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J. M. McDonald

University of Nebraska - Lincoln

Merlyn K. Nielsen

University of Nebraska - Lincoln, mnien1@unl.edu

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Renewed selection for heat loss in mice: Direct responses and correlated responses in feed intake, body weight, litter size, and conception rate¹

J. M. McDonald and M. K. Nielsen²

Department of Animal Science, University of Nebraska, Lincoln 68583-0908

ABSTRACT: Divergent selection in mice was renewed in 3 independent replicates for high (MH) and low (ML) heat loss. An unselected control (MC) was maintained in all replicates. Heat loss was measured for individual male mice for 15 h, overnight in direct calorimeters. After 16 initial generations of selection followed by 26 generations of relaxed selection, divergent selection resumed for 9 generations. The realized selection applied was very close to the maximum possible selection according to the criteria and protocol. Selection differentials were greater for high than for low selection due to greater variation in the MH line. When corrected for SD, standardized selection differentials were similar for MH and ML selection. Unintended selection in MC was negligible. Realized heritability for divergence was 0.14 ± 0.01 , which was considerably

less than that realized during the initial generations of selection (0.28 ± 0.03). Realized heritabilities for MH selection (0.16 ± 0.05) and for ML selection (0.07 ± 0.06) were less, especially for ML selection, than were observed in the earlier generations. The difference in heat loss between MH and ML males was 55.7% of the MC mean at generation 51, compared with a difference of 53.6% in generation 15; this difference had decreased to 34.4% at the end of the relaxed selection (generation 42). For feed intake between 8 and 11 wk, MH and ML males differed by 34.0% of the MC mean by the end of the selection process. Body weight at 12 wk for MH and ML males was less than for MC males. Litter size response was positively related to the heat loss response. Conception rate was poorer in MH matings than in MC and ML matings.

Key words: conception rate, feed intake, heat loss, litter size, mice, renewed selection

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INTRODUCTION

Maintenance feed energy requirements of animals represent large economic inputs in livestock production, and they are more variable than the costs above maintenance for feed per unit of production (i.e., milk production, growth, etc.). As animals metabolize food, energy that is not stored in a product is lost in the form of heat. Nielsen et al. (1997a,b) showed that it is possible to change maintenance requirements in mice through selection using total heat loss as the indicator trait. Existence of variation in heat loss made it possible to select animals based on their heat production/loss as a method to produce more efficient animals. Mousel et al. (2001) demonstrated a large correlated response in

locomotor activity, and Eggert and Nielsen (2006) reported no differences in partial efficiencies for growth due to selection. McDonald and Nielsen (2006) reported a correlated response in lactation yield resulting from a positive genetic correlation with the maintenance requirement.

Nielsen et al. (1997a,b) showed that the initial selection practiced for heat loss in mice was effective through 15 generations in the high (MH) and low (ML) directions. Selection for heat loss produced a divergence between the MH and ML lines (MH – ML) of 20.6% relative to the control (MC) mean for maintenance feed costs, with the ML lines consuming the least. After the initial 16 generations, selection was suspended, and the effective population size was expanded in all lines to reduce the rate of inbreeding. At generation 42, heat measurements and selection were resumed following the initial protocol for the MH, ML, and MC lines.

The objective of this study was to report the direct response to renewed selection for heat loss in male mice from generations 42 through 51, as well as the correlated responses in feed intake, male BW, litter size, and conception rate.

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²Corresponding author: mnielsen1@unl.edu

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MATERIALS AND METHODS

Experimental Animals

All procedures involving animals were approved by the University of Nebraska–Lincoln Institutional Animal Care and Use Committee. The lines of mice used for this study have been previously described by Nielsen et al. (1997a) and represent the outcomes after divergent selection for heat loss. All lines were originally derived from a base population resulting from a 4-way cross of 4 outbred lines. There were 3 criteria for selection: MH = selection for high heat loss, ML = selection for low heat loss, and MC = no selection. Breeders for each new generation were chosen from the previous generation's 16 litters in a line-replicate.

After the initial selection for 16 generations, selection was suspended, and the lines were maintained through generation 41 using breeders that equally represented 26 litters per line-replicate-generation to reduce the rate of inbreeding. The experiment was carried out in 3 replicates, each separated by a 5-wk interval. Three lines with 3 replicates yielded 9 unique selection lines with a generation interval of 15 wk. For this study, selection began again within the heat loss lines; thus, line sizes of only 16 litters began again at generation 42 and continued through generation 50, with the final response measured in generation 51. Mean inbreeding coefficients were similar across lines and replicates and averaged approximately 0.16, 0.28, and 0.36 at generations 16, 42, and 51, respectively.

Heat Loss and Feed Intake Measurements

Ten direct, gradient-layer, individual-animal calorimeters (Model 0601-S, gradient-layer Seebeck envelope, Thermo-netics Corporation, San Diego, CA) were used to obtain single heat loss measurements ($\text{kcal} \cdot \text{kg}^{-0.75} \cdot \text{d}^{-1}$) from only male animals. Animals ranged from 9 to 11.5 wk of age at the time of measurement. The design of the direct, gradient-layer calorimeters and the setup of the data-acquisition system were described in Nielsen et al. (1997a).

