

Nesting Behavior of House Mice (*Mus Domesticus*) Selected for Increased Wheel-Running Activity

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Nest building was measured in “active” (housed with access to running wheels) and “sedentary” (without wheel access) mice (*Mus domesticus*) from four replicate lines selected for 10 generations for high voluntary wheel-running behavior, and from four randombred control lines. Based on previous studies of mice bidirectionally selected for thermoregulatory nest building, it was hypothesized that nest building would show a negative correlated response to selection on wheel-running. Such a response could constrain the evolution of high voluntary activity because nesting has also been shown to be positively genetically correlated with successful production of weaned pups. With wheel access, selected mice of both sexes built significantly smaller nests than did control mice. Without wheel access, selected females also built significantly smaller nests than did control females, but only when body mass was excluded from the statistical model, suggesting that body mass mediated this correlated response to selection. Total distance run and mean running speed on wheels was significantly higher in selected mice than in controls, but no differences in amount of time spent running were measured, indicating a complex cause of the response of nesting to selection for voluntary wheel running.

KEY WORDS: Artificial selection; evolutionary constraint; correlated response; genetic correlation; nesting behavior; wheel-running behavior.

INTRODUCTION

The rate of adaptive microevolution can be either limited or enhanced by genetic correlations. The evolution of a trait under positive directional selection can be retarded by negative genetic covariances with other traits that enhance fitness; conversely, evolutionary response can be accelerated by positive genetic covariances with other traits that enhance fitness. The former situation, in which selection for one trait causes a maladaptive response in another trait, is usually de-

scribed as an “evolutionary constraint” on phenotypic evolution (review in Schwenk, 1995).

Genetic correlations most commonly reflect pleiotropy. Because morphological, physiological, and behavioral traits often function in a highly integrated and interactive way, pleiotropic gene action is expected to be the rule rather than the exception (Wright, 1968). Since Lande’s (1979) paper, which refocused the attention of evolutionary biologists (see also Lande and Arnold, 1983), the study of genetic correlations has become increasingly common in evolutionary studies of both behavior (e.g., Boake, 1994) and physiology (e.g., Arnold, 1987; Garland and Carter, 1994; Gibbs *et al.*, 1997; Zera *et al.*, 1998; Gibbs, 1999). Several methods can be used to identify genetic correlations between characters (Falconer and Mackay, 1996; Roff 1997; Lynch and Walsh, 1998). For example, any breeding design that permits estimation of heritabilities in multiple traits also allows estimation of genetic correlations. Another approach is to impose artificial

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selection on one trait and measure the correlated response in another, because such a correlated response necessarily depends on the existence of an additive genetic covariance (Falconer and Mackay, 1996).

In the context of ecological and evolutionary physiology, an outstanding example of the artificial selection approach is the work of Carol B. Lynch (1986, 1994) and colleagues, who have studied the quantitative genetics and correlated evolution of cold adaptation in house mice. In addition to conducting various breeding designs and crosses of selected lines, they imposed replicated within-family selection for thermoregulatory nesting by choosing breeders based on the total amount of cotton used by mice to build nests over a 4-day period. In the base population, mice used approximately 16 grams of cotton. In the two replicate low-selected lines, cotton usage was almost eliminated by generation 24 (see Figure 13.1 in Lynch, 1994). In the two high-selected lines, cotton usage reached a maximum (a selection limit) of about 47 grams of cotton by generation 14. Lynch tested for correlated responses at various generations, both before and after selection limits had been reached. Many traits demonstrated positive correlated responses, including body mass and litter size (Lynch, 1980), body temperature (Lacy *et al.*, 1978), nesting at lower temperatures (Lynch and Possidente, 1978; Marsteller and Lynch, 1983), and maternal nesting (Lynch, 1981); food consumption after cold acclimation showed a negative response to selection for increased nesting (Lacy *et al.*, 1978). One overall interpretation of the correlated responses of these traits to selection for nesting is that mice selected for high nest-building behavior exhibit a suite of traits that generally facilitate function at low ambient temperatures (reviewed in Bult and Lynch, 1997 and in Lynch, 1994): increased body mass and increased nest building improve adaptation to low ambient temperatures, and both are positively genetically correlated with each other and with increased fertility; hence, selection that occurs because of low temperature is predicted to result in larger mice that build larger nests and have larger litters.

