

Exercise physiology of wild and random-bred laboratory house mice and their reciprocal hybrids

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Dohm, Michael R., Christopher S. Richardson, and Theodore Garland, Jr. Exercise physiology of wild and random-bred laboratory house mice and their reciprocal hybrids. *Am. J. Physiol.* 267 (Regulatory Integrative Comp. Physiol. 36): R1098–R1108, 1994.—We conducted a “common garden” experiment to compare aspects of exercise physiology and voluntary wheel-running behavior in wild and random-bred (i.e., non-inbred) laboratory house mice and their reciprocal crosses. Analysis of covariance indicated that, after effects of body mass and other appropriate covariates (e.g., age at testing) were accounted for, wild (range 2.46–3.30 m/s, $n = 12$) and hybrid (range 1.69–3.30 m/s, $n = 24$) mice exhibited forced maximal sprint running speeds that averaged ~50% higher than those of random-bred laboratory mice (range 1.11–2.12 m/s, $n = 19$). Wild and hybrid mice also had significantly higher (+22%) mass-corrected maximal rates of oxygen consumption ($\dot{V}O_{2\max}$) during forced exercise and greater (+12%) relative ventricle masses than lab mice. Wild and hybrid mice also showed statistically higher swimming endurance times relative to body mass than lab mice, although these differences were insignificant when body mass was not used as a covariate. No significant differences were found for relative gastrocnemius muscle mass, liver mass, hematocrit, or blood hemoglobin content. During a 7-day test on voluntary activity wheels, both wild and hybrid mice ran significantly more total revolutions (+101%), ran at higher average velocities when they were active (+69%), and exhibited higher maximum revolutions in any single 1-min period (+41% on the 7th day of testing), but the total number of active 1-min intervals did not differ significantly among groups. In general, the behavioral and/or whole organism performance traits showed greater differences than the lower-level traits; thus, during the domestication of house mice, behavior may have evolved more rapidly than physiology.

behavior; directional dominance; domestication; endurance; evolution; locomotion; maximal oxygen consumption; sprint speed; wheel running

random-bred laboratory mice compared with a Wisconsin population of wild (commensal) house mice and with hybrids between the lab and wild mice.

Domestication is an evolutionary process; animals become adapted to a human-defined environment by some combination of genetic changes occurring over multiple generations and environmentally induced developmental events reoccurring during each generation (30). Intuition suggests that we should find genetically based differences between lab and wild mice for aspects of locomotor performance and exercise physiology. For instance, compared with natural environments, the laboratory differs in providing a constant supply of food and water and in lacking predators and other factors that may place a premium on high abilities for locomotor performance. Domestication may, therefore, have resulted in relaxed selection for locomotor and exercise capacities, leading to lowered abilities in lab mice compared with their wild counterparts. The ancestors of many laboratory *Mus* strains (e.g., Swiss Webster) were derived from wild European stocks of *Mus domesticus* about 100 years ago (3, 13–15, 26, 29, 35). Therefore, with the assumption of 3–4 generations per year, lab mice have been under domestication for ~300–400 generations, providing ample opportunity for genetic response to relaxed selection on exercise performance.

Divergence between lab and wild stocks for exercise capacity is likely to have a genetic component. First, substantial genetic variation (as assessed by electrophoresis) exists among laboratory strains (15) and among wild populations of house mice (see references in Ref. 15). Second, new mutations have likely occurred during the development of laboratory strains (12 and references therein). Thus genetic changes following relaxed selection may have occurred initially (when wild mice were first brought into the laboratory for breeding programs), may have occurred during the development of a particular strain of mice, or both.

Some authors believe that the process of domestication leads ultimately to degeneracy, or the elimination of some adaptive traits, as a correlated response to rapid-acting natural selection during adaptation to the domestic environment (7, 14, 30 and references therein). Because selection, both in nature and during domestication, acts most directly on behavior and/or organismal performance capacities (18, 20), we focused on measures of locomotor performance and behavior.

Operationally, *performance* refers to an organism's ability or capacity to execute some activity (18, 20, 24). The performance traits included in this study were chosen because they represent valid and reproducible indexes of performance capacity at the whole animal level. Sprint speed and endurance are ecologically relevant measures of locomotor abilities (11, 20). For

LABORATORY HOUSE MICE have served as model organisms in numerous physiological, behavioral, and quantitative genetic studies (12, 25, 35, and references therein). In exercise physiology, laboratory rats have been used more commonly than mice (4). For logistical reasons, however, mice are better candidates for study of the quantitative genetic basis of variation in physiological and associated behavioral traits. As a prelude to quantitative genetic analyses and artificial selection experiments with random-bred, genetically variable laboratory house mice, we conducted a series of studies to establish baseline information and to consider how appropriate a random-bred strain of mice may be for drawing evolutionary conclusions about metabolism and exercise physiology in small mammals (16, 22, 31, cf. 35). In this study we present information on the exercise capacities and associated behavioral traits of a strain of

example, swimming endurance may reflect the ability to escape from periodic flooding (23) or to disperse across water (23), and sprint speed is likely to be important in escaping from predators or capturing prey. The maximal rate of oxygen consumption ($\dot{V}O_{2\max}$), which sets an upper limit to the intensity of activity that can be sustained aerobically, was also measured. From a comparative perspective, $\dot{V}O_{2\max}$ may be an important determinant of the levels of activity that free-living animals can sustain (20, 24, and references therein). Several suborganismal traits (e.g., hematocrit, blood hemoglobin content, gastrocnemius muscle mass) known to correlate with locomotor performance or metabolic rates were also measured.

Various authors have proposed that, during domestication, behavioral traits should respond first or at least more rapidly to selection, compared with associated traits at lower levels of biological organization (30 and references therein). To investigate this hypothesis, we also recorded several aspects of voluntary wheel-running behavior during a 7-day trial. Wheel running is a useful measure, because this behavior has obvious potential ties to a number of underlying physiological traits associated with exercise physiology. For example, innate aerobic capacities may affect voluntary wheel-running behavior in untrained mice (16). Thus, if wild and lab mice differ more for aspects of wheel-running behavior than for the physiological traits associated with activity capacities, this difference suggests that behavior has evolved more rapidly than has physiology during domestication of the house mouse.