Individual mice were weighed and placed in stainless steel cages with approximately 3.5 g of feed. Each cage was placed in 1 of the 10 calorimeters, and the lids were used to seal the units. Mice are nocturnal animals; therefore, data were collected overnight for 15 h. Within each replicate, heat loss measurements occurred over a 3-wk period. During this period, all of the males from the MH and ML lines were measured (between 75 and 80 in each line-replicate), as were 25 to 35 males from the MC line.

During this same time period, feed intake was collected on male littermate cages, and the mice were housed in plastic cages (Ancare Corp., Waupaca, WI). Feed intake measurements began at 8 wk of age and were calculated as the amount of feed that disappeared over a period of 1 wk, divided by the number of animals

in the cage. Feed intake measurements continued through 11 wk of age. Final feed intake data were totaled for the 3-wk period and expressed as daily grams of feed per unit of metabolic BW ($\text{kg}^{0.75}$). Throughout the feed intake trial, mice were given ad libitum access to water and were fed a maintenance diet (Teklad 8604: 24% CP, 4% crude fat, 4.5% crude fiber, and 3.93 kcal of GE/g of feed, Harlan Teklad, Madison, WI). Individual BW were recorded on the first and last days of the 3-wk trial and then averaged over all mice in that line-replicate.

Selection of Breeder Males and Matings

Once individual heat loss and cage feed intake measurements were taken, the heat loss data were sorted, and males were selected to become breeders at 12 wk of age. In the MH lines, the 16 males with the greatest heat loss were chosen to produce the next generation. The opposite was true for the ML line. Matings were designed to place 1 male with 2 full-sibling females that had the lowest available relationship with that male to avoid excessive inbreeding within the lines. Males were selected based on their own individual heat loss estimate; thus, some MH and ML litters produced multiple males that were selected for breeding, whereas some litters produced none. Two extra males ranking #17 and #18 on the heat loss criterion in the MH and ML lines were also chosen and mated to 2 females. These males provided extra litters for the MH and ML lines in case one or more of the top 16 males failed to produce litters for the next generation.

In the MC line, 16 males (1 randomly chosen from each of the 16 litters) were mated to 2 females each, again using a pair of full sisters. A combination of 2, circular mating designs was used that showed accumulation of inbreeding similar to that of the MH and ML lines. A spare (17th) male was also mated to 2 females in the event that 1 of the 16 MC males failed to produce a litter. The animals remained in the mating cages for 16 d and were given ad libitum access to feed (Teklad diet 8604) and water.

Cumulative selection differentials (**CSD**) for MH, MC, and ML for generations 43 through 51 were calculated as:

$$\text{CSD}_n = 0.5 M_{n-1} + 0.25 \sum_{i=42}^{n-2} (M_i + F_i),$$

n-2
for
n≥44

where *n* is the number of generations of selection completed, and **M** and **F** are male and female selection differentials. Male selection differentials are calculated as the sum of the deviations of selected male records from the generation-replicate-line mean ($P_i - \mu$), weighted by the number of sons that had records, and divided by the number of males measured in the sons' generation (*N*):

$$M = \sum_{i=1}^{16} (P_i - \mu)(\text{number of sons})/(N).$$

“Female” selection differentials were calculated in the same manner as the male differentials, except that deviations from the generation-replicate-line mean were weighted by the number of grandsons (with records) through daughters rather than the number of sons. Here, N represented the number of males measured in the grandsons’ generation:

$$F = \sum_{i=1}^{16} (P_i - \mu)(\text{number of grandsons})/(N).$$

Littering and Selection of New Litters

After the 16-d mating period, females were transferred to individual littering cages. Dams were given a handful of Tek-Fresh nesting material (Harlan Teklad) to build littering nests, ad libitum access to a lactation diet throughout the littering and lactation period (Teklad 8626: 20% CP, 10% crude fat, 2% crude fiber, and 4.25 kcal of GE/g, Harlan Teklad), and ad libitum access to water. Within 24 h of birth, the date, number of pups of each sex, and total number of fully formed pups (alive or dead) were recorded. With a 100% conception rate, we expected 36 litters in each of the MH and ML lines, and 34 litters in the MC line. If litters were larger than 8 live pups at birth, they were standardized to 8 total pups with a desired sex ratio of 5 males and 3 females.

Litters were selected based on the sex ratio and birth date and identified according to the rank of the sire. The sex ratio of 5 males and 3 females was not always obtained; therefore, litters with less-desirable sex ratios were used. Sixteen litters were chosen to contribute males for calorimeter measurements in the next generation, and litters whose sires ranked #17 and #18 were selected as spares. When the pups reached 10 d of age, their toes were clipped for identification and the dam and litter were placed in clean cages. Litter size was measured as the total number of live and dead fully formed pups at birth. Conception rate was the fraction of females exposed to breeding that had litters.

Weaning

In all replicates, mice were weaned at 21 d of age. At this time, males and females were placed in separate cages by full-sib family. Generally, no more than 5 mice were placed in each cage. Males and females were given ad libitum access to a maintenance diet (Teklad 8604) and water.