To study the correlated evolution of locomotor behavior and exercise physiology, we have selected for increased wheel-running in house mice. Beginning with a base population of outbred Hsd:ICR house mice, we have produced four lines of mice selected for high voluntary wheel-running activity while maintaining four randomly bred lines as controls (Swallow *et al.*, 1998a). After 10 generations of selection, the high-selected lines were running, on average, 75% more (total revo-

lutions per day) than the control lines (Swallow *et al.*, 1998a; Koteja *et al.*, 1999a). This level of activity exceeds that of wild house mice born and raised under the same conditions (Dohm *et al.*, 1994). Selection was within family, and body mass was allowed to respond to selection (i.e., the effect of body mass was not removed statistically before choosing breeders). Body mass (see also Swallow *et al.*, 1999) and food consumption at 76 days of age showed a correlated response to selection by generation 10, with mice from selected lines being smaller and eating more food (on a mass-adjusted basis) than those from control lines (Koteja *et al.*, 1999a). In addition, at generation 10 the selected lines showed a maximal aerobic capacity (oxygen consumption elicited during forced treadmill exercise, termed $\dot{V}O_2$ max) that was approximately 6% higher than in control lines (Swallow *et al.*, 1998b). Maximal aerobic capacity is an important determinant of the capacity for sustained activity and may also be related to resting metabolic rates, thermoregulatory abilities, and overall energy requirements (review in Hayes and Garland, 1995).

The fact that several of the traits for which we measured a correlated response also changed in Lynch's mice selected for nesting behavior (see above) suggests that wheel running and nesting behavior may be related. In addition, a study of circadian rhythms in Lynch's lines (Bult *et al.*, 1993), demonstrated increased wheel running in mice selected to build small nests, but no differences in wheel running between control lines and the lines selected to build large nests. Our primary purpose herein is to explicitly examine the relationship between wheel running and nesting by testing the hypothesis that mice selected for high wheel-running activity will show reduced thermoregulatory nesting. Such a difference would indicate the existence of a negative genetic correlation between nesting and wheel-running, and hence would suggest that the evolution of increased activity levels might be constrained by reduced nesting and a decline in the successful production of weaned pups (Lynch, 1994; Bult and Lynch, 1997).

METHODS

Mice were from generation 10 of an artificial selection experiment for increased wheel-running activity, and were raised and housed as described in Swallow *et al.* (1998a), with the exception that individuals used in this study were produced by second matings of parents. Two males and two females from each of 10 separate families from each of the 4 selected lines and

from each of the 4 control lines were randomly chosen for inclusion in this experiment. One male and one female from each family were housed individually in standard cages ("sedentary" group); the remaining male and female from each family were housed individually in cages attached to running wheels ("active" group), as described in Swallow *et al.*, (1998b). Mice were placed in these housing situations at weaning (21 days of age). The mice with wheel access were the same individuals later studied by Koteja *et al.* (1999a).

Nesting behavior was scored at approximately 7 weeks of age by measuring the amount of cotton nesting material (Mountain Mist 100% cotton batting, the same as used by Lynch [1980]) used by the mice over a total of four days. Standard clear plastic cages (see Swallow *et al.*, 1998a) were used for all mice, but lids and food hoppers differed for individuals housed with or without attached wheels. The cages attached to running wheels had rectangular cup-style food hoppers, of dimensions 8.0 cm tall, 7.0 cm wide, and 5.0 cm deep. Two of these hoppers were placed in each cage, side by side. The hopper nearest the wheel was filled with a preweighed amount of cotton. The other hopper was filled completely with Harlan Teklad Rodent Diet (W) 8604. Lids for these cages were sheet metal with holes. The cages without attached wheels had wire-topped lids with space for food. Each mouse was provided with five pellets of food each day in the wire-topped lid, which was more than their *ad libitum* daily consumption. Preweighed amounts of cotton were placed next to the food in the wire lid. Because of the different styles of food hoppers used to hold the cotton, the cotton was packed more tightly in the hoppers used in the wheel cages. Therefore, it may have been more difficult for the mice in wheel cages to remove cotton from their hoppers, and absolute nesting scores for mice with and without wheels should be compared with caution.