A "common garden" experiment is required to determine whether genetically based differences exist between lab and wild *Mus domesticus* populations (17). In other words, measurements of traits to be compared must be made on offspring of wild and lab mice bred and raised under the same environmental conditions. Without such a design, observed phenotypic differences may simply reflect environmental effects (e.g., acclimatization). For example, numerous studies have demonstrated that physical conditioning or general activity level can affect $\dot{V}O_{2\max}$ in humans and other mammals (4) and in lizards (19). Our comparisons also included hybrids, obtained by crossing lab mice with wild mice. Comparisons of hybrid mice with pure wild and/or lab mice (all bred and raised in the laboratory) can elucidate the underlying nature of any genetically based difference (e.g., the presence of genetic dominance). Because the lab and wild mice we studied differed considerably in body size, the hybrids, which were of intermediate size, also facilitated statistical comparisons by analysis of covariance when body mass was used as a covariate. Finally, a comparison of the reciprocal hybrid offspring (wild dam \times lab sire vs. lab dam \times wild sire) indicates whether maternal influences exist.

MATERIALS AND METHODS

Animal husbandry and breeding design. We studied laboratory-reared offspring derived from reciprocal crosses of wild and laboratory house mice. The wild parents were captured using Sherman live traps during the spring and summer of

1992 from a single population inhabiting a barn located in Dane County, WI (31). The population tested negative for antibodies to *Borrelia burgdorferi* (31), the cause of Lyme disease. The laboratory parents were from the albino, random-bred Breeder:HSD/ICR strain of mice (hereafter called ICR) obtained from Harlan Sprague Dawley, Indianapolis, IN (Bldg. 202, Barrier A). Again, we wish to emphasize that the random-bred ICR mice are substantially genetically variable (21), and levels of heterozygosity [e.g., 25% (21)] are similar to those reported for wild populations of house mice (see review in Ref. 15). ICR mice have been used in several quantitative genetic studies (32, 33), and the physiology, morphology, behavior, and life history of this strain have been extensively studied (e.g., 16, 21, 22, 31–33).

Mice were housed in standard clear plastic cages (27 cm long, 17 cm wide, 12.5 cm deep) with metal or wire tops and wood shavings as bedding. All lab males and females were housed in same-sex groups of four or five. Wild males were housed singly. Room temperature was maintained at $\sim 22^{\circ}\text{C}$. Wild-caught females were housed in groups of three per cage in constant darkness for ≥ 3 wk after capture and were disturbed as little as possible; we used this protocol to enhance the breeding success of wild mice (see Ref. 31). Water and feed (Harlan Teklad Laboratory Rodent Diet) were always available except before measurements of nonshivering thermogenesis and basal metabolism (see below).

Wild and lab breeder males were assigned randomly to each cross group; wild breeder females were randomly paired to wild or lab males; lab females were arbitrarily assigned to wild or lab males. All pairs were then kept in constant darkness and disturbed as little as possible. Tin cans (12.6 cm long, 7.8 cm diameter) were placed in all cages for nesting and remained in the cages until offspring were weaned.

Litters were born between August 16 and September 15, 1992. At 7 days of age, photoperiod was changed to a 12:12-h light-dark cycle (centered at 1300 CST). Seven of 17 wild pairs and 13 of 17 wild dam \times lab sire pairs produced litters, compared with 12 of 13 wild sire \times lab dam pairs and 19 of 20 lab pairs producing litters (see Ref. 31). At 21 days of age, offspring were weaned from the dam, weighed, toe-clipped, and housed in groups of 3 or 4 by sex and cross. [Toe-clipping had no significant effect on sprint speed or swimming endurance in these mice (unpublished results).] After weaning, mice were housed in same-sex and cross groups of 3 to 4. Additional details of husbandry and breeding design are reported in a companion paper (31).

Subjects and measurement chronology. One female offspring per family was randomly chosen for measurement to ensure statistical independence of the data points. However, because of the relatively low breeding success of the wild pairs, a second female was also randomly selected for 5 of 7 wild \times wild families, thus yielding a total number of 56. We studied only females because we wanted to eliminate possible sex-related variation and because four of the litters contained no males. Offspring were assigned to one of four measurement blocks ($n = 14$ mice per block) to reduce age variation within and among cross groups. Mean age at first $\dot{V}O_{2\max}$ measurement was 45.1 ± 7.33 (SD) days, and age at testing was used as a covariate for all statistical analyses (see below).

In addition to the measurements presented in this report, nonshivering thermogenesis (NST) and basal metabolic rate (BMR) were also determined on these mice (31). All whole animal measurements occurred from September 20 through October 22, and all mice were killed by cervical dislocation from November 16 to December 11, 1992. The sequence of testing was as follows: day 1, food removed at 1800; day 2, measurement of NST; day 3, rest, food removed at 1800; day 4,

measurement of BMR; *days 5 and 6*, rest, no measurements; *days 7 and 8*, measurement of $\dot{V}O_{2\max}$; *days 9 and 10*, measurement of forced sprint speed; *days 11, 12, and 13*, swimming endurance; *days 14–21*, voluntary wheel-running behavior.

Locomotor performance. Forced sprint running speed was measured with standard techniques on an 8-m long \times 7.5 cm-wide photocell-timed racetrack, with short-pile plastic artificial grass substrate (11, 16). Twelve sets of photocells spaced at 0.5-m intervals were interfaced to a computer. On each trial, mice were timed while chased five times in succession along the racetrack with a padded meter stick; reported values are the highest speeds attained over 1.0-m intervals (see Ref. 16). Trials were conducted on two successive days. The highest value from both trial days was assessed for repeatability, which was high ($r = 0.903$, $n = 55$); the single higher value for each individual was then used for group comparisons.

Swimming endurance was measured following standard protocols (16). Mice were rinsed in a mild detergent solution (Ivory liquid) to prevent air bubbles clinging to fur, and a 0.9-g weight was attached to their tails with a plastic paper clip. Testing was completed over 3 days, the 1st consisting of a 10-min training swim without added weight, followed on the 2nd and 3rd days by the actual endurance trials. Both values from *days 2 and 3* were assessed for repeatability ($r = 0.723$ on a log scale, $n = 55$); higher values were used for group comparisons. Mice swam in plastic buckets (water depth \sim 30 cm) containing water at a temperature of \sim 32°C (mean = 32.3; SD = $\pm 0.55^\circ\text{C}$), a temperature yielding the highest swimming times (see Ref. 16 and unpublished data). Exhaustion was judged and mice were removed from buckets when they remained under water for eight consecutive seconds; this period of time is about one-third of what mice can tolerate (6). Initial and final water temperatures were recorded for each trial, and the average value was used as a covariate in statistical analyses (see below).

