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Selection for increased length of reproductive life in mice

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Summary. An experiment was conducted in mice to examine whether selection can increase reproductive life and lifetime production of progeny. Mice in two lines with litter size standardized at birth and in two lines without standardization were pair-mated at 7 weeks of age and maintained as long as they produced litters up to 382 days. Progeny from the sixth litters were used to maintain the four selected lines, while progeny from the first litters were bred to maintain unselected control lines. Selected and control lines were compared at five and six generations of the selected lines. Contemporary comparisons revealed that the length of reproductive life and most lifetime production traits were significantly greater in the selected than in control lines. Realized heritability of the length of reproductive life ranged from 0.08 to 0.13. It was concluded that the length of reproductive life and lifetime production in mice can be increased by selection.

Key words: Mice – Lifetime – Performance – Longevity – Selection

Introduction

The length of reproductive life in domestic and laboratory animals (e.g., cattle and mice) is usually considered a fitness trait. Reproductive fitness is among the most difficult traits to study and is the least understood area of quantitative genetics and animal breeding, yet reproductive fitness traits are among the most important in animal production (Frankham 1982).

The length of reproductive life was measured in female mice that were pair-mated at early adult age and maintained as long as they produced litters (Nagai et al. 1986). Heritability of the length of reproductive life, estimated from bivariate full-sib mixed model analysis, was 0.01 and 0.05 from the sire and dam component, respectively, while the heritability estimated from the analysis based on a sire-dam hierarchial structure was 0.24 and 0.26 (Nagai et al. 1988). It has been suggested that low heritability could be due to variation in heritability among different periods of reproductive life. Non-linear heritability of reproductive fitness was discussed by Frankham et al. (1988), who were able to prevent a decline in reproductive fitness by culling on low fitness in *D. melanogaster*. Their experiments were motivated by Gowe's prediction (1983) that heritabilities of reproductive fitness traits were non-linear, being close to zero in the upper 80%–90% of the range, and moderate in the lower 10%–20% of the range in egg-laying chickens.

In relation to the length of reproductive life, lifetime production of progeny in mice has been studied (Nagai and Lee 1981; Nagai and McAllister 1985). Further analyses of the accumulated data revealed that progeny from parents who reproduced for a long time had a tendency for prolonged production of their litters (J. Nagai, unpublished results), and that lines of mice differed in their survival, particularly at the last stage of reproductive life (Nagai et al. 1980). Lints (1981) concluded in his review that lifespan of mice is heritable. Heterosis was important in lifetime reproduction traits of mice (Newman et al. 1987a, b). Liljedahl et al. (1984) obtained evidence indicating that new genetic variation in egg production traits appeared parallel to an increase in the environmental variation with age of chickens.

It was hypothesized that the magnitude of heritability of length of reproductive life is adequate for selection to

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be successful in mice. As a result, measures of lifetime production, such as number of offspring produced by a female, will be increased (Nagai and Lee 1981; Nagai and Yokoyama 1985). Evidence to support this hypothesis would be of value for practical applications in economic animal species. The objectives of the present study were to examine the response to selection for increased length of reproductive life and to estimate its realized heritability.

Materials and methods

Mice

Two lines of mice selected for increased postnatal maternal performance and two lines of mice selected for increased adult weight (Nagai et al. 1978) were used to synthesize a population for the present study. The synthetic population was maintained under random mating without selection for 12 generations. At generation 13, mice at 7 weeks of age were mated at random at a ratio of 1 male to 4 females (80 males and 320 females in total) to produce first litters. Litter size was reduced at birth to eight, four females and four males, wherever possible. The progeny were used to set up four lines to be selected for longer reproductive life (SA1, SA2, SN1, and SN2) and four unselected control lines (UA1, UA2, UN1, and UN2), where S and U indicate selected and unselected lines, A and N indicate lines with and without control (adjustment) of litter size, and 1 and 2 indicate line replication. In the A lines, litter size was standardized to eight at birth. It was expected that adjustment of litter size would affect length of reproductive life and lifetime production through maternal effects, including the effect of litter size on growth. Each selected line (S) contained 100 females and 100 males as breeders, and each unselected line (U) contained 150 females and 150 males. At 7 weeks of age, pair-matings were conducted at random to produce offspring (generation 0).

In selected lines, cohabited pairs were maintained in the same cage continuously as long as they produced litters, up to 333 days after cohabitation at 7 weeks of age. Paris that did not produce a litter for 50 days after a previous parturition or the initial mating were discarded. Progeny born to a pair were discarded at 18 days of age, inclusive up to the fifth parity. At the sixth parity, progeny from about 33 pairs that were still producing were retained for breeding in the next generation. Basically, three progeny in each litter/sex subclass were pair-mated randomly at 7 weeks of age. Full-sib matings were avoided. The procedure was repeated every generation.