Statistical Analysis

Realized cumulative selection differentials for MH and ML, and divergence of the response (difference in means, MH – ML) for heat loss were regressed on gener-

ation number within each replicate. Divergence of the response (MH – ML) was regressed on the difference of the realized cumulative selection differential (MH – ML) to obtain heritability estimates for each replicate. Responses in the upward and downward directions (MH – MC and ML – MC, respectively) were regressed on differences in cumulative selection differentials (MH – MC and ML – MC, respectively) within each replicate. For all regressions, estimates were averaged across all 3 replicates, and empirical SE were calculated for the mean regressions and tested with 2 degrees of freedom.

Male feed intake calculation yielded average grams consumed per unit of metabolic weight per day ($\text{g} \cdot \text{kg}^{-0.75} \cdot \text{d}^{-1}$) in each line-replicate from 8 to 11 wk of age. Divergence of the response (MH – ML), as well as the responses in the high and low direction (MH – MC and ML – MC, respectively) for feed intake adjusted for mean metabolic weight were regressed on generation number for each replicate. Regression estimates were averaged across replicates, and empirical SE were calculated.

Litter size means and conception rates were fitted to the model

$$Y_{ijkl} = \text{rep}_i + \text{line}_j + \text{generation}_k + (\text{rep} \times \text{line})_{ij} \\ + (\text{rep} \times \text{generation})_{ik} + (\text{line} \times \text{generation})_{jk} \\ + (\text{rep} \times \text{line} \times \text{generation})_{ijk} + e_{ijkl},$$

where Y_{ijkl} is the mean litter size or the conception rate, rep_i specifies the random effect of the replicate (replicate 1, 2, or 3), line_j is the fixed effect of the line (MH, ML, or MC), generation_k is the fixed effect of the generation (generation 42 through 51); the remaining terms are the interaction effects and residual error to complete the model. Contrasts of MH vs. ML and (MH + ML)/2 vs. MC were carried out to test the effect of selection and asymmetry of the response.

RESULTS AND DISCUSSION

Selection Applied

Cumulative intended, realized, and standardized realized selection differentials after 9 generations of resumed selection for high and low heat loss are given in Table 1. Realized cumulative selection differentials were similar to intended cumulative selection differentials. The proportion of cumulative selection achieved ranged from 99 to 102% in MH and ML replicated lines, and averaged 100% across all selection lines. This shows that the top 16 ranking males from each generation-replicate-line were generally successful at producing sons and grandsons to be measured for heat loss in subsequent generations. Although the mean observed here is slightly greater than the average of 98% selection achieved reported for the first 15 generations of these lines, Nielsen et al. (1997a) observed a similar range of 97.3 to 100% selection achieved.

Table 1. Cumulative intended and realized (both as kcal·kg^{-0.75}·d⁻¹) and standard realized selection differentials, and the averages across all 3 replicates (Rep)

Line ¹ and replicate	Cumulative intended	Cumulative realized	Cumulative standard realized
MH Rep 1	93.36	92.51	5.35
MH Rep 2	83.71	85.78	5.79
MH Rep 3	97.12	97.04	5.24
MH mean	91.40	91.78	5.46
MC Rep 1	0.00	-1.43	-0.10
MC Rep 2	0.00	-3.42	-0.23
MC Rep 3	0.00	-1.37	-0.02
MC mean	0.00	-2.07	-0.12
ML Rep 1	-54.61	-54.84	-4.89
ML Rep 2	-53.05	-54.28	-5.30
ML Rep 3	-54.45	-54.61	-4.92
ML mean	-54.04	-54.75	-5.04

¹MH = High heat loss selection; MC = no intentional selection; and ML = low heat loss selection.

Realized cumulative selection differentials ranged from 83.71 to 97.12 kcal·kg^{-0.75}·d⁻¹ in the MH lines and averaged 91.40. The ML cumulative selection differentials ranged from -54.61 to -53.05 kcal·kg^{-0.75}·d⁻¹ and averaged -54.04. Realized cumulative selection differentials, adjusted by generation-line-replicate SD, ranged from 5.24 to 5.79 in the MH lines and averaged 5.46. A range of -5.30 to -4.89 was observed in the ML lines, and ML had an overall average of -5.04. Because variation was much greater in the MH than in the ML lines, standardized selection differentials were more similar comparing MH to ML selection than were the unstandardized selection differentials. Realized cumulative differentials were calculated for the MC to determine if selection had unintentionally occurred in these lines. Realized cumulative differentials ranged from -3.42 to -1.37 kcal·kg^{-0.75}·d⁻¹ and averaged -2.07, whereas standardized realized differentials ranged from -0.23 to -0.02 and averaged -0.12 in the MC lines. Thus, unintended selection was negligible.

Normality of the heat loss distribution was tested in the MH and ML lines by analyzing residuals from the replicate-generation means of each line with a Shapiro-Wilk test (Shapiro and Wilk, 1965). In the MH line, normality was rejected ($P = 0.01$); skewness and kurtosis coefficients were -0.2197 and 1.3774, respectively. This demonstrated that the distribution of MH heat loss measurements was slightly skewed to the right and was much taller than a normal distribution. In the ML line, normality was also rejected ($P < 0.01$); skewness and kurtosis coefficients were 0.0853 and 1.0845, respectively. The distribution of heat loss measurements in the ML line was clearly skewed to the left and was also taller than a normal distribution. Distributions with these shapes explain why the standardized selection differentials were greater for the MH selection than the ML selection, even though similar

numbers of animals were measured and selected in both lines.

