

SELECTION EXPERIMENTS FOR REPRODUCTIVE RATE IN MICE

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SUMMARY

Selection for increasing litter size has a realized heritability of .10 to .20, while selection for decreasing litter size has higher realized heritability but reaches a selection limit in less generations. Selection for larger litter size has usually not responded beyond 30 generations. Using multiple-parity number born for the selection criterion has been successful. Selection for components of litter size has, in most cases, shown response in number born. Use of selection on testes size has not been consistently helpful for increasing litter size. One future direction may be to practice selection for a combination of ovulation rate and uterine capacity.

INTRODUCTION

There have been several experiments in mice centered on selection for some aspect of reproductive performance. Most of these have been selection for increased litter size at first parity. However, some have also investigated selection for decreased litter size, selection for components of litter size, selection for litter size over several parities, and selection for testis size. The intent of this paper is to summarize several of these experiments, identifying consensus of conclusions in some cases and the lack of consensus in others.

The paper will flow through examination of direct and some correlated selection responses, estimated heritabilities, selection limits, and some explanations for the observed responses. Readers are referred to Eisen (1986) for a broader review of genetic variation in reproduction.

DIRECT SELECTION FOR LARGER LITTER SIZE

Falconer (1960) reported that after 20 generations of with full-sister selection, response plateaued to a gain of 1.6 pups, and realized heritability was .15 up to the point of plateau. Joakimsen and Baker (1977) practiced mass selection and reported no plateau of response through 15 generations. The response to that point was about 4 pups and the realized heritability was .18; litter size was standardized to 8 pups at birth. Mass selection was also practiced and reported by Eisen (1978; L+ line). Litters were standardized to 8 pups, and after 12 generations, the response was 4 pups and the realized heritability was .19.

Bakker et al. (1978) reported no plateau in response at Generation 29. Response to that point was about 6 pups, and the realized heritability was .11; no standardization of litter size for rearing was practiced. The Wageningen experiment has one very interesting aspect that is unique to it. The original selections were made by choosing the top 24 females of about one thousand, then mass selection began. Thus, a large(?) population screening program, analogous to hyper-prolific swine screening and multiple-birth cattle screening, was used to increase intensity for the first generation. Luxford and Beilharz (1990) also reported selection for increased first litter size without standardization of litters. Their report only covered 7 generations, and the rate of response was .13 per generation with a realized heritability of .10.

Bradford (1968 and 1979) has described the results from three lines, with litter size standardized to 10 pups in all lines. Mass selection in a population derived from crossing 8 inbred lines showed no plateau at generation 11 after a gain of 3 pups. Realized heritability was .22. Mass selection in another line (S1) derived from 4 inbred lines was quite good after 15 generations (realized heritability of .16). After Generation 16, rate of response tapered off and reached a plateau after 30 generations; total response was 4.3 pups. In another line derived from the 4-line base, Bradford practiced within full-sister selection. There was no plateau at Generation 8 when the line was terminated, and realized heritability adjusted to a mass selection basis, was .25. But, due to working with only the within family variability, response was only .8 pup.

Vangen (1986 and 1990a) gave results from a selection study comparing different levels (4 pups=H4, 8 pups=H8, 12 pups=H12, or no standardization=HI) of standardization of litter size at birth and subsequent effectiveness of selection; the control (K) was standardized at 8 pups. Phenotypic variability and selection differentials were very similar in all selection lines. After 10 generations, response in H4 was large (response of about 4 pups and realized heritability of .37), similar to other studies in H8 and H12 (response of about 2 pups and realized heritability of .20), and non-existent in HI where no standardization was practiced. However at the end of 16 generations, realized heritabilities were .12 in H4, <.0 in H8, .16 in H12, and .08 in HI. In the long term, there was no clear benefit from standardizing litters to gain more selection response.

Vangen (1990b) reported on continued selection in the high (H) line developed at Ås and the high litter size B line imported from Wageningen. The H and B were crossed to form a new population (X) for selection. Line H was at Generation 21 and line B at Generation 33 when the study period of 20 more generations began. Litters were standardized to 8 pups in all lines. Very little further response was attained in lines H and B; they reached their maximum within 5 generations of extra selection. The X line showed more response and had an average advantage of 2.4 pups over the average of L and B during the first 10 generations of selection, but only 1.1 pups average advantage for the subsequent 10 generations. Realized heritability was only positive for the X selection (.02); the decrease in performance of the B and L lines gave negative regressions of response on selection applied.