In the unselected lines, progeny in the first litter were used as breeders for line maintenance. One female and one male of each litter were selected at random and pair-mated randomly at 7 weeks of age, avoiding full-sib mating. During the period of 6 generations in the selected lines, unselected lines had approxiamtely 18 generations. Expected increase in inbreeding coefficient at generations 6 and 18 in the selected and unselected lines were 0.76% and 1.25%, respectively. It was assumed that the low inbreeding would not affect the results comparing the selected and unselected lines.

Throughout the experiment a commercial pellet feed (Lab Chows, Ralston Purina) and tap water were supplied ad libitum. Mice were maintained in a specific-pathogen-free building where temperature and humidity ranged from 20° to 24 °C and from 40% to 55%, respectively.

Measurements

The following records were taken individually: length of reproductive life as measured by days from mating (at 7 weeks of age) to the last parturition, number of parturitions during female's lifetime, total number of young born alive and weaned (at 18 days) by a female during lifetime, and total body weight of young born alive and weaned by a female. Total number of young weaned at 18 days (LS18) and total weight of young weaned at 18 days (LW18) were each divided by days of reproductive life (D) to obtain measurements showing production efficiency of a female.

Comparisons between the selected and control lines

The length of reproductive life and lifetime production were compared between the selected and control lines twice: at generation 5 (test 1) and generation 6 (test 2) of the selected lines. For the comparisons, one-half of the control lines (UA1 and UN1) was used at generation 5 of the selected lines, while the remaining half of the control lines (UA2 and UN2) was used at generation 6 of the selected lines. Breeders of both selected and control lines were maintained as long as they produced litters, up to 333 days after cohabitation at 7 weeks of age.

Results

Least-squares means of lifetime performance in the selected and control lines are shown in Table 1. The SA1 and SA2 lines, and SN1 and SN2 lines were combined, since the preliminary analyses of variance revealed that the two replicate lines in each selection treatment did not differ significantly for any traits examined. Days of reproductive life and other traits differed between the selected and control lines at both tests 1 and 2 (Table 2). Differences between the selected lines with adjustment of litter size and those without adjustment (SA and SN lines) were not significant for days of reproductive life (D), number of parturitions, litter weight at 18 days (LW18), and LW18/D in the two tests. Within the A (litter size adjusted) and N (litter size not adjusted) group, differences between the selected and control lines were significant in all traits, except LS18/D and LW18/D. Thus, selection for increased length of reproductive life was effective in increasing reproductive life and lifetime production. Incidentally, reproductive life in most mice stopped by the imposed rule (no parturition for 50 days), not by death, in both selected and control lines (tests 1 and 2).

The selection differential weighted by the number of progeny contributed to the next generation was calculated for each generation in the four selected lines. Figure 1 shows the changes in days of reproductive life against selection differentials accumulated over generations. Although days of reproductive life fluctuated over generations, they showed a tendency to increase. Realized heritabilities estimated from regression of the length of reproductive life on accumulated selection differential in the four selected lines are shown in Table 3. The real-

Table 1. Least-squares means of lifetime performance traits in selected lines at generations 5 and 6 and their control lines

Test[a]	Trait	Litter size adjusted		Litter size not adjusted	
		Selected	Control	Selected	Control
1	Days of reproductive life (D)	202.5 ± 6.5	132.5 ± 7.7	202.1 ± 6.2	174.2 ± 7.6
	No. of parturitions during lifetime	8.11 ± 0.26	4.96 ± 0.30	7.91 ± 0.25	6.62 ± 0.30
	Litter size at birth[b]	75.9 ± 2.5	48.5 ± 2.9	72.6 ± 2.4	62.8 ± 2.9
	Litter wt. (g) at birth[b]	103.2 ± 3.9	65.8 ± 4.6	127.1 ± 3.8	109.2 ± 4.6
	Litter size at 18 days (LS18)[b]	54.0 ± 2.1	34.2 ± 2.5	68.0 ± 2.0	57.9 ± 2.4
	Litter wt. (g) at 18 days (LW18)[b]	691.1 ±23.3	474.9 ±27.6	719.9 ±22.3	624.2 ±27.2
	No. of weaned young per day (LS18/D)	0.27 ± 0.01	0.27 ± 0.01	0.34 ± 0.01	0.35 ± 0.01
	Wt. of weaned young per day (LW18/D)	3.47 ± 0.07	3.70 ± 0.08	3.65 ± 0.07	3.83 ± 0.08
	No. of pairs (line)	177 (SA1 and SA2 combined)	127 (UA1)	193 (SN1 and SN2 combined)	130 (UN1)
2	Days of reproductive life (D)	200.4 ± 6.6	155.7 ± 7.8	191.5 ± 6.5	168.5 ± 7.9
	No. of parturitions during lifetime	8.01 ± 0.26	6.03 ± 0.31	7.58 ± 0.25	6.27 ± 0.31
	Litter size at birth[b]	77.6 ± 2.6	58.5 ± 3.0	68.4 ± 2.5	56.5 ± 3.1
	Litter wt. (g) at birth[b]	103.1 ± 3.9	77.1 ± 4.6	120.0 ± 3.9	102.8 ± 4.8
	Litter size at 18 days (LS18)[b]	53.5 ± 2.1	40.0 ± 2.5	62.2 ± 2.1	51.0 ± 2.5
	Litter wt. (g) at 18 days (LW18)[b]	696.6 ±24.1	526.5 ±28.5	673.3 ±23.8	560.7 ±29.2
	No. of weaned young per day (LS18/D)	0.27 ± 0.01	0.26 ± 0.01	0.33 ± 0.01	0.30 ± 0.01
	Wt. of weaned young per day (LW18/D)	3.57 ± 0.08	3.45 ± 0.01	3.61 ± 0.08	3.31 ± 0.10
	No. of pairs (line)	184 (SA1 and SA2 combined)	132 (UA2)	190 (SN1 and SN2 combined)	126 (UN2)