Regressions of realized cumulative selection differentials and realized standardized cumulative selection differentials on generation number are presented in Table 2. Regressions on generation number ranged from 10.57 to 12.22 in the MH and -6.92 to -6.59 in the ML. Averaged across all 3 replicates, the regressions were 11.48 ± 0.49 and -6.74 ± 0.10 in the MH and ML, respectively. The cumulative selection differentials for MH selection were approximately 70% greater than the cumulative selection differentials for ML selection. However, cumulative selection differentials for MH selection realized by Nielsen et al. (1997a) were only 40% greater than the differentials for ML selection.

Regressions of realized standardized cumulative selection differentials on generation number ranged from 0.65 to 0.69 for MH and from -0.66 to -0.61 for ML. This range is identical to the range of 0.65 to 0.69 for MH and very similar to -0.65 to -0.63 for ML, as observed by Nielsen et al. (1997a) for the first 15 generations of selection for heat loss in these lines.

Response in Heat Loss over 9 Generations

A graphical representation of mean heat loss (kcal·kg^{-0.75}·d⁻¹) estimates for the MH, ML, and MC lines for each generation of initial and renewed selection (generations 0 to 15 and 42 to 51) averaged across all 3 replicates is shown in Figure 1. Heat loss means for 9 generations of renewed selection are listed in Table 3 and ranged from 151.6 to 159.8, 130.0 to 133.7, and 109.7 to 111.9 for MH, MC, and ML, respectively, in generation 42. In generation 51, heat loss means ranged from 159.7 to 172.9, 123.1 to 130.1, and 93.6 to 97.3 for MH, MC, and ML, respectively. When selection was resumed at generation 42, the difference in heat loss (kcal·kg^{-0.75}·d⁻¹) between the MH and ML lines averaged 34.4% as a percentage of the MC mean. By generation 51, this difference averaged 55.7%. After the original 15 generations of selection, divergence was 53.6%, as a percentage of the MC, between the MH and ML lines.

During the 26 generations of relaxed selection, response achieved in the ML during the initial 16 generations of selection was maintained; the ML and MC means for heat loss were essentially the same when selection was renewed as when selection had ceased. However, response achieved in MH selection was partially lost during the 26 generations of relaxed selection. About 40% of the response that had been achieved in the up direction was lost, presumably due to natural selection, to unintended selection for some other characteristic, or from breakup of linkages (recombination losses) that had been enhanced or built up during the initial selection phase. The latter possibilities seem less likely because we expanded line size during the relaxed phase so that inbreeding accumulated at less than 0.5% per generation and because we did not see a similar loss of response in the low direction. The MH mice react

Table 2. Regressions of line cumulative selection differential (CSD) and standardized CSD on generation number (gen), divergence of the response ($\text{kcal}\cdot\text{kg}^{-0.75}\cdot\text{d}^{-1}$) on generation number

Regression ¹	Replicate 1	Replicate 2	Replicate 3	Mean across replicates
MH CSD on gen	11.66	10.57	12.22	11.48 ± 0.49
ML CSD on gen	-6.72	-6.59	-6.92	-6.74 ± 0.10
MH standard CSD on gen	0.67	0.69	0.65	0.67 ± 0.01
ML standard CSD on gen	-0.61	-0.66	-0.62	-0.63 ± 0.02
MH – ML on gen	2.12	2.27	3.07	2.49 ± 0.30
MH – ML on CSD	0.11	0.13	0.16	0.14 ± 0.01
MH – MC on CSD	0.07	0.14	0.25	0.16 ± 0.05
ML – MC on CSD	0.18	0.05	-0.02	0.07 ± 0.06

¹MH CSD on gen = regression of high heat loss CSD on generation number; ML CSD on gen = regression of low heat loss CSD on generation number; MH standard on gen = regression of MH standardized CSD on generation number; ML standard on gen = regression of ML standardized CSD on generation number; MH – ML on gen = regression of divergence of selection response on generation number; MH – ML on CSD = regression of divergence of selection response on divergence of CSD; MH – MC on CSD = regression of selection response in the upward direction on difference of MH and MC CSD; and ML – MC = regression of selection response in the downward direction on difference of ML and MC CSD.

more strongly to stressors with greater corticosterone production (Y. Zhou, University of Nebraska, Lincoln, personal communication); thus, mice in this line may be affected more by natural selection. Nonetheless, loss of 40% of the response during the relaxed selection phase seems large.

Regressions of divergence of response (MH – ML) on generation number are listed in Table 2. Regressions of divergence of response and responses in the upward and downward directions (MH – MC and ML – MC, respectively) on difference in realized cumulative selection differentials are also listed in Table 2. The average change in heat loss per generation was calculated by regressing divergence of response on generation number. These estimates ranged from 2.12 to 3.07 and averaged $2.49 \pm 0.30 \text{ kcal}\cdot\text{kg}^{-0.75}\cdot\text{d}^{-1}$ for the 3 replicates. During the original selection, Nielsen et al. (1997a) observed an average divergence of 4.70 ± 0.09 .