We have also done direct selection for increasing litter size (Gion et al., 1990 and Kirby and Nielsen, 1992; criterion LS). We standardized litters to 10 pups at birth and practiced selection in three replications with contemporary control lines (criterion LC). Response after 13 generations averaged 1.7 pups with a realized heritability of .09. After 21 generations, the response was 3.5 pups and realized heritability through all generations of selection was .10. Selection ceased at Generation 21, and response maintained during the following 6 generations of relaxed selection was higher at 4.1 pups.

Realized heritability in selection for increased litter size has generally been in the range of .10 to .20. Some have suggested that a negative maternal effect (mice from larger litters are smaller in size and this suppresses size of litters they produce) has clouded expression of genetic variation, explaining some of the difference between heritability estimates in experiments that have or have not standardized litter size for rearing. The work by Vangen (1990a) disputes the importance of size of rearing group in expression of genetic variation. Whether in standardized litters or not, females selected for breeding are reared under similar competition for nutrients, thus they would have similar maternal environment within an experiment.

DIRECT SELECTION FOR SMALLER LITTER SIZE

Falconer (1960), in a line contemporary to the large litter size selection line, selected for smaller number born with full-sister families. After 20 generations, response plateaued to a decrease of 1.6 pups; realized

heritability was .40 on a mass-selection basis. Bradford (1979) initiated selection for small litter size (CN). Mean performance dropped by 2.3 pups in number born after 17 generations, but then increased so that the final response observed was about 1.5 pups at the plateau. Joakimsen and Baker (1977) selected for small litter size in conjunction with their line for large litters. Response plateaued for them after 17 generations as well (decrease of about 3 pups), and the realized heritability was .22. Continued selection in the low line (L) at Ås (Vangen, 1990b) produced very little additional response and produced the lowest mean in Generation 28. Thereafter, its performance increased through Generation 41.

SELECTION FOR COMPONENTS OF LITTER SIZE

Selection for ovulation rate has received more attention than other components of litter size. Land and Falconer (1969) practiced high and low selection for ovulation rate. Primiparous females were measured and existing litters were retrospectively selected, reared, and mated. After 12 generations, realized heritability for divergence was .31, with response of 5 ova in the high line and a loss of 2 ova in the low line. There was no corresponding response in litter size which is in disagreement with the following experiments.

Bradford (1969) produced two parties from females, and based on the ovulation rates of the first-parity daughters, second-parity litters were selected to become the next generation parents. Realized heritability with up selection after 11 generations was .10, and response was 2.6 ova with no corresponding change in litter size. However at Generation 15, a 5-ova response had been achieved with a concomitant response of 2 pups in litter size.

Bradford (1969) also practiced selection for increasing "embryonic survival". He actually practiced selection on the criterion $(\text{number of fetuses})^2 / (\text{number of corpora lutea})$ to avoid putting negative selection on ovulation rate. Like the selection for ovulation rate described above, females produced two litters. Females and males in the second litters were selected based on data from the measurement in the first-litter females. After 11 generations of selection, $(\text{number of fetuses}) / (\text{number of corpora lutea})$ increased from .8 to .9, and there was a little response in ovulation rate. Consequently, the response in litter size was 2 pups.

Along with selection for increased litter size in our laboratory, we have also done replicated selection for a linear index (criterion IX) of $I = 1.21 * \text{ovulation rate} + 9.05 * \text{ova success}$ (proportion of ova shed resulting in fully formed pups) and for "uterine capacity" (criterion UT). Selection in UT was for number born to unilaterally (right excised) ovariectomized females, and the index in IX was the one that would maximize response in litter size using base population parameters (Clutter, et al. 1990, Gion et al., 1990, and Kirby and Nielsen, 1990). Response in litter size of intact animals with UT selection was .8 pups after 13 generations and 1.7 pups during the 6 generations of relaxed selection following the full 21 generations of selection. Realized heritability for uterine capacity as defined here was .08.

Selection under criterion IX yielded a response in litter size of 1.9 after 13 generations and 2.9 pups after 21 generations. The response increased to 3.2 pups during the period of relaxed selection. Realized heritability, broadly defined here as the regression on response in litter size on the cumulative selection differential (standard deviation of the index intended to be same as litter size) was .12 at Generation 13 but dropped to .10 over the 21 generations. Through 13 generations, IX selection produced more response than selection on litter size (LS) as was predicted from the index derived from the base-generation estimates of parameters. However through the next 8 generations, LS selection was much better, resulting in more total response by Generation 21 than the IX selection. We never changed the index, and with changing parameters, the effectiveness of the index became poorer than the natural index of number born.

