the placental sac. It is thus possible that some of the animals recorded as being born dead actually were born alive, but the dam failed to remove the membranes and the young subsequently suffocated. This leads to the speculation that the increase in frequency of individuals recorded as being born dead reflects a change in maternal behavior associated with inbreeding, rather than an increase in mortality of the young per se.

Some of the possible causes of the selection limit were eliminated by the results from the various lines derived from S1. Natural selection, or favorable epistatic combinations maintained by selection were not important, as indicated by the fact that realized and intended selection differentials were similar in all lines throughout the experiment, and that relaxed selection did not cause any decline in litter size. Overdominance as a major cause for the plateau was rejected on the basis that the mean of the lines inbred with selection did not decline. Some genetic variance did exist, however, since the reversed line responded to selection for small litter size.

The most plausible explanation for the selection limit is reduction of additive variance to the point that response was negligible, but with a number of recessive alleles for small litter size still segregating at low frequency. Assuming the above model is correct, it is then possible to estimate the number of genes segregating in line S1 at the beginning of the selection experiment and at the beginning of the selection plateau.

In order to estimate the number of genes for a quantitative trait, several assumptions about the genetic constitution have to be made. In the present experiment it was assumed that only two types of alleles were segregating at each locus, that alleles at different loci had similar effects, and that linkage and epistasis were not present. Furthermore, the observed reduction of litter size due to inbreeding (Table 3) and the heterosis shown by SX females (Figure 3) suggest that the alleles for large litter size were dominant, and it was assumed that the genotypic value of the heterozygotes and that of the homozygous dominant were similar. (If not all genes show complete dominance, the estimate of number of genes obtained will be a minimum estimate.) Taking the above assumptions into consideration, the genotypic model for the $i^{th}$ locus in line S1 in generation 1 would be as follows:

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Genotypic frequency</th>
<th>Genotypic effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AA$</td>
<td>$(1-q)^2$</td>
<td>$\alpha$</td>
</tr>
<tr>
<td>$Aa$</td>
<td>$2q(1-q)$</td>
<td>$\alpha$</td>
</tr>
<tr>
<td>$aa$</td>
<td>$q^2$</td>
<td>$-\alpha$</td>
</tr>
</tbody>
</table>
The mean \( (X_0) \) and additive genetic variance \( (V_A) \) is given by Falconer (1960a) and for the above model they can be expressed as:

\[
X_0 = n\alpha(1-2q^2)
\]

and

\[
V_A = 8n\alpha^2q^3(1-q)
\]

where \( n \) is the number of loci.

Since the base population was a four-way cross, the value of \( q \) could be 0.25, 0.50 or 0.75. While this represents the range of values possible, it seems unlikely that deleterious recessive alleles would have been fixed at more than 50% of the loci in the inbred lines contributing to the four-way cross.

The additive genetic variance was estimated in S1 from the realized heritability and the phenotypic variance, as \( V_A = V_p h^2 \), and amounted to 0.74 for generations 1 through 15. The genetic variation in line C was estimated from heritability, based on daughter-dam regression, and was 1.60 for the same period. The higher value in line C may be due to the fact that this line was randomly selected and thus the genetic variation is expected to be constant for the entire period. In line S1, on the other hand, the additive variance will decrease for each generation of selection (assuming \( q_0 \leq 0.75 \)) and thus the additive variation estimated in this line represents a value lower than that expected in the base population. In addition, the genetic variance in line C contains not only an additive component, but also a fraction of the interallelic interactions and maternal effects (Dickerson 1969). It is reasonable to assume that the additive genetic variance in the base population lies somewhere between 0.74 and 1.60 and the average of 1.17 was used in the following computations. Assuming all favorable alleles segregating in the base population were fixed in line SX, the mean in this line \( (X_1) \) would equal \( n\alpha \). The total response to selection \( (\bar{d}) \), i.e., the average difference between lines C and SX, amounted to 5.66 and may be expressed as:

\[
\bar{d} = \bar{X}_1 - \bar{X}_0 = 2n\alpha q^2
\]

Equations II and III yield estimates for \( n \) and \( \alpha \) of 164 and 0.28, respectively, for \( q = 0.25 \) and 54 and 0.21 for \( q = 0.50 \).