Heritability estimates were calculated by regressing divergence of response on the difference (MH – ML) in realized cumulative selection differentials. Realized heritability estimates ranged from 0.11 to 0.16 and averaged 0.14 ± 0.01 (Table 2). These estimates are lower than the regression estimates reported by Nielsen et al. (1997a) for the first 15 generations of selection. They observed an average realized heritability estimate of 0.28 ± 0.003 . The difference in realized heritability estimates between the original and renewed selection is reflected by the lack of response in the ML lines in later generations. For generations 42 through 46, realized heritability, based on divergence, ranged from 0.23 to 0.29 and averaged 0.25 ± 0.02 across the 3 replicates, which was comparable to the estimates obtained during the original selection.

Heritability estimates for response in the upward and downward directions were calculated by regressing the average difference in heat loss ($\text{kcal}\cdot\text{kg}^{-0.75}\cdot\text{d}^{-1}$) for MH – MC and ML – MC on the difference in realized cumula-

tive selection differentials. The regression estimates for increased heat loss ranged from 0.07 to 0.25 and averaged 0.16 ± 0.05 for all replicates (Table 2). The estimates for decreased heat loss ranged from -0.02 to 0.18 and averaged 0.07 ± 0.06 . Estimates reported here were much lower than those obtained by Nielsen et al. (1997a) for all 3 replicates of MH selection. They observed that the regression of response in the upward direction on selection differential ranged from 0.28 to 0.33. Also, Nielsen et al. (1997a) reported that regressions of response in the downward direction on selection differential ranged from 0.23 to 0.26, which is close to the estimate of 0.18 in replicate 1, but much greater than the estimates of replicates 2 and 3.

Response in Feed Intake

Means for feed intake adjusted for metabolic size of male mice between the ages of 8 and 11 wk are listed

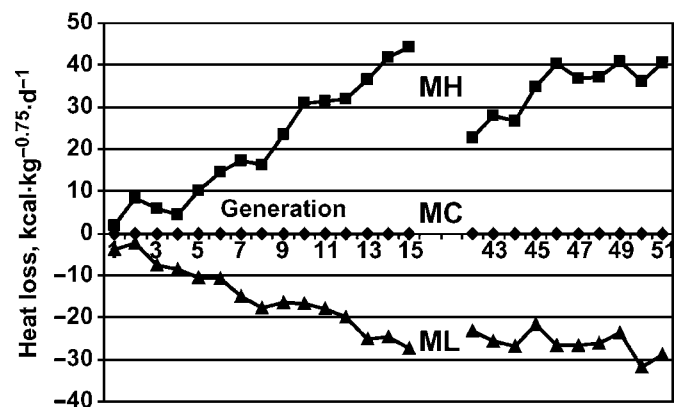


Figure 1. Line (MH = high; ML = low; and MC = control, set to zero) means for heat loss ($\text{kcal}\cdot\text{kg}^{-0.75}\cdot\text{d}^{-1}$) averaged across all 3 replicates of selection. Selection ceased between generations 16 and 42 and then was renewed.

Table 3. Means for heat loss ($\text{kcal}\cdot\text{kg}^{-0.75}\cdot\text{d}^{-1}$) in 3 replicates during 9 generations of renewed selection¹

Generation	Replicate 1			Replicate 2			Replicate 3			Mean across replicates		
	MH	MC	ML	MH	MC	ML	MH	MC	ML	MH	MC	ML
42	159.8	133.7	111.9	155.8	135.2	109.7	151.6	130.0	108.2	155.7	133.0	109.9
43	155.9	136.3	107.2	169.0	137.9	105.0	157.9	125.1	110.6	160.9	133.1	107.6
44	165.7	140.5	112.7	163.5	127.5	105.4	158.8	140.2	109.2	162.7	136.1	109.1
45	165.7	129.1	110.3	165.5	126.3	105.0	163.0	133.9	108.9	164.7	129.8	108.1
46	173.8	138.7	109.0	173.2	131.3	104.6	175.0	131.2	107.7	174.0	133.7	107.1
47	168.8	135.6	107.8	167.6	132.1	101.2	166.0	124.3	103.0	167.5	130.7	104.0
48	159.9	125.1	101.1	166.5	130.0	98.9	161.9	121.6	98.1	162.8	125.6	99.4
49	160.5	133.5	95.2	154.3	105.0	90.6	159.9	113.8	95.6	158.2	117.4	93.8
50	160.7	130.5	97.7	163.1	129.4	89.0	159.5	114.7	92.2	161.1	124.9	93.0
51	172.9	130.1	95.8	162.0	123.1	93.6	159.7	119.8	97.3	164.9	124.3	95.6

¹MH = High heat loss selection; ML = low heat loss selection; and MC = no intentional selection.