$\dot{V}O_{2\max}$. $\dot{V}O_{2\max}$ rates attained during forced exercise were measured on a motorized treadmill by using a stepped series of increasing speeds (2, 16, 22, 24). A mouse was placed in a small Plexiglas chamber held just above the surface of the treadmill belt. From an initial speed of 0.28 m/s, treadmill speed was increased every 2 min by 0.14 m/s up to a maximum of 1.25 m/s. Trials were terminated when O_2 consumption ($\dot{V}O_2$) failed to increase as tread speed increased and/or the mouse did not keep pace with the moving belt.

We used an open-circuit respirometry system to monitor $\dot{V}O_2$. Air was drawn from the chamber through columns of Drierite and Ascarite II for removal of water vapor and CO_2 , respectively, and then passed through a thermal mass flow controller set at 2,500 ml/min (a flow rate sufficient for rapid chamber washout). We also determined the effective volume of the system (540 ml) and made “instantaneous” corrections for chamber washout (1), because the standard equations (Eq. 4A in Ref. 37) are for use under steady-state (equilibrium) conditions. With the rapid washout of this system, the instantaneous correction was relatively minor (see RESULTS). O_2 concentration in the excurrent air was recorded every second by an Applied Electrochemistry S-3A/II oxygen analyzer interfaced to an analog-to-digital converter and a computer. Values were recorded each second as the average of 20 consecutive readings by the data acquisition program. $\dot{V}O_2$ generally increased with increasing speed, and the highest 1-min period of $\dot{V}O_2$ during a trial was taken as $\dot{V}O_{2\max}$, consistent with previous studies (2, 16, 22). A data analysis program corrected for drift in the baseline O_2 concentration, using linear regression, and then calculated steady-state and instantaneous $\dot{V}O_2$ values. $\dot{V}O_2$ generally decreased before a trial was ended, and a

brief elevation in $\dot{V}O_2$ was evident after every run. As in previous studies using this technique (16, 22; unpublished data), $\dot{V}O_{2\max}$ was significantly repeatable between trials (whole animal steady-state values on a log scale, $r = 0.57$; instantaneous values, $r = 0.54$; both $n = 54$).

Voluntary wheel-running behavior. Voluntary wheel-running behavior was monitored for 7 consecutive days. Mice were placed in normal housing cages with 7.7-cm-diameter holes drilled in their sides to allow access to attached activity wheels (35.5 cm diameter, Lafayette Instruments, Lafayette, IN), thus allowing individuals continuous access to the wheels. Food and water were available ad libitum. The wheels had attached photocell counters and were interfaced to an IBM PC-compatible computer; software allowed for monitoring of the number of revolutions occurring during each 1-min interval (San Diego Instruments, San Diego, CA). We analyzed, for each day, the number of 1-min intervals during which any running occurred, the average number of revolutions occurring per minute of activity, the maximum revolutions occurring in any 1-min interval, and the total number of revolutions per 24-h period. We also used a measure of the rotational resistance of each wheel as a covariate in statistical analyses.

Hematocrit and hemoglobin. Before killing of the animals at 86–92 days of age, heparinized microcapillary tubes (75 mm long, 1.1–1.2 mm ID) were used to take blood samples from the suborbital sinus. For measurement of hematocrit, tubes were centrifuged for 6.5 min in a Clay-Adams microfuge (Autocrit Ultra 3). Hematocrit was determined immediately after centrifugation. For measurement of hemoglobin concentration, 25- μl blood samples (drawn from a heparinized microcapillary tube) were added to 5 ml of Drabkin’s reagent. Concentration of cyanmethemoglobin was determined at 540 nm with a Beckman spectrophotometer, using Sigma. Hematocrit and blood hemoglobin content were determined in duplicate, and means were analyzed.

Organ masses. After a midventral incision, the heart was lifted with forceps, and the ventricles were cut free from the atria and major blood vessels. The ventricles were blotted, and any coagulated blood was removed. The gastrocnemius muscle was removed by cutting the muscle from the lateral condyle of the tibia and medial condyle of the fibia and then by cutting the Achilles tendon approximately midway between its origin and the muscle’s insertion. The liver was removed and the gall bladder excised before weighing. Wet mass was recorded to the nearest 0.1 mg on an electronic balance.

Statistical analyses. Statistical analyses were performed using SPSS/PC+ Version 5.0 (SPSS, Chicago, IL). Multiple regression was used to perform analysis of covariance (ANCOVA), using several covariates (e.g., body mass, age, time of day) as appropriate and with cross-type scored as one or more 0–1 indicator (dummy) variables. Plots of residuals from the regression equations were visually inspected, and data were transformed as necessary to meet assumptions of regression analysis (e.g., normality of residuals, homogeneity of variances). Tests for slope heterogeneity were performed as required for ANCOVA. Statistical significance of the independent variables was evaluated at the $P < 0.05$ level.

Our analytic procedures and genetic interpretations of the population comparisons were as follows. For each trait, we first tested for differences between the two hybrid groups. A statistical difference between the reciprocal hybrid groups may indicate a maternal effect; i.e., the offspring’s phenotype was associated with the maternal environment. If the hybrids did not differ, then they were combined for subsequent analyses. Only forced sprint speed differed significantly between the hybrids.

Second, we tested for group differences among the lab, pooled hybrid, and wild groups in a three-group comparison. This comparison was the most appropriate test for wild and lab differences because the mean body mass of the hybrids overlapped the body masses of the lab and wild mice. Wild and lab groups were not compared separately because mass showed no overlap between the two groups, thus causing a high correlation between the dummy variable and body mass, leading to problems of multicollinearity. For all analyses involving the lab group, lab mice were coded 0 for all dummy variables. Last, we also compared the pooled hybrids separately with both wild and lab mice to test for directional genetic dominance (see DISCUSSION).

Body mass, age, and time of day at measurement were used as covariates for all traits. Z-transformed time at measurement squared was also used to allow for any nonlinear

association between time and the dependent variable (the Z-transform reduces the correlation between time and time²). Water temperature was used as a potential covariate for analyses of swimming endurance.