The above estimates are subject to several errors, the most serious one probably resulting from the assumption that all favorable alleles were fixed in line SX. In spite of selection, some unfavorable alleles no doubt became fixed due to drift, (a result confirmed by the difference between SX and SF), which would bias the estimate of \( n \) downwards.

From the previous section it was shown that in spite of the cessation of response to selection in line S1, a number of alleles were still segregating. Methods for a direct estimation of the proportion of genes expected to be segregating in a population selected for a given number of generations do not appear to be available. In the present study, an approximate value of the number of genes still segregating in line S1 at the beginning of the selection plateau (generation 31) was calculated, based on the expected time to fixation or loss of an allele in a finite population (Carr and Nassar 1970).
In order to use the proposed method, the effective population size \( N_e \) and the selection coefficient \( s \) have to be determined. \( N_e \) was estimated from the observed and expected inbreeding in generation 31 as follows:

\[
F_t = 1 - (1 - \frac{1}{2N_e})^t \quad \text{(Falconer 1960a)}
\]

For \( t = 31 \) generations and \( F_{31} = 0.71 \), the effective population size becomes 12.6. The selection coefficient is estimated as:

\[
s = \frac{2\alpha}{\sigma_p} \quad \text{(Falconer 1960a)}
\]

\( \alpha \) was estimated in the previous section to be between 0.21 and 0.28 and for a selection intensity of \( i = 0.53 \) and a phenotypic variance of \( \sigma_p = 2.58 \), \( s \) will take on a value between 0.09 and 0.12.

From graphs provided by Carr and Nasser (1970), the expected time for a gene to become fixed or lost can be determined by means of interpolation. For an initial gene frequency of 0.25 and a selection coefficient of 0.12, the expected time for a gene to become fixed or lost is approximately 27 generations with a standard deviation of 24 and for an initial gene frequency at 0.50, the corresponding values will be 33 and 25. Assuming that means follow a normal distribution, it is then possible to estimate the probability that a gene is segregating after a given number of generations. In the present study the probability that a gene was still segregating in line S1 after 31 generations was between 0.44 and 0.53.

From the estimated number of genes in the base population and from the above probabilities, the expected number of genes still segregating in line S1 by the beginning of the selection plateau was estimated to be between 29 and 72. The difference between SX and SR (3.0, Table 5) requires a minimum of 11–14 genes. This is in reasonable agreement with at least the lower estimate of number of genes, assuming some chance fixation in both populations.

The similarities between the results from this experiment and those of Falconer (1971) are striking. Falconer did not carry any reversed or relaxed lines, but his conclusion about the nature of the selection plateau was the same as in this experiment. The number of genes segregating in Falconer’s plateaued line was estimated to be between 30 and 60, which is similar to that estimated in this study. An interesting difference between the two experiments is the behavior of the inbred lines. The unweighted mean of Falconer’s inbred lines was about 1.5 young per litter below his plateaued population, and when he crossed the inbred lines he obtained an increase of about 3.0 young per litter. It thus seems that inbreeding and crossing in the present study had less impact on litter size than in Falconer’s experiment. This might be explained by the fact that selection in the present experiment was more intense, and response greater, which would indicate less residual variance at the time of the plateau. This is consistent with the lower range of estimates of \( \alpha \) found in the present experiment as compared to those found by Falconer.

The method of selection with inbreeding as a means of overcoming a selection
plateau was shown to be effective both in the present experiment, and in that of Falconer (1971). Al-Murrani and Roberts (1974) and Barria (1976), on the other hand, did not succeed in improving populations of mice plateaued for body weight and gain by using this method. The failure of the two populations to respond to selection with inbreeding was attributed to lack of directional dominance. These observations are in good agreement with the results from a simulation study by Madalena and Hill (1972), who showed that, with complete dominance, selection within and between sublines is more effective than selection from a single population, but the situation is reversed for additive gene action.

It thus may be concluded that selection with inbreeding is an effective method to overcome selection plateaus for litter size in mice and probably in other species. The method should also be applicable to other traits controlled by genes with directional dominance.

The computer program used to compute inbreeding coefficients was supplied by Mr. P. Morrow, Department of Avian Sciences, University of California, Davis.

LITERATURE CITED


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