SELECTION FOR TESTES MASS

High and low selection for testes mass measured at 11 weeks to hopefully change ovulation rate and hence litter size (Islam et al., 1976) and at 5 weeks as part of a larger project to study selection to change maturing rate (Hill et al., 1990) has been done in replicated lines at Edinburgh. Direct selection for testes mass at 11 weeks had a high realized heritability (.52) as did selection at 5 weeks (.44). Response after 5 generations in the experiment selecting for testes size at 11 weeks was 1.6 ova, but there was no corresponding change in litter size. The difference between the high and low in the experiment selecting at 5 weeks was 2.5 in first litter size with a similar difference in ovulation rate. It appears that either selection at a less mature age (5 versus 11 weeks) or for more generations, hence there is more correlated response in ovulation rate, is needed to show ultimate response in number born.

Adding further to the confusion are the correlated responses in testes mass observed after selection for litter size. Joakimsen and Baker (1977) reported significant positive correlated responses in males after sexual maturity (greater testes mass in the high litter selection and the opposite in the low selection). In comparison of our LS to LC selection (difference of about 4 pups), we found no difference in testes mass at 12 weeks of age (after mating).

SELECTION FOR MULTIPLE-PARITY LITTER SIZE

Selection for increased (L+) and decreased (L-) total number born in the first 3 parities (85 days of production) has been practiced and reported through 13 generations (Fuente and San Primitivo, 1985 and Bayon et al., 1988). Litters were standardized to 8 pups, and those from the first parity became the replacements if their dam was selected. After 8 generations, the response was 3.8 pups in L+ and -3.4 pups in L-, and the realized heritabilities were .28 for L+ and .21 for L-. Because the characteristic is the sum of three parities, we would expect, barring negative covariances, the heritability to be higher than for a single parity. Response in first-parity litter size was 1.9 in L+ and -2.7 pups in L-. During Generations 9-13, selection was much less effective, especially in L-, and the realized heritabilities through 13 generations were reduced to .18 in L+ and .06 in L-, and the responses for the selection criteria were 5.1 and -2.1 pups in L+ and L-, respectively.

RESPONSE IN LIFETIME REPRODUCTION FROM FIRST-PARITY SELECTION

In the high litter size and control lines after 25 generations of selection in the Wageningen work, Wallinga and Bakker (1978) compared 308-day litter production of females under interval (out before pupping and in after weaning) and continuous exposure to males. The high line was superior under interval exposure to males, but the control was better under continuous exposure to males. Performance in the high line dropped with each parity with continuous-exposure. Both the Wageningen and As high litter size lines have been studied in a report by Luxford et al. (1986); 10-week-old females were exposed continuously to males for 240 days. The mean litter size in the two selected lines was over 3 pups higher than the control, but the interval between successive litters was less in the control, and .6 more litters were produced on average in the control. Total number born in this management was not higher in the two selected lines.

LIMITS OBSERVED IN SELECTION FOR LITTER SIZE

Many experiments have hit plateaus in response near 30 generations of selection for larger litter size (Eisen, 1980 and Buis, 1988). Reasons given for cessation of response with selection for larger litter size have been: little additive variation left to apply selection, increased embryonic/fetal mortality due to a negative

genetic correlation with ovulation rate that has increased with selection, and magnified negative maternal effect expressed in large litters limiting body size and hence ovulation rate and litter size. Loss in fertility or in variance have not been factors. Pregnancy rates have dropped some, less than might be expected with the accumulated inbreeding, but they are offset by the selection for reproduction. Most experiments report rates of near 90%; our lines at Lincoln showed pregnancy rates of 93-95% through 21 generations. In our three selections, variation in number born has increased significantly over generations of selection.

In the long-term selection at Wageningen, including selection for smaller litters in the line already plateaued following high selection, Buis (1988) concluded that additive variation still remained because new selection in the opposite direction yielded significant response or there were segregating recessives affecting some component (embryonic mortality?). The latter, genetic variation present due to recessive alleles for lowering litter size at low but not extinguishable frequencies, seems to be a plausible explanation. This downward response in a line at a plateau following high selection was also seen in earlier work at Davis (Eklund and Bradford, 1977).