The day before the experiment, all cages were cleaned and filled with a uniform amount of pine wood shavings, approximately 12 g. On day one of the experiment, the following procedure was followed: 30 g (+/- 1 g) of cotton was placed in its hopper. The mouse was weighed, and then both mouse and hopper were placed in a cage. On each of the next four days, the amount of cotton remaining in each hopper was weighed and recorded, but no attempt was made to assess nest quality (Lynch, 1994). If more than 1 g of cotton was used, then additional cotton was added to the hopper until the total was again approximately 30 g. All cotton that had been pulled from the hopper into the cage was discarded. The mice were weighed again

on day five at the end of the experiment. Photoperiod was a constant 12:12, and temperatures in the animal rooms were approximately 22°C.

Dependent variables were analyzed in SAS using Type III sums of squares in the GLM procedure. Females were analyzed separately from males because significant differences were measured in wheel running (and in body mass) between the sexes even before the imposition of selection (Swallow *et al.*, 1998a). The fixed main effect was Linetype (selected vs. control); Line nested with Linetype was a random main effect. Covariates used in all analyses were age, the square of the z-score of age, and the number of toes clipped for identification purposes. Number of toes clipped for identification has been shown to have significant effects on sprinting ability as well as body mass (Dohm, 1994; Dohm *et al.*, 1996). Age was included as a covariate because even small variations in age can have significant effects on some phenotypes (Cheverud *et al.*, 1996). To test for non-linear effects of age, the z-score of age was squared and included in the model (a z-transform was used to eliminate the correlation between age and age²). Mean body mass between day 1 and day 5 of the experiment was used as a covariate in some analyses, and was also analyzed as a dependent variable. Some of the sedentary mice were also part of an experiment involving measurement of aggression after the nesting trials, and had blood drawn the week prior to the start of the nesting trials. The potential effect of this treatment was tested by inclusion of a cofactor in the analyses described above; it was never significant ($P < 0.05$) and so was dropped from analyses. Finally, interactions between each covariate and linetype were tested over the mean square of covariate*line(linetype); if the interaction was not significant at $P < 0.05$, then it was dropped from the model. All tests were 2-tailed.

RESULTS

Repeatability, calculated as the intraclass correlation coefficient, sets an upper limit to heritability (Lesells and Boag, 1987; Falconer and Mackay, 1996). Size of nest built each day, body mass measured on days 1 and 5, and daily wheel running in active mice were all significantly repeatable across days for each of the experimental groups (Table I). All subsequent analyses use the sum of nest size for all four days, following Lynch (1980).

No significant differences in nest size were measured between selected and control females housed without wheels (sedentary group) using the GLM

Table I. Repeatability (t, the intraclass correlation coefficient), significance of individual effects (P), coefficient of number of measures per individual (n_0 , which is smaller than mean number of measures per individual when unequal numbers of measures per individual are taken), and number of individuals measured (a). Calculations and terminology are based on those found in Lessells and Boag (1987)

Trait		Wheel Access Control Females	Wheel Access Selected Females	Wheel Access Control Males	Wheel Access Selected Males	Sedentary Control Females	Sedentary Selected Females	Sedentary Control Males	Sedentary Selected Males
Nest Mass	t	.2112	.4755	.3474	.4361	.3914	.4406	.5676	.5516
	P	.002	<.001	<.001	<.001	<.001	.001	<.001	<.001
	n_0	4	4	4	4	4	3.798	3.899	3.896
	a	38	38	40	38	40	40	40	39
Body Mass	t	.8528	.9396	.7352	.9145	.9264	.9382	.8907	.9852
	P	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
	n_0	2	2	2	2	2	2	2	2
	a	38	38	40	38	40	40	40	39
Wheel Running	t	.5948	.6725	.8668	.7387				
	P	<.001	<.001	<.001	<.001	X	X	X	X
	n_0	4	4	4	4				
	a	38	38	40	38				

Table II. P-values from nested ANCOVA of mass of nests built over 4 days^{ab}

	Sedentary Females	Wheel Access Females	Sedentary Males	Wheel Access Males
LINETYPE	0.1310	0.0044	0.5086	0.0487
LINE (LINETYPE)	0.1457	0.2573	0.0146	0.1469
BODY MASS	0.0001	0.0154	0.0646	0.0005
AGE	0.6906	0.1432	0.7373	0.8953
AGE ²	0.2032	0.3597	0.1182	0.8924
TOES CUT	0.2238	0.9135	0.1903	0.2117
N	74	72	72	76

^a Both nest mass and body mass \log_{10} transformed in all analyses.