in Table 4. Line averages in the 3 replicates ranged from 72.0 to 79.0, 65.1 to 69.5, and 55.2 to 59.1 $\text{g}\cdot\text{kg}^{-0.75}\cdot\text{d}^{-1}$ for MH, MC, and ML, respectively. Regressions of response in feed intake on generation number are listed in Table 5. Average regressions of MH – ML, MH – MC, and ML – MC were 0.79 ± 0.28 , 0.84 ± 0.27 , and 0.05 ± 0.01 , respectively. By generation 51, divergence of MH and ML males in feed intake per unit metabolic size was 34.0% of the MC mean. This is greater than the difference of 20.6% at generation 15 that was observed by Nielsen et al. (1997b). At the end of selection, reduction in feed intake in the low direction was approximately 15% of the control mean. Although part of the response in heat loss in the upward direction (MH) was lost during the generations of relaxed selection; the same was not true in the response achieved in feed intake. When selection resumed (generation 42), divergence of MH from ML relative to MC mice (21.5%) for feed intake was at least as great as had been measured at generation 15.

Sharp et al. (1984) investigated responses in several lines of mice, which included lines selected for high and low feed intake. They found that the high and low feed intake lines diverged by 17% of the control mean and

had a heritability estimate of 0.15. This estimate of heritability was for the entire feed intake of growing animals and consisted of maintenance and growth components. Bishop and Hill (1985) and Selman et al. (2001) confirmed these results by conducting related studies with the same lines of mice in Scotland.

Sutherland et al. (1970) selected mice on increased efficiency of feed usage (gain/feed), increased feed intake, and increased rate of gain. They observed heritability estimates of 0.17 ± 0.04 for the overall gain:feed ratio estimate and 0.20 ± 0.06 for feed intake. Comparison of results between Sutherland et al. (1970) and this study are difficult due to differences in traits measured.

Residual feed intake is defined as the difference between actual feed intake and predicted feed intake, the latter based on BW maintained and gain (Koch et al., 1963). Variation in residual intake is most likely due to variation in the partial efficiency coefficient for maintenance requirement, assuming the partial efficiency coefficient for growth is constant. One might then expect that heritability of residual feed intake would be similar to heritability for heat loss for animals that are growing very little. Jensen et al. (1992) estimated residual energy intake in Holstein Friesian and Brown

Table 4. Means for feed intake ($\text{g}\cdot\text{kg}^{-0.75}\cdot\text{d}^{-1}$) of male mice measured over a 21-d period between the ages of 8 and 11 wk in 3 replicates¹

Generation	Replicate 1			Replicate 2			Replicate 3			Mean across replicates		
	MH	MC	ML	MH	MC	ML	MH	MC	ML	MH	MC	ML
42	72.7	72.1	57.8	72.9	66.9	56.9	70.5	67.4	56.9	72.0	68.8	57.2
43	76.3	70.8	62.1	75.9	68.9	57.3	70.4	66.8	57.8	74.2	68.8	59.1
44	75.6	72.6	58.7	74.4	66.1	56.5	70.2	64.1	56.6	73.4	67.6	57.3
45	73.8	66.4	58.5	72.3	63.7	55.7	72.5	65.2	54.4	72.9	65.1	56.2
46	77.4	68.6	57.0	76.1	65.3	54.4	74.5	66.5	59.7	76.0	66.8	57.0
47	80.7	69.6	60.3	73.4	66.2	56.6	72.4	64.9	53.8	75.5	66.9	56.9
48	76.3	68.7	56.8	71.6	63.7	53.6	75.1	64.5	55.2	74.3	65.6	55.2
49	75.4	67.6	55.8	71.6	63.5	54.3	77.7	65.4	57.4	74.9	65.5	55.8
50	81.4	76.4	61.9	76.8	65.5	55.0	78.9	66.7	56.2	79.0	69.5	57.7
51	84.1	66.8	57.3	73.9	64.8	55.6	77.1	64.0	55.7	78.4	65.2	56.2

¹MH = High heat loss selection; ML = low heat loss selection; and MC = no intentional selection.

Table 5. Regressions of the response in feed intake ($\text{g} \cdot \text{kg}^{-0.75} \cdot \text{d}^{-1}$) on generation number for each replicate, and averages and SE across replicates

Regression ¹	Replicate 1	Replicate 2	Replicate 3	Mean
MH – ML	1.03	0.24	1.11	0.79 ± 0.28
MH – MC	1.05	0.31	1.16	0.84 ± 0.27
ML – MC	0.02	0.07	0.04	0.05 ± 0.01

¹MH – ML = Regression of divergence of MH and ML feed intake on generation number; MH – MC = regression of response in the upward direction on generation number; and ML – MC = regression of response in the downward direction on generation number.

Swiss bulls. The heritability estimate of 0.30 that they reported for residual energy intake was similar to our estimate of 0.28 for heat loss during the initial 15 generations of selection. Fan et al. (1995) derived estimates of residual feed intake and observed a genetic correlation between actual daily energy intake and residual energy intake of 0.89. Luiting and Urff (1991) worked with White Leghorn laying hens and demonstrated that repeatability of residual feed intake estimates was between 0.52 and 0.58. Jensen et al. (1992) and Luiting and Urff (1991) predicted individual feed intake from regression equations derived from their data, whereas Fan et al. (1995) predicted individual feed intake from standard energy equations.