ELABORATION ON RESPONSES IN THE LINCOLN SELECTION

In addition to the responses in number born through our 21 generations of selection on alternative criteria (IX, UT, LS and LC) that were described above, we have also studied other characteristics during the relaxed selection phase. Differences created by selection have remained consistent during 14 generations of relaxed selection. In Generations 22 and 23, we recorded left- or right-side ovulation rate and uterine capacity in females from all lines that were unilaterally ovariectomized at 4 weeks and mated at 9 weeks and then measured at 17 days of gestation (Clutter et al., 1994). Ovulation rate increased 3, 2.8 and .9 ova in LS, IX and UT relative to LC. Uterine capacity, estimated from an exponential equation, increased 2.2, .9 and 1.6 fetuses on the left side and 2.5, 1.9 and 1.3 on the right side for LS, IX and UT compared to LC. Uterine capacity was highest on the right side compared to the left, and the largest response to selection usually occurred on the right side. Ova success in this unilateral model (defined as number of fetuses at 17 days divided by number of corpora lutea) was clearly higher on the right side as compared to the left side (.76 versus .70 in LC control), and the UT selection exceeded all other criteria in ova success on both sides (.75 versus .67-.71 on left, and .81 versus .76-.77 on right). We had seen a similar effect for intact animals in a Generation 13 evaluation (Gion et al., 1990).

Two experiments were done using Generation 27 animals from all lines, 6 generations after selection ceased. Pre-implantation (Day 3.5) embryonic development was investigated in a cooperative project at Stillwater (Al-Shorepy et al., 1992). Selection (IX, LS and UT) increased the average stage of embryonic development on the left side of the uterus and tended to do the same on the right side. There was an increase in the proportion of expanded blastocysts and a concomitant decrease in the proportion of two-cell embryos. The variation in stage of embryos was significantly less on the right side in the IX, LS and UT animals compared to the LC; this was most pronounced in the UT.

The second experiment, done with Generation 27 animals, measured uterine mass and uterine blood volume at either 3 or 6 days of gestation in females mated at 10 weeks of age. Uterine mass and uterine blood volume, whether expressed relative to body size or not, were significantly larger in the three selection groups than in the control. Females derived from IX and LS selection also had greater uterine mass and blood volume than those from UT selection.

Another study was done (Generation 34) to measure pup birth weight and its variation within litter. There were no differences between selection criteria in mean pup weight, even though there were 3.9 more pups per litter in LS compared to LC. The regression of mean pup weight on litter size was only -.027 g; thus, an increase of 4 pups (37%) from the level of LC would only result in a decrease in mean weight of .108 g (-7%). The variation within litter was less in UT compared to IX and LS, however UT was not different from LC. Thus differences in stage of development seen in the earlier experiment may affect number born but not variation of those pups reaching term.

POSSIBLE FUTURE DIRECTIONS FOR SELECTION RESEARCH

The ovulation rate--potentially viable embryo--uterine capacity model described and simulated for pigs by Bennett and Leymaster (1989) merits further study in mice beyond our UT selection, to provide support or detraction of that model, particularly in pigs. We have simulated a phenotypic model at Lincoln to mimic phenomena observed in our LS, IX, UT and LC selections. Ovulation rate must be split between left and right sides, and uterine capacity for both sides must also be modelled to account for the duplex uterus in mice versus pigs. Using our observed means and variances for ovulation rate and embryonic survival to implantation, plus parameters for uterine capacity means and variances derived through iteration, we have produced litter size records (left and right sides) that have the means, variances and correlations as observed in our selected groups (Generation 13 data). We next plan to integrate genetic and environmental effects and simulate the selection process using different criteria. Perhaps weighting selection for ovulation rate and/or uterine capacity, depending on the mean (and variance?), will be the new frontier in practicing selection to increase reproductive rate.

ACKNOWLEDGEMENTS

I am grateful for the contributions of many people, some contributing data for this paper that are not yet published, to the on-going program at Lincoln to better understand genetic variation in reproductive rate in mice. These people are: A. Clutter, J. Gion, J. Hauptman, Y. Kochera Kirby, E. Ribeiro, M. van Engelen, B. Freking, R. Johnson, K. Leymaster, L. Young, G. Bennett and G. Dickerson.

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