^b Statistically significant results ($P < 0.05$) are in bold face.

procedure in SAS with all covariates included in the model (Table II). However, body mass had a significant positive effect on size of nests built (Table II). To present these results graphically, residuals were calculated from a regression of nest size on age, age², and toes cut, and then plotted as a function of body mass (upper-left panel of Fig. 1). In females with wheel access, significant differences were measured between selected and control females using the statistical model that included all covariates, with control females building significantly larger nests than selected females (Table II). Again, body mass was a significant covariate (Table II), with larger females building larger nests (see lower-left panel of Fig. 1).

Similar results were obtained in males. As in females, no significant differences in nest size existed between selected and control sedentary males, but signif-

icant differences were measured between selected and control males with wheel access (Table II), with control males building significantly larger nests. Residual nest size, derived as described above for females, is plotted for sedentary and wheel-access males in the two right panels of Fig. 1. A statistically significant line effect was also measured in sedentary males (Table II), indicating significant variation among lines within selected and control groups. Body mass was a significant covariate in wheel-access males, with larger mice building larger nests, but not in sedentary males. Hence, in both females and males, selected mice with wheel access built significantly smaller nests than control mice, but no differences were detected for mice housed without wheels.

As noted in the Introduction, body mass at 76 days of age showed a correlated response to selection at generation 10 (Koteja *et al.*, 1999a). Because body mass