[a] Tests 1 and 2 were conducted at generations 5 and 6 of the selected lines, respectively

[b] Summed over litters produced by a female during lifetime

Table 2. The level of significance for linear contrasts

Trait	Test 1[a]			Test 2		
	SA vs. SN[b]	SA vs. UA1	SN vs. UN1	SA vs. SN	SA vs. UA2	SN vs. UN2
Days of reproductive life (D)	n. s.	**	**	n. s.	**	*
No. of parturitions during lifetime	n. s.	**	**	n. s.	**	*
Litter size at birth[c]	n. s.	**	**	*	**	*
Litter wt. (g) at birth[c]	**	**	**	**	**	**
Litter size at 18 days (LS18)[c]	**	**	**	**	**	**
Litter wt. (g) at 18 days (LW18)[c]	n. s.	**	**	n. s.	**	**
No. of weaned young per day (LS18/D)	**	n. s.	n. s.	**	n. s.	**
Wt. of weaned young per day (LW18/D)	n. s.	*	n. s.	n. s.	n. s.	*

[a] Tests 1 and 2 were conducted at generations 5 and 6 of the selected lines, respectively. SA represents SA1 and SA2 combined, and SN represents SN1 and SN2 combined

[b] Line codes: S – selected, U – unselected control, A – litter size was adjusted, N – litter size was not adjusted

[c] Summed over litters produced by a female during lifetime

* Significant $P < 0.05$; ** Significant $P < 0.01$

Table 3. Realized heritabilities (h^2) of the length of reproductive life

Line	Realized $h^2 \pm$ S. E.	R^2
SA1	0.13 ± 0.03 *	0.74
SA2	0.12 ± 0.04 *	0.65
SN1	0.08 ± 0.04	0.44
SN2	0.11 ± 0.04	0.56
Combined	0.11 ± 0.04 *	0.61

* Significant $P < 0.05$

ized heritabilities in the lines with litter size adjusted at birth were significant ($P < 0.05$), while those in the lines without adjustment of litter size were not significant. Adjustment of litter size at birth did not affect days of reproductive life (Table 2). The realized heritability for all lines combined was estimated as 0.11 ± 0.05 ($P < 0.05$) with the R-square value of 0.61 (Table 3). When data at generation 3 were omitted, the realized heritability was virtually the same, with 0.10 ± 0.03 ($P < 0.05$) for all lines combined.

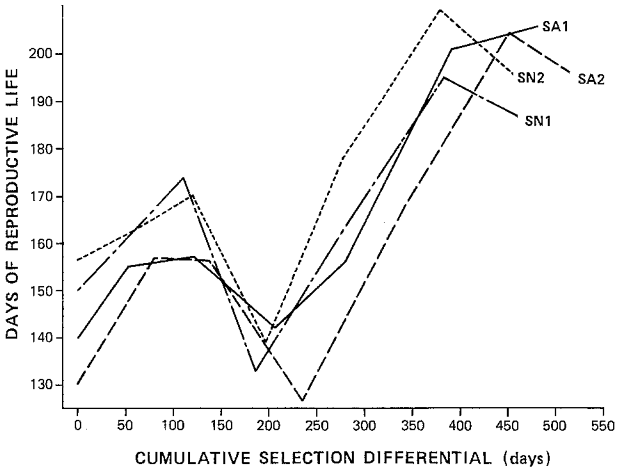

Fig. 1. Response to selection for increased days of reproductive life in four lines of mice

Discussion

In the present study, reproductive life was examined up to 382 days of age, when most mice (more than 94%) have finished their reproduction. Thus, the mean length of reproductive life presented in this study reflects the mean reproductive life under the condition where all mice are kept until they terminate their reproduction. We consider that the effect of truncation on heritability estimates is practically negligible. Incidentally, reproductive life defined in the present mouse study differs from "herd life" in dairy cattle (Gill and Allaire 1976; McAllister et al. 1987), where culling is made partly on a managemental basis (e.g., barn space).