RESULTS

Descriptive statistics for the physiological and morphological traits are reported for each group in Table 1; descriptive statistics for voluntary wheel-running behavior are in Table 2. Transformations used for statistical analyses are reported in Tables 3–7; adjusted means from ANCOVA values are also reported in Tables 1 and 2 (reported adjusted means were calculated using all covariates, whether significant or not). The two recipro-

Table 1. Descriptive statistics for traits measured on lab-reared house mice

Traits, U	Wild	Lab	Hybrid	
			Wild dam	Lab dam
Forced sprint speed, m/s				
Mean ± SD	2.88 ± 0.243	1.38 ± 0.247	2.68 ± 0.354	2.47 ± 0.486
Range	2.46–3.30	1.11–2.12	2.14–3.27	1.69–3.30
Adjusted mean	2.71	1.55	2.66	2.38
n	12	19	12	12
Swimming endurance, min				
Mean ± SD	13.2 ± 18.11	15.8 ± 31.27	31.6 ± 42.85	10.1 ± 9.45
Range	0.9–66.8	1.2–131.8	1.1–122.3	0.9–33.8
Adjusted mean	32.3	1.9	14.0	7.7
n	12	19	12	12
VO_{2max}*, ml O₂/h				
Mean ± SD	212.5 ± 42.15	249.4 ± 27.85	247.3 ± 65.53	243.6 ± 38.19
Range	127.7–267.8	197.3–291.1	148.5–201.2	192.7–135.3
Adjusted mean	265.0	202.8	253.2	258.3
n	12	19	11	12
Body mass at VO_{2max}†, g				
Mean ± SD	12.47 ± 1.473	21.68 ± 2.046	16.71 ± 2.646	15.99 ± 1.576
Range	10.31–15.53	17.51–24.98	13.69–20.63	13.16–18.79
Adjusted mean	12.04	21.55	16.37	16.59
n	12	19	12	12
Hematocrit, %				
Mean ± SD	53.3 ± 2.46	51.7 ± 2.36	51.7 ± 1.61	51.8 ± 1.53
Range	49.2–57.5	48.0–56.8	49.2–54.0	49.8–56.8
Adjusted mean	54.3	51.3	51.8	51.3
n	12	17	11	12
Hemoglobin, g/100 ml				
Mean ± SD	17.9 ± 0.82	17.7 ± 0.65	17.3 ± 0.98	17.6 ± 0.77
Range	16.6–19.3	16.4–18.4	16.0–19.0	16.3–19.0
Adjusted mean	18.6	17.2	17.5	17.5
n	12	17	11	12
Ventricle mass, mg				
Mean ± SD	75.3 ± 6.18	104.9 ± 10.31	90.8 ± 13.23	89.1 ± 7.54
Range	66.0–87.0	92.0–128.0	70.0–114.0	80.0–104.0
Adjusted mean	100.4	84.3	88.7	91.4
n	12	17	11	12
Gastrocnemius mass, mg				
Mean ± SD	80.0 ± 6.48	143.6 ± 14.31	118.6 ± 13.55	114.8 ± 12.09
Range	69.0–87.0	120.0–169.0	101.0–143.0	90.0–133.0
Adjusted mean	106.2	115.8	115.8	117.6
n	12	17	11	12
Liver mass, mg				
Mean ± SD	637.6 ± 104.9	1,498.8 ± 246.48	1,060.7 ± 178.00	915.2 ± 153.38
Range	524.0–853.0	1,153.0–2,108.0	796.0–1,430.0	690.0–1,099.0
Adjusted mean	1,011.5	1,033.1	988.1	992.6
n	12	17	11	12

Descriptive statistics for voluntary wheel running are reported in Table 2. Adjusted means are from 4-group analysis of covariance (ANCOVA) comparisons, adjusted for all covariates whether significant or not. *Reported VO_{2max} values were corrected for washout characteristics of respirometry system (1, 22; see text). †Body mass adjusted for age (45.1 ± 7.33 days), time at measurement, and squared time at measurement.

Table 2. Descriptive statistics for voluntary wheel-running behavior on day 7 of a 7-day test

Trait	Wild	Lab	Hybrid	
			Wild dam	Lab dam
Total revolutions/24 h				
Mean ± SD	11,404 ± 4,441	7,100 ± 3,309	11,475 ± 5,609	12,029 ± 5,998
Range	3,042–19,338	2,715–12,377	1,970–20,375	740–21,500
n	12	17	12	12
No. 1-min intervals of running/24 h				
Mean ± SD	456 ± 89.7	467 ± 106.0	470 ± 115.6	455 ± 159.8
Range	294–582	262–656	263–607	130–646
Adjusted mean*	454	468	468	457
n	12	17	12	12
Average running rpm				
Mean ± SD	24.3 ± 6.34	15.0 ± 6.10	23.0 ± 7.88	25.0 ± 8.45
Range	10.4–34.8	8.4–27.6	7.0–34.5	5.7–37.0
n	12	17	12	12
Maximum revolutions/1-min interval				
Mean ± SD	36.5 ± 7.98	25.5 ± 7.44	34.3 ± 7.77	36.3 ± 9.73
Range	25–53	16–41	21–46	16–50
n	12	17	12	12

* Adjusted for wheel resistance, the only significant covariate.

cal hybrid groups did not differ significantly for any trait except forced sprint running speed (see below), so we do not report statistics for this comparison for the other traits.

Figure 1A suggests a negative relationship between body mass and forced sprint running speed; however, body mass was not significantly correlated with sprint speed within any of the four groups. We therefore report the analyses both with and without body mass as a covariate (Table 3). With body mass included as a covariate, both wild (+52.4%) and hybrid (wild dam: +61.7%; lab dam: +44.9%) mice had significantly higher sprint speeds than lab mice (Table 3). Dropping body mass as a covariate did not alter the conclusions; both wild and hybrid mice were substantially faster than the laboratory mice. Squared time at measurement was also significant with a positive slope ($b = 0.14$), suggesting a nonlinear effect on sprint speeds, which were measured between 1100 and 1900 CST.

Hybrid mice from wild dams had significantly higher sprint speeds than hybrids from lab dams (ANCOVA with body mass: $F = 6.134$, $df = 1,18$, $P = 0.0217$;

ANCOVA without body mass: $F = 7.320$, $df = 1,19$, $P = 0.0140$). Thus a maternal effect on sprint speed was evident. For ANCOVA including body mass, the only other significant covariate was squared time at measurement ($b = 0.27$, $F = 10.345$, $df = 1,19$, $P = 0.0048$). For ANCOVA excluding body mass, time ($b = 0.19$, $F = 8.703$, $P = 0.0082$, $df = 1,19$) and squared time ($b = 0.30$, $F = 11.954$, $P = 0.0026$, $df = 1,19$) at measurement were both significant.