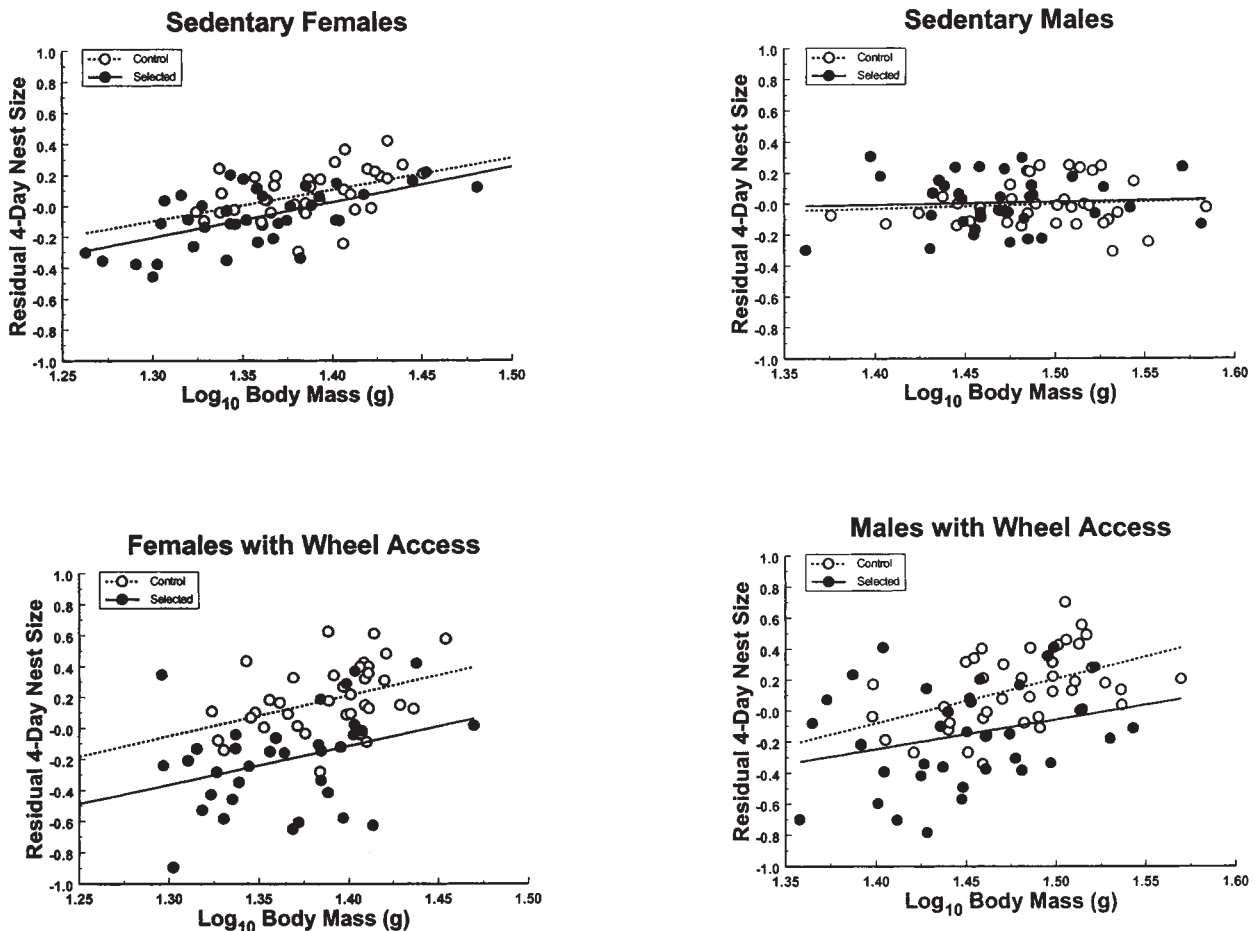


Fig. 1. Residual 4-day nest mass plotted as a function of \log_{10} body mass for sedentary and wheel-access females and males. Residuals were calculated from a multiple regression of nest mass on age, age^2 , and toescut. Outliers dropped from the statistical analysis (Table II) are also excluded from this figure. Interaction terms between body mass and nest mass were non-significant for both sedentary and wheel-access males and females. Lines are least-squares regressions fitted separately to mice from selected and control lines.

had a significant effect on size of nests built by females and by wheel-access males, we reanalyzed nest size after excluding body mass from the statistical model (Table III). When body mass is not included in the model, marginally significant differences in nest size were measured between selected and control sedentary females; the results for wheel-access females, wheel-access males, and sedentary males remain qualitatively the same as in the analyses in which body mass was included. Body mass was itself analyzed. Although Figs. 1-3 suggest a trend for mice from selected lines to be smaller than controls, no statistically significant differences in body mass were measured between selected and controls in any group, although this difference was only marginally non-significant in sedentary females and in wheel-access males (Table IV).

For mice with wheel access, wheel-running data were collected each of the four days that nest building was recorded. Selected females and selected males both ran a significantly greater distance over the 4-day period than did their control counterparts (Table V and Fig. 2a for females; Table VI and Fig. 3a for males). The total distance run on wheels can be decomposed into two components: time spent running, and mean running speed during the minutes that showed any wheel revolutions (Swallow *et al.*, 1998a, b; Koteja *et al.*, 1999a). The total number of 1-minute intervals run by females and males are presented in Figs. 2b and 3b, respectively; no significant differences between selected and control in time spent running were identified (Tables V and VI). Instead, selected mice ran significantly faster than controls (Tables V and VI;

Table III. P-values from nested ANCOVA of mass of nests built over 4 days with body mass excluded from the model^a

	Sedentary Females	Wheel Access Females	Sedentary Males	Wheel Access Males
Transform	None	Log ₁₀	Square root	Square root
LINETYPE	0.0417	0.0019	0.9208	0.0078
LINE (LINETYPE)	0.2066	0.2782	0.1102	0.1880
AGE	0.1625	0.0420	0.4426	0.3028
AGE ²	0.8217	0.3531	0.2763	0.7390
TOESCU	0.9342	0.7812	0.6587	0.6384
N	80	74	79	77

^a Statistically significant results ($P < 0.05$) are in bold face.**Table IV.** P-values from nested ANCOVA of body mass^a