The length of reproductive life is a difficult trait to analyze. Firstly, measurements on the reproductive life can be obtained only through mating procedures. Under pair-matings where a female was cohabited permanently with a male as long as they reproduced, such as in this study, lengths of reproductive life of a male and female in a pair are mutually dependent. A model was proposed where male's effect was considered as "environmental" to a female (Nagai et al. 1984). Although the male's contribution to heterosis in lifetime performance was evaluated using the model (Nagai et al. 1984), it is still true that the effect of the male on a female's reproductive life per se cannot be adequately evaluated under the pair-mating system. Secondly, under the pair-mating system the length of reproductive life for a female or male is identical to that for its mate. Therefore, the midparent value is the same as the uniparent value, and the heritability estimated from regression of offspring on parent(s) is uninterpretable.

Although the mice were maintained in a specific-pathogen-free building throughout the experiment, lengths of reproductive life in all four selected lines decreased at generation 3 (about 200 days of cumulative selection differential in Fig. 1). The observed decrease in reproductive life may have been due to immuno-deficiency associated with aging (Weksler et al. 1982). Although unselected control lines were maintained, they could not be used to measure environmental changes such as age-associated sub-clinical infection because the control lines, by design, must be maintained in such a way that mice do not reproduce for a long time, e.g., for a period of producing five litters as in the selected lines.

Although responses to selection for increased length of reproductive life fluctuated over generations, regressions of the response on accumulated selection differentials were, in general, positive ranging from 0.08 to 0.13 (Table 3 and Fig. 1). Contemporaneous comparisons between the selected and control lines at the fifth and sixth generations of selected lines revealed that selected lines expressed longer length of reproductive life than control lines. It was concluded that selection was effective in increasing reproductive lifespan and that the additive genetic variation in reproductive life existed. As mentioned above, the exact size of genetic variation in females is difficult to estimate. Nevertheless, it is clear that the size of the genetic variation was adequate to allow selection for increased reproductive life. To the authors' knowledge, this paper is the first report that increased reproductive lifespan could be obtained from selection of mice. It is surmised that the selected mice did not have any deleterious genes affecting survival.

What physiological differences may exist between selected and control lines of mice? Several mechanisms may be involved, including rate of oxygen consumption (Sacher and Duffy 1979), feed intake, and nutritional metabolism (Weindruch and Walford 1982), and the major histocompatibility complex, H-2, has been shown to influence lifespan in mice (Yunis et al. 1984; Smith and Walford 1977). Of course, hormone systems capable of functioning in mice of advanced age are associated with the long reproductive life.

Since measurements on ancestors' reproductive life were available, selection index procedures were examined theoretically at the outset of the present study (Nagai et al. 1986). The results showed that the selection index would not increase the accuracy of selection substantially. For this reason, selection index was not used in the selection experiment. In retrospect, we feel that although the selection method applied was effective, index selection would have been helpful in selecting the 33 pairs used to reproduce the selected lines. Increased accuracy of selection resulting from the use of selection index needs to be evaluated using estimates of genetic parameters, taking into account possible non-linearity of heritability over periods of reproduction life. It is noteworthy that the realized heritability of reproductive life (0.08–

0.13, Table 3) was estimated from data of mice which produced five litters and were maintained up to 382 days of age.

When production of an animal is evaluated over a long period of time, rather than at a single point of time, the true worth of the animal can be evaluated for breeding and economic values. For this reason, lifetime production in farm animals has been of concern to animal geneticists. Lifetime performance was evaluated for weaning traits (Gaines et al. 1985), economy of heterosis (Nunez et al. 1985), and reproductive efficiency (Weise et al. 1985) in cows, and for the mating system (Baker et al. 1978) and range conditions (Ercanbrack and Knight 1985) in sheep. Although "lifetime" in domestic animals means usually "herd life" under limited herd conditions (Gill and Allaire 1976; McAllister et al. 1987) and differs from lifetime as defined in the present study, the basic concept of evaluating animals for long-term performance is the same. Results from studies of reproductive life in mice (Newman et al. 1985a, b, c, d) have implications for farm animals. Particularly, results from selection for reproductive life are of value to farm animals, because experiments selecting for reproductive life are practically impossible in farm animals.

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