Figure 1B shows a general lack of correlation between swimming endurance times and body mass. Log-transformed endurance times were not significantly correlated with log body mass within either the wild ($r = 0.10$, $P = 0.764$) or the lab ($r = 0.16$, $P = 0.520$) group; however, correlations were significantly positive within both hybrid groups (wild × lab $r = 0.66$, $P = 0.018$; lab × wild $r = 0.72$, $P = 0.004$). Tests for heterogeneity of slopes found no significant differences among groups. Therefore we analyzed swimming endurance both with and without body mass as a covariate. ANCOVA with body mass as a covariate indicated that both wild and (pooled) hybrid mice had greater swimming endurance times than lab mice (Table 4). Also, hybrid mice tended to have lower endurance times than wild mice ($F =$

Table 3. Analysis of covariance comparing lab vs. wild and vs. hybrid mice for forced sprint speeds

Source of Variation	Mass Included			Mass Not Included		
	df	F	P	df	F	P
Group (Wild)	1	10.802	0.0019	1	103.530	<0.0001
Group (Wild dam hybrids)	1	41.234	<0.0001	1	105.882	<0.0001
Group (Lab dam hybrids)	1	18.274	0.0001	1	52.098	<0.0001
Log ₁₀ body mass	1	4.573	0.0377			
Age	1	3.212	0.0796	1	1.007	0.3207
Time at measurement	1	0.567	0.4553	1	1.460	0.2329
Time at measurement ²	1	5.816	0.0198	1	4.764	0.0340
Model	7	33.974	<0.0001	6	36.181	<0.0001
Residual	47			48		

Table 4. Analysis of covariance comparing lab vs. wild and vs. pooled hybrid mice for log₁₀ swimming endurance

Source of Variation	Mass Included			Mass Not Included		
	df	F	P	df	F	P
Group (Wild)	1	6.565	0.0137	1	0.193	0.6621
Group (Pooled hybrids)	1	9.157	0.0040	1	0.961	0.3318
Log ₁₀ body mass	1	9.761	0.0031			
Age	1	0.145	0.7046	1	0.652	0.4232
Time at measurement	1	0.003	0.9596	1	0.596	0.4441
Time at measurement ²	1	0.586	0.4477	1	0.880	0.3528
Water temperature	1	0.006	0.9400	1	0.008	0.9299
Model	7	1.851	0.0995	6	0.451	0.8410
Residual	47			48		

Table 5. Analysis of covariance comparing lab vs. wild and vs. pooled hybrid mice for $\dot{V}O_{2\max}$ and ventricle mass

Source of Variation	$\dot{V}O_{2\max}$			Ventricle Mass		
	df	F	P	df	F	P
Group (Wild)	1	1.567	0.2167	1	8.733	0.0050
Group (Pooled hybrids)	1	5.870	0.0192	1	5.901	0.0193
Body mass	1	8.828	0.0046	1	91.043	<0.0001
Age	1	0.562	0.4573	1	2.180	0.1469
Time at measurement	1	2.454	0.1238	1	0.004	0.9509
Time at measurement ²	1	0.567	0.4553	1	0.136	0.7141
Model	6	4.930	0.0005	6	58.932	<0.0001
Residual	48		44			

3.854, df = 1,29, P = 0.0593). As indicated from the regression equations (using all covariates, and using the overall mean \log_{10} body mass of 1.234), wild mice were predicted to swim for ~32 min, hybrids for ~8–14 min, and lab mice for only 2 min. However, absolute swimming times of mice from the different groups overlapped completely (Fig. 1B), and in a previous study of 297 ICR mice (of both sexes) we found no significant relationship between log swimming times and log body mass ($F = 0.668$, $P = 0.4143$, df = 1,294; unpublished results). Omitting body mass as a covariate, ANCOVA indicated that the lab mice did not differ significantly from the wild or pooled hybrid mice (Table 4). Therefore we are somewhat undecided as to the significance of group differences.

Figure 2 shows the expected positive relationship between $\dot{V}O_{2\max}$ and body mass. Compared with the instantaneously corrected values shown in Fig. 2, steady-state values (not shown) averaged $6.41 \pm 3.318\%$ (SD) lower for the 1st trial day, $8.83 \pm 4.645\%$ lower for the 2nd trial day, and $8.44 \pm 4.409\%$ lower for the higher of the two trials. The correlation between the instantaneously corrected and steady-state values was 0.97. Our basic conclusions hold regardless of which value is analyzed; therefore, unless otherwise indicated, we report results for the instantaneously corrected values only.

Both wild (+18.5%) and hybrid (+21.0%) mice tended to have higher mass-corrected $\dot{V}O_{2\max}$ than lab mice (Fig. 2; Table 5), although the difference between wild and lab mice was not statistically significant (Table 5). However, wild and hybrid mice had similar $\dot{V}O_{2\max}$ values (2-group ANCOVA main effect: $F = 0.042$, df = 1,30, $P = 0.8390$;

body mass: $F = 4.796$, df = 1,30, $P = 0.0364$). When wild mice were pooled with both hybrid groups, they had significantly higher (+22%) $\dot{V}O_{2\max}$ than the lab mice ($F = 7.442$, df = 1,48, $P = 0.0089$). We conclude, therefore, that the magnitude of the difference between wild and lab mice should also be considered significant. Furthermore, steady-state $\dot{V}O_{2\max}$ values of lab and wild mice differed significantly in the three-group ANCOVA ($F = 4.770$, df = 1,48, $P = 0.0339$).

Wild (+18.4%) and hybrid (+6.1%) mice had significantly larger ventricles for their body mass than lab mice (Fig. 3; Table 5). As indicated in Table 6, we found no statistically significant group differences for gastrocnemius muscle mass, liver mass, or hematocrit or blood hemoglobin content (Fig. 4).