	Sedentary Females	Wheel Access Females	Sedentary Males	Wheel Access Males
Transform	Log ₁₀	Square	Log ₁₀	Log ₁₀
LINETYPE	0.0888	0.2064	0.1422	0.0593
LINE (LINETYPE)	0.0070	0.0010	0.0019	0.0414
AGE	0.0043	0.0424	0.0092	0.0040
AGE ²	0.3210	0.9893	0.1297	0.8532
TOESCU	0.5235	0.9140	0.1326	0.7168
N	80	73	78	78

^a Statistically significant results ($P < 0.05$) are in bold face.**Table V.** P-values from nested ANCOVA of female wheel-running traits during the 4 days of the nesting trials^a

	Total Revolutions	Minutes Active	Mean RPM
LINETYPE	0.0295	0.1018	0.0194
LINE (LINETYPE)	0.0001	0.0028	0.0001
BODY MASS	0.8656	0.7044	0.9421
AGE	0.1562	0.0363	0.8100
AGE ²	0.5905	0.8964	0.5696
TOESCU	0.8834	0.6735	0.5805
N	75	73	74

^a Statistically significant results ($P < 0.05$) are in bold face.

Figs. 2c and 3c). Thus, the selected mice ran a greater distance not by running longer, but by running faster, a result reported previously for siblings of the mice studied herein (Swallow *et al.*, 1998a).

At the level of individual variation, the relationship between wheel running and nesting was estimated by correlating residual nest size and residual wheel running. Nest size residuals were derived separately for wheel-access males and wheel-access females from the ANCOVA models presented in Table II;

wheel-running residuals for females were derived from the ANCOVA model for total revolutions in Table V, and wheel running residuals for males were derived from the ANCOVA model for total revolutions in Table VI. The correlation for females was $r = -0.261$ ($P = 0.026$, $n = 73$) and for males was $r = -0.403$ ($P = 0.0005$, $n = 72$). Thus, a significant phenotypic correlation exists between wheel running and nesting when effects of selection group and covariates are removed.

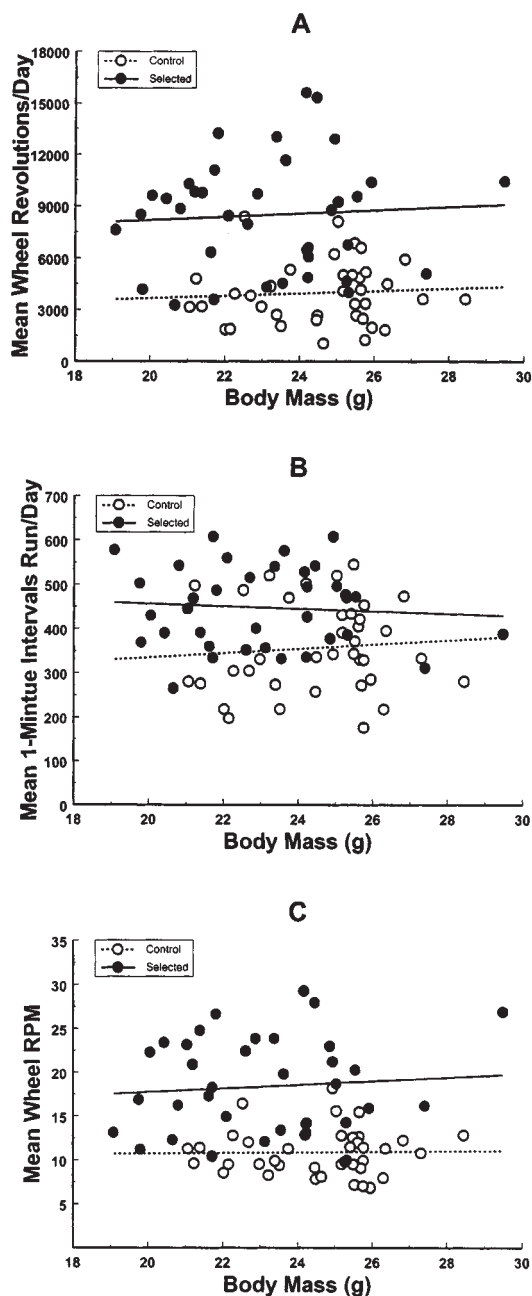


Fig. 2. Wheel running traits for females during the 4-day nesting trial: (A) total wheel-revolutions run, (B) total time spent running, (C) mean wheel RPMs during running. Wheel circumference equals 1.12 meters. Lines are least-squares regressions.