Response in Male BW

Means for male BW at time of heat loss measurement in 3 replicates during 9 generations of renewed selection are given in Table 6. Means ranged from 31.4 to 32.6 g for MH, 33.7 to 36.5 g for MC, and 30.5 to 34.1 g in ML. Regressions of divergence of male BW on generation number are available in Table 7. The average regression of divergence of MH and ML male BW on generation number was 0.33 ± 0.13 , which is much greater than the estimate (-0.04 ± 0.10) found by Nielsen et al. (1997b) over the first 15 generations. The average regressions of MH – MC and ML – MC on generation number were 0.04 ± 0.11 and -0.28 ± 0.23 , respectively.

Table 7. Regressions of divergence in male BW on generation number, averages across replicates and SE

Regression ¹	Replicate 1	Replicate 2	Replicate 3	Average ± SE
MH – ML	0.58	0.19	0.21	0.33 ± 0.13
MH – MC	-0.17	0.09	0.20	0.04 ± 0.11
ML – MC	-0.75	-0.10	-0.01	-0.28 ± 0.23

¹MH – ML = Regression of divergence of response in male BW on generation number; MH – MC = regression of the difference in BW between the high heat loss and control lines on generation number; and ML – MC = regression of the difference in BW between the low heat loss and control lines on generation number.

Regressions of weight differences on generation number suggest that selection for lower heat loss and less feed intake per unit size, and thus greater efficiency, in the ML line resulted in decreased BW when compared with the MC mean. This result is different than what was found by Nielsen et al. (1997b). They did not observe a noticeable trend in BW of males over 15 generations of selection in the MH, MC, and ML lines. Analysis of average BW showed that the MC mice were on average 2.86 ± 0.12 g heavier than the MH mice ($P < 0.01$) and 3.10 ± 0.12 g heavier than the ML mice ($P < 0.01$). Thus far, all of the observed traits within these lines have seemed to diverge with selection. However, male BW decreased in both of the selection lines when compared with the control. This suggests that there must be 2 separate mechanisms controlling BW of MH and ML mice relative to MC mice.

During the initial generations of selection, no correlated selection occurred for BW (regressions of CSD for BW on generation number averaged 0.02 and 0.04 g for MH and ML, respectively). During the renewed selection, no correlated selection was applied for MH (average = 0.05 g per generation), but some unintentional selection was applied for ML (-0.50 ± 0.03 g per generation). With heat loss arising from energy used for maintenance and from the inefficiency of energy used for gain, and given that mice at this measurement age still experience some growth, this could explain part of the limited negative selection on body size and the resulting

Table 6. Means for male weight (g) at the time of heat loss measurement in 3 replicates during 9 generations of selection¹

Generation	Replicate 1			Replicate 2			Replicate 3			Mean across replicates		
	MH	MC	ML	MH	MC	ML	MH	MC	ML	MH	MC	ML
42	34.5	35.2	37.0	30.8	37.8	32.5	29.8	36.6	32.9	31.7	36.5	34.1
43	35.0	33.8	35.4	31.9	36.7	32.4	30.1	34.3	32.3	32.3	34.9	33.4
44	36.6	33.2	34.8	30.8	34.5	32.4	29.5	33.5	31.4	32.3	33.7	32.9
45	35.3	33.6	34.2	31.2	35.3	32.3	30.2	34.8	31.5	32.2	34.6	32.7
46	35.7	35.5	34.5	30.5	35.5	32.4	29.1	33.9	30.4	31.8	35.0	32.4
47	35.3	34.7	34.4	31.2	35.5	31.3	30.0	33.9	30.2	32.2	34.7	32.0
48	34.9	33.9	30.9	31.2	35.5	31.3	30.5	33.5	29.5	32.2	34.7	30.5
49	34.6	36.1	30.9	30.3	35.3	31.0	29.2	33.6	29.8	31.4	35.0	30.6
50	36.4	35.3	32.2	31.4	36.5	31.0	29.9	33.8	31.6	32.6	35.2	31.6
51	35.9	36.7	33.4	30.4	34.4	30.4	29.1	32.8	30.3	31.8	34.6	31.4

¹MH = High heat loss selection; ML = low heat loss selection; and MC = no intentional selection.

response. As noted previously, MH mice express greater response to stress. The MH mice are more active (Mousel et al., 2001) and also have less body fat than the MC and ML lines (Moody et al., 1997; Nielsen et al., 1997b). The difference in body fat between the MH and MC mice amounts to over 1.0 g. Thus, part of the smaller BW of the MH mice is due to indirect selection responses in body fatness.

Sutherland et al. (1970) found that mouse lines that were previously selected for greater efficiency of gain (gain:feed ratio) had greater rates of gain than lines selected solely on greater feed intake. They also showed that rate of gain had a high positive correlation (0.91 ± 0.04) with gain:feed ratio. Sharp et al. (1984) selected mice based on appetite, percent fat, or percent lean tissue. Their findings were that mice in the high appetite line were heavier at any age but had greater gain:feed ratios. In related studies, Bishop and Hill (1985) and Selman et al. (2001) used the same selection lines of mice as Sharp et al. (1984), and in all of these studies, lines of mice selected for greater gain had responses in gain:feed ratio similar to the response achieved in our ML line.