Mice from all cross groups exhibited a temporal trend for increasing total activity on the running wheels (Fig. 5). Figure 5 also indicates that after the first 2 days with access to wheels, both wild and hybrid mice consistently ran more total revolutions per day than did lab mice. Considering only day 7, both wild and hybrid mice ran at higher average revolutions per minute while active and showed higher maximum numbers of revolutions in any single 1-min period (Fig. 6; Tables 2 and 7). Note that the comparison of wild and lab mice for total revolutions run on day 7 was not statistically significant. However, because hybrid and wild mice showed similar values for total revolutions (2-group ANCOVA: $F = 0.028$, df = 1, 31, $P = 0.8686$), we conclude that the magnitude of difference between wild and lab mice for total revolutions on day 7 should also be regarded as significant. Importantly, wild, hybrid, and lab mice did not differ for the amount of time on the running wheels, as indicated by the number of 1-min intervals per day during which any running occurred (Table 7). Wild and hybrid mice also did not differ in the number of 1-min intervals active per day ($F = 0.123$, df = 1,31, $P = 0.7280$), average revolutions per minute of activity ($F = 0.313$, df = 1,31, $P = 0.5798$), or the maximum number of revolutions in any single 1-min interval ($F = 0.495$, df = 1,31, $P = 0.4870$).

DISCUSSION

Domestication involves both evolutionary (genetic) and physiological adaptation to laboratory conditions that differ in many ways from natural environments (3, 30). Laboratory strains of small mammals, for example,

Table 6. Analysis of covariance comparing lab vs. wild and vs. pooled hybrid mice for \log_{10} gastrocnemius muscle mass, \log_{10} liver mass, hematocrit, and blood hemoglobin content

Source of Variation	\log_{10} Gastrocnemius Muscle Mass			\log_{10} Liver Mass			Hematocrit			Blood Hemoglobin Content		
	df	F	P	df	F	P	df	F	P	df	F	P
Group (Wild)	1	1.866	0.1787	1	0.041	0.8404	1	1.634	0.2077	1	2.714	0.1065
Group (Pooled hybrids)	1	0.036	0.8512	1	1.303	0.2596	1	0.015	0.9023	1	0.464	0.4991
\log_{10} body mass	1	60.549	<0.0001	1	113.514	<0.0001	1	1.246	0.2702	1	1.555	0.2188
Age	1	0.327	0.5700	1	0.027	0.8713	1	5.567	0.0227	1	0.174	0.6782
Time at death	1	0.186	0.6681	1	18.872	0.0001	1	6.578	0.0137	1	4.845	0.0329
Time at death ²	1	0.126	0.7242	1	2.825	0.0997	1	0.283	0.5975	1	0.665	0.4190
Model	6	102.674	<0.0001	6	164.081	<0.0001	6	2.857	0.0192	6	1.653	0.1548
Residual	45			45			45			45		

Table 7. Analysis of covariance comparing lab vs. wild and vs. pooled hybrid mice for voluntary wheel running on day 7 of a 7-day test

Source of Variation	Total Revolutions			Total Number of Intervals Active			Average Revolutions Per Minute			Maximum Revolutions Per Minute		
	df	F	P	df	F	P	df	F	P	df	F	P
Group (Wild)	1	2.860	0.0974	1	0.032	0.8583	1	4.503	0.0391	1	4.904	0.0317
Group (Pooled hybrids)	1	7.235	0.0099	1	0.350	0.5571	1	9.248	0.0038	1	8.629	0.0051
Log ₁₀ body mass	1	0.910	0.3451	1	0.609	0.4392	1	0.625	0.4331	1	0.495	0.4850
Age	1	0.105	0.7477	1	3.511	0.0672	1	0.307	0.5819	1	0.602	0.4418
Wheel resistance	1	2.307	0.1355	1	6.647	0.0131	1	0.674	0.4156	1	0.001	0.9701
Model	5	2.783	0.0278	5	2.298	0.0600	5	3.900	0.0049	5	3.994	0.0042
Residual	47			47			47			47		

are thought to have faced relaxed selection related to thermoregulation (25, 31, and references therein). Similarly, we might expect that laboratory mice have faced relaxed selection for exercise abilities. Using a common garden experimental design that controlled for possible effects of acclimatization, we found that genetically variable, random-bred laboratory mice of the ICR strain did indeed have lower forced maximal sprint running speeds, possibly lower swimming endurance, and lower $\dot{V}O_{2\max}$ during forced exercise, and exhibited less voluntary running on activity wheels than wild mice from a Wisconsin population. Consistent with these differ-

ences, the laboratory mice also had smaller ventricles, although they showed no reduction in relative gastrocnemius muscle mass, liver mass, hematocrit, or blood hemoglobin content.

Of the traits we studied, the greatest differences between lab and wild mice were for aspects of voluntary wheel-running behavior and for forced sprint speed. Over a 7-day test, wild mice ran significantly more total revolutions, ran at higher average velocities when they were active, and attained higher maximal numbers of revolutions in any single 1-min period than did lab mice. Wild, hybrid, and lab mice did not differ, however, in terms of the number of 1-min intervals per day during which any running occurred. Therefore, the difference in total revolutions run during a 24-h period can be attributed to the higher average running speeds of the wild and hybrid mice relative to the lab mice during bouts of activity on the wheels. By day 7, the differences in the amount of running on the wheels were substantial; wild and hybrid mice ran, on average, almost 12,000 revolutions, whereas lab mice ran only $\sim 7,000$ revolutions (Fig. 5). Clearly, the random-bred ICR lab mice are behaviorally different from wild mice.

Forced sprint running speeds of lab mice averaged $\sim 50\%$ lower than those of wild or hybrid mice, and the distributions of individual values for lab and wild mice did not overlap (Fig. 1A, Table 3). Whether differences in