DISCUSSION

Because both body mass and wheel running are free to respond to selection in the main experiment (Swallow *et al.*, 1998a), the best estimate of the overall correlated

response of nest building to selection on wheel running is provided by the statistical model which does not include body mass as a covariate (Table III). In this analysis, highly significant differences were measured between selected and control mice in wheel-access males and wheel-access females, whereas selected and control mice were marginally significantly different in sedentary females and not significantly different in sedentary males. Hence, nesting behavior demonstrated a correlated response to selection on wheel running in 3 of 4 groups of mice in this study, when possible effects of body mass were ignored.

Analyzing the data with body mass included as a covariate in the statistical model provides an estimate of the effect of body mass on the correlated response. First, body mass has a positive and significant or marginally non-significant effect on nest size in all groups (Table II). Second, when the effects of body mass are removed statistically, only wheel-access mice show significant differences between selected and control. This suggests that the correlated response in nest size measured for sedentary females may be largely a function of differences in body mass, whereas the correlated responses measured in the wheel-access males and females are not.

High-selected mice ran a significantly greater distance on wheels than did control mice, and built significantly smaller nests. However, no significant difference was measured between high-selected and control mice in the amount of time spent on running wheels, so simple differences in time allocation cannot explain the small nests built by high-selected mice. In addition, a focal-animal study of behavior in the cage-wheel complex at Generation 13 demonstrated essentially no differences between selected and control mice in the frequencies of 27 categories of behavior, including sleep (Koteja *et al.*, 1999b: females showed differences in the frequency of sniffing and biting at wires of wheels or cages). Therefore, no other behavioral differences in time allocation (e.g., differences in amount of time resting) are likely to account for the differences in nesting described herein. The high-selected mice did run significantly faster on wheels than did control mice, which suggests that the mechanism of the correlation may be found in traits related to running speed. Such differences are not likely caused by differences in energy expenditure because, at the whole-animal level, selected and control mice do not consume different amounts of food when housed with wheel access (although mass-adjusted consumption is 4% higher in selected mice: Koteja

Table VI. P-values from nested ANCOVA of male wheel-running traits during the 4 days of the nesting trials^a

	Total Revolutions	Minutes Active	Mean RPM
Transform	Cube Root	None	Cube Root
LINETYPE	0.0387	0.1525	0.0221
LINE (LINETYPE)	0.0017	0.0001	0.1533
BODY MASS	0.0800	0.2438	0.0203
AGE	0.0703	0.0775	0.1476
AGE ²	0.0982	0.1418	0.1048
TOESCUT	0.1669	0.6416	0.0603
N	77	78	78

^a Statistically significant results ($P < 0.05$) are in bold face.

et al., 1999a). More likely, the correlated response in nesting behavior is related to changes in hormones or neurotransmitters.

Our results show interesting similarities and differences with those of Bult *et al.* (1992, 1993), who measured wheel-running traits and the number of arginine-vasopressin (AVP) neurons in Lynch's mice selected for high and low nest-building behavior. AVP neuron number is a component of the pathway that controls circadian rhythms. Bult *et al.* found that mice selected for low levels of nest building had a higher number of AVP neurons than control mice and mice selected for high nest building. Mice selected for low nest building showed different circadian activity profiles (time of maximum activity and free-running period in constant darkness), and ran greater distance per day, than did high-selected and control mice. However, their results suggest that mice selected for low nest building probably ran greater distances by spending more time running (although this cannot be determined conclusively from their data), which is clearly not the case for the mice studied herein. This suggests the possibility of multiple mechanisms by which wheel-running and nesting may be genetically correlated in different strains of mice.