The selection practices of Sutherland et al. (1970), Sharp et al. (1984), Bishop and Hill (1985), and Selman et al. (2001) have focused on increasing efficiency through increases in gain, which would ultimately result in mathematically greater efficiency (Equation 1). In these cases, partial efficiencies for maintenance and growth may or may not be changed. These methods are slightly different than our method of selection, which focuses on changing the partial efficiency coefficient associated with the maintenance energy requirement component of feed intake. Eggert and Nielsen (2006) reported no evidence that divergent selection for heat loss in mice changed the costs of deposition of fat and lean tissues associated with growth. Selection only affected the partial efficiency of maintenance per unit size.

Pym and Nicholls (1979) investigated direct and correlated responses to selection for lower feed conversion ratios calculated as feed:gain ratio (the inverse of equation 1), increased gain, or increased intake in broiler chickens. They found that weight gains increased in all 3 of the selection lines and observed a realized heritability estimate of 0.37 ± 0.04 for BW gain. However, this estimate reflects the heritability of only the gain component of efficiency.

Kownacki et al. (1975) studied the effects of selection for postweaning growth rate on basal metabolic rate in mice. Their findings were that the postweaning growth rate of a mouse was inversely related to its basal metabolic rate. Therefore, mice with low basal metabolic rates will have greater gains and thus greater mathematical efficiency. In a related study, Kownacki and Keller (1978) confirmed that selection for postweaning gain is related to a physiological mechanism that influences basal metabolic rates by showing that mice selected for high postweaning growth rates had basal

metabolic rates that were, on average, 8.5% lower than those of the unselected control group.

Rios et al. (1986) worked with lines of rats that had been previously selected for high or low 3 to 9 wk gain. They observed that rats selected for lesser gains had a 3% decrease in average daily intake when compared with controls. They were also able to obtain estimates of heat loss for rats in these lines. Rios et al. (1986) found that rats in the low 3 to 9 wk gain line had 1% lower heat loss estimates when compared with the control mean. These results are consistent with the current study in that selection for reduced heat loss has produced male mice that consume less feed and have reduced BW when compared with the control lines.

Effects of Selection on Litter Size and Conception Rate

Mean litter sizes per generation-line are presented in Table 8. Least-squares means were 12.0 ± 0.23 , 11.6 ± 0.20 , and 10.4 ± 0.26 for MH, MC, and ML, respectively. The ML dams produced, on average, 1.6 fewer pups than MH dams ($P = 0.05$). The test for selection response was significant ($P < 0.05$), and there was no evidence for asymmetry of selection response ($P = 0.41$). These results are similar to what was observed by Nielsen et al. (1997b), except that the difference between the MH and ML lines was more significant after generation 15 than in the recent generations. As in the earlier report, MH dams produced more pups than ML dams, and MC dams were intermediate for litter size born. Nielsen et al. (1997b) demonstrated that differences among the lines in litter size were due to differences in ovulation rate.

Conception rate was calculated as the number of females that produced litters divided by the number of females exposed to males in breeding cages. Average conception rates for each generation-line are presented in Table 8. The ML dams, on average, had a 6.7% greater conception rate than MH dams. The test for selection response (MH vs. ML) tended toward significance ($P = 0.08$); there was no evidence for asymmetry of selection response ($P = 0.24$). Kgwatalala et al. (2004) measured conception rate using these same heat loss lines of mice in normal, hot, and cold environments. They did not observe any differences in conception rate due to line or environment \times line interaction.

IMPLICATIONS

Several generations of relaxed selection for reduced heat loss, and hence reduced feed intake, were not characterized by loss of response. Additional response in feed intake through renewed selection to reduce heat loss was difficult to attain. Reduction in feed intake, attained through reduction in maintenance requirements, was approximately 15%. Litter size was reduced, but conception rate was not affected, when selec-

Table 8. Means for litter size at first parity and conception rate averaged across 3 replicates during 9 generations of selection

Generation	Line ¹					
	MH		MC		ML	
	Litter size	Conception rate	Litter size	Conception rate	Litter size	Conception rate
42	11.5	86.7	11.9	97.2	10.3	95.3
43	12.4	88.0	11.4	95.1	11.3	91.5
44	11.7	84.3	11.7	94.2	10.9	87.9
45	11.7	89.8	11.1	97.1	10.7	98.1
46	12.0	89.8	11.5	85.2	10.1	92.4
47	12.7	93.5	11.7	92.2	10.4	93.5
48	11.7	75.9	12.2	92.2	10.0	94.4
49	12.2	94.5	12.1	98.1	10.0	92.6
50	12.1	83.3	11.7	95.6	10.1	97.2
51	11.6	90.7	10.9	87.2	10.1	92.6
Average	12.0 ± 0.23	87.6 ± 1.9	11.6 ± 0.20	93.7 ± 1.9	10.4 ± 0.26	93.5 ± 1.9

¹MH = High heat loss selection; ML = low heat loss selection; and MC = no intentional selection.

tion was practiced to reduce feed intake. Thus, selection to reduce feed intake in livestock species should be possible, but some aspects of reproduction could be adversely affected.

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