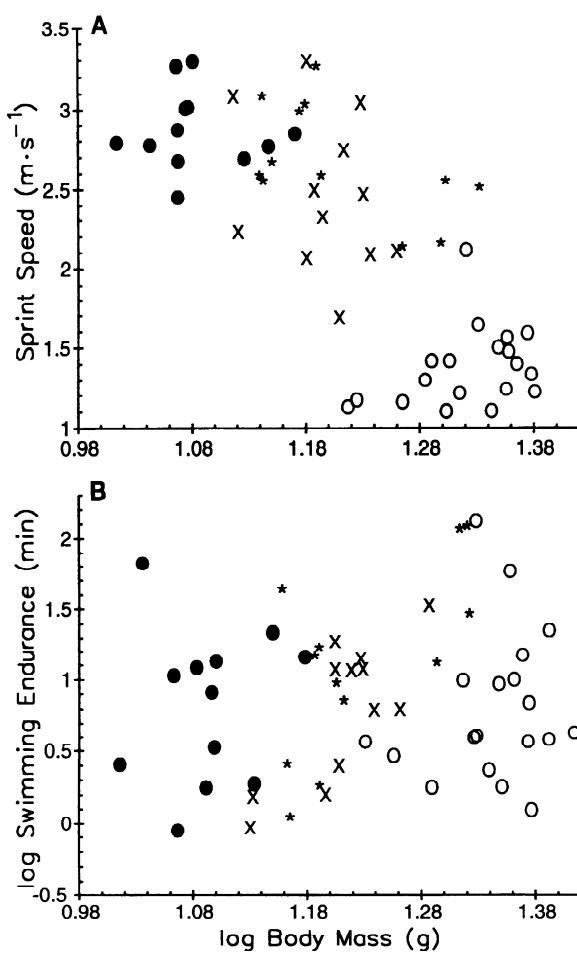


Fig. 1. *A:* scattergram of forced sprint speed vs. \log_{10} body mass in lab (\circ), wild (\bullet), and hybrid (wild dam, $*$; lab dam, \times) house mice. *B:* scattergram of \log_{10} swimming endurance vs. \log_{10} body mass in house mice (symbols as in *A*).

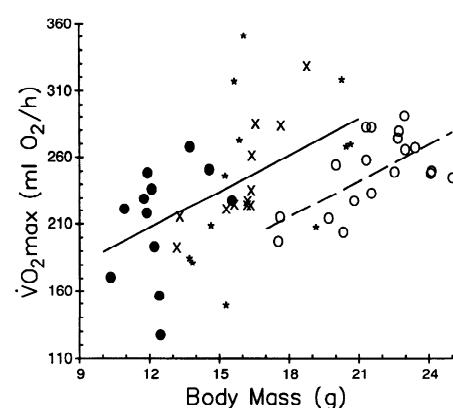


Fig. 2. Scattergram showing relationship between maximal oxygen consumption ($\dot{V}O_{2\max}$) during forced treadmill exercise and body mass in lab and wild house mice and their reciprocal hybrids (symbols as in Fig. 1). $\dot{V}O_{2\max}$ values were corrected for chamber washout characteristics (see text). Regression lines represent pooled within-groups slope from an analysis of covariance comparing pooled wild and hybrid with lab mice; $\dot{V}O_{2\max}$ of the former averages $\sim 22\%$ higher than for lab mice.

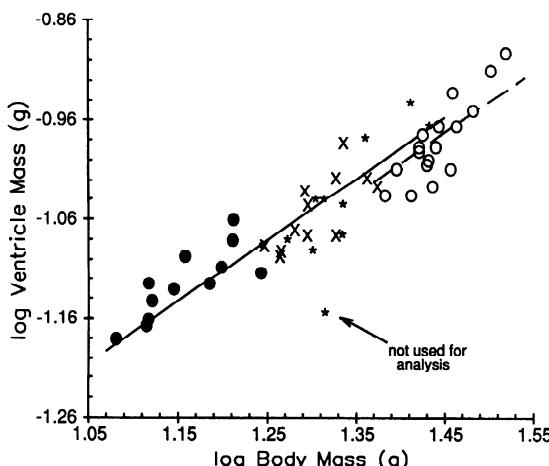


Fig. 3. Scattergram of \log_{10} ventricle mass vs. \log_{10} body mass in lab and wild house mice and their reciprocal hybrids (symbols as in Fig. 1). Regression lines represent pooled within-groups slope from an analysis of covariance comparing pooled wild and hybrid with lab mice; on an arithmetic scale, ventricles of the former average ~12% heavier than those of lab mice.

sprint speed, as measured here, represent behavioral differences, physiological differences, or both, is unclear (11, 16, 20). We found no significant differences in gastrocnemius muscle mass among groups, even though in a previous study involving >300 ICR mice (of both sexes) we found a slight, but significant, positive relationship between individual differences in sprint speed and relative gastrocnemius muscle mass (unpublished results).

Lab mice may also have lower swimming endurance times than wild or hybrid mice, at least if apparent mass effects are included in the statistical comparison (Table 4). However, absolute swimming times of mice from the different groups showed complete overlap (Fig. 1B). Moreover, we found no significant relationship between swimming times and body mass in a previous study of nearly 300 ICR mice (range of body mass 17.6–36.0 g). Given the foregoing, we are unable to conclude with confidence whether significant group differences exist for swimming endurance.

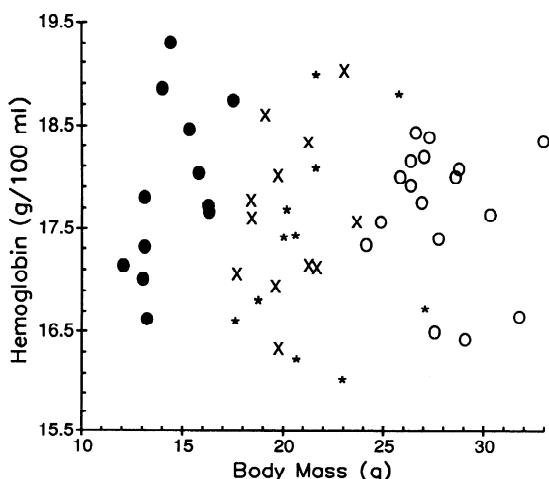


Fig. 4. Scattergram of blood hemoglobin content vs. body mass in lab and wild house mice and their reciprocal hybrids (symbols as in Fig. 1).

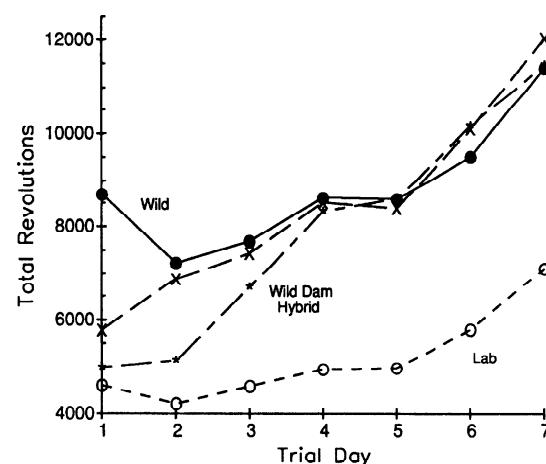


Fig. 5. Mean total number of revolutions run in 24 h by lab and wild house mice and their reciprocal hybrids during a 7-day test on voluntary activity wheels (diameter 35.5 cm). Symbols as in Fig. 1.