At the level of correlated responses in behavior, our results generally complement those of Bult *et al.* (1992, 1993). We demonstrated that nesting responds in correlated fashion to selection on wheel running, whereas they showed that wheel running responds in correlated fashion to selection on nesting. A correlated response to selection is indicative of a genetic correlation (Falconer and Mackay, 1996); hence, both studies identified a negative genetic correlation between nesting and wheel-running activity. Although genetic correlations can change rapidly (Brodie, 1993 and references therein; Leroi *et al.*, 1994), in both

these selection experiments the negative genetic correlation between nesting and wheel running is not qualitatively different, suggesting that it is relatively strong and unchanging. In addition, both selection experiments considered in total demonstrate the complex genetic and phenotypic relationships among multiple behavioral and physiological traits (including body mass), and clearly show that selection for one trait may result in evolutionary changes in a host of other traits as well.

Genetic correlations may increase or retard the speed of adaptive phenotypic evolution. Our results suggest that evolution of increased voluntary activity may ultimately be constrained by the negative correlated response in nesting behavior, because thermoregulatory nest building is correlated with maternal nest building and with the ability to successfully wean pups (Bult and Lynch, 1996). (Likewise, both sets of results suggest that the evolution of increased nest building may at some point be constrained by the negative correlated response in activity, if very low levels of activity impose a fitness cost.) We, therefore, expect females from our high-selected lines also to build smaller maternal nests, and hence to produce fewer and/or lower-quality offspring, especially when they have access to running wheels and/or are exposed to low temperatures. As in most colonies of laboratory mice, the routine protocol in our selection experiment involves housing of pregnant and lactating females in standard cages without wheels, at a temperature of approximately 22°C (Swallow *et al.*, 1998a), which is well below the thermoneutral zone; under these conditions, no differences in number of weanlings or in total mass of weanlings were measured in generation 10 (Swallow *et al.*, unpublished). In the future, experiments housing dams in cages with wheels will be conducted, which should fur-

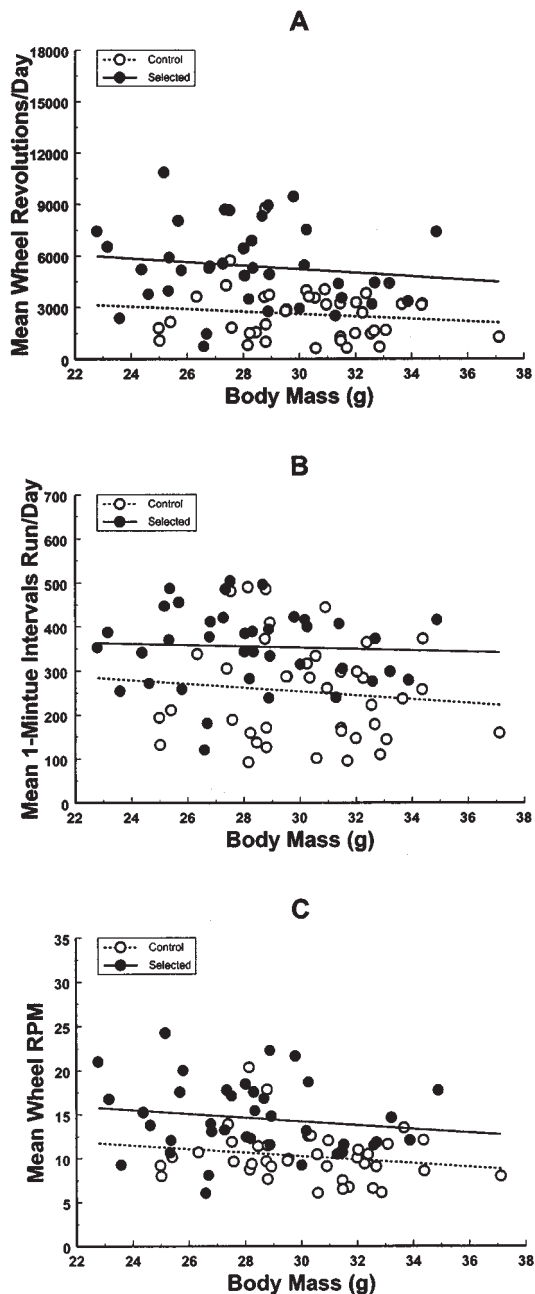


Fig. 3. As in Fig. 2, but for males.

ther clarify the evolutionary relationships of nesting and locomotor activity.

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