Maximal rates of $\dot{V}O_2$ during forced exercise averaged ~1.5 times the maximal rate of NST and 10 times that of BMR values measured on these same mice (31). Our mass-specific values for exercise-induced $\dot{V}O_{2\max}$ were comparable to those reported by Pasquis et al. (28) for wild and albino lab mice (unspecified strain) when either exercise or cold was used to induce $\dot{V}O_{2\max}$, and they were greater than values obtained when He-O₂ mixtures were used to induce cold exposure in both wild and lab strains of mice (34).

Considered together, both wild and hybrid mice had statistically higher $\dot{V}O_{2\max}$ rates during a treadmill step-test than did the lab mice. Similarly, wild and hybrid mice had relatively larger ventricles than did the lab mice. However, the magnitude of the differences between wild and lab mice for both of these traits was relatively small, and the extent of overlap between groups in the distributions (Figs. 2 and 3) suggests that aerobic capacity has not “degenerated” greatly in the random-bred ICR strain. Similarly, the magnitude of differences between wild and lab mice for BMR and NST

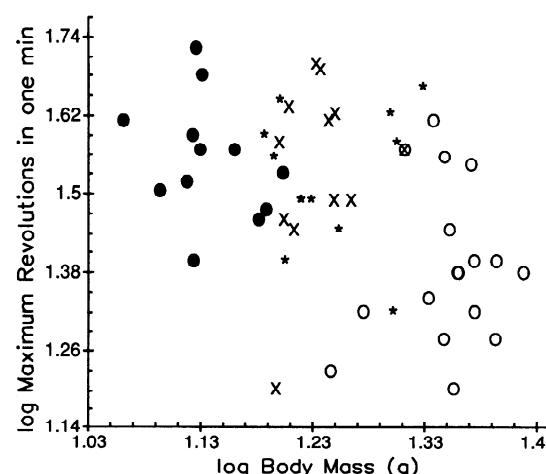


Fig. 6. Log₁₀-log₁₀ scattergram of maximum number of revolutions run during any 1-min interval on day 7 of a 7-day test on voluntary activity wheels (symbols as in Fig. 1).

was small, indicating that the thermogenic capacity of laboratory mice has not decreased substantially (31).

Clear and significant differences between wild and lab mice were found for forced sprint speed, average and maximal voluntary running speeds on the wheels, and relative ventricle mass. We also conclude that differences between lab and wild mice exist for "instantaneously corrected" $\dot{V}O_{2\max}$ (Table 5) and for total revolutions run on the running wheels (Table 7), although for neither trait were the differences between wild and lab mice statistically significant at the $P < 0.05$ level. The lack of significance for the wild vs. lab comparison, in contrast to the significance of the pooled hybrid vs. lab difference, is attributable to the approximately twofold higher sample size of the pooled hybrid group compared with the wild group. Our conclusion that real differences between wild and lab mice exist is warranted, because 1) the wild and hybrid mice in our study differed from the lab mice by similar magnitudes, and 2) the differences between pooled hybrid and lab mice were statistically significant. Also, the steady-state $\dot{V}O_{2\max}$ values of lab and wild mice did differ significantly, suggesting that the instantaneous correction introduced additional error variance.

The lab and wild mice used in this study differed substantially in body mass. Thus differences in body mass may confound our interpretation of the differences in other traits. We were, however, able to test for group differences using ANCOVA, because the body masses of the hybrid mice overlapped those of both wild and lab mice (see Figs. 1–4 and 6). As noted in the results, we found no evidence to suggest that the relationship between body mass and the other traits differed significantly among the cross groups. We do not have data for lean body mass because tissues were needed for allozyme determination. For several reasons, however, a simple difference in lean body mass cannot be a general explanation for the differences observed in this study. First, the ICR mice were not found to be noticeably fatter during dissection; thus, if a difference exists, it is likely to be small. Larger differences in percent body fat might occur in older mice, but all of our lab mice were <3 mo old when killed. Second, inspection of Fig. 2 indicates that for body fat to account for the difference in $\dot{V}O_{2\max}$, the lab mice would have to contain ~ 5 g of additional body fat for a mouse of ~ 21 g total mass. Moreover, the $\dot{V}O_{2\max}$ values obtained for our lab mice fall well within the range expected for small mammals of this body mass. Small differences in lean body mass might account for the statistically significant difference in relative ventricle mass between groups. However, no group differences were found for gastrocnemius mass and liver mass, which should have been affected similarly by a difference in body fat.

Genetically based differences between lab and wild mice for such traits as speed, endurance, and $\dot{V}O_{2\max}$ are most likely caused by differences at multiple gene loci (12). On the other hand, a link between low activity in the open field and the albino locus (*c*) in strains of laboratory mice has been documented in some detail (9, 10, 27, and additional references in 29). For example,

the albino locus increased in frequency in response to selection for low activity levels in the open field while being eliminated in two lines selected for high activity (9). The effect of the albino locus on activity seems to be pleiotropic (i.e., not due to linkage with other loci) and probably is mediated through the visual system (10, 27). Interestingly, albino and pigmented mice did not differ in open-field activity levels measured under red light (10).

Our forced sprint speed trials were conducted under normal levels of white-light illumination; thus pleiotropic effects at the albino locus may account in part for the lower sprint speeds of the lab mice. It seems unlikely, however, that the albino locus mediates differences for voluntary wheel running, at least in the manner described for open-field activity (9, 10, 27), because both wild and lab mice were primarily active during the scotophase. The extent to which the albino locus may account for differences between lab and wild mice in $\dot{V}O_{2\max}$, relative ventricle mass, possibly swimming endurance, or NST (see 31) is unknown.

When hybrid individuals exhibit phenotypes intermediate to those of their parents (e.g., wild or lab mice in the present study), the alleles affecting the phenotype are interpreted to be additive in their effects. If, on the other hand, hybrids resemble one or the other parent, then directional dominance (nonadditive genetic interactions within loci) is interpreted to be present at some or all of the loci affecting the trait. For most of the traits that differed between lab and wild mice, hybrid mice displayed values similar to wild mice, suggesting that alleles present in the wild mice tend to show dominance in the direction of higher activity or physiological capacities. A possible exception to this general pattern is swimming endurance, in which the hybrid values tended to be intermediate to those of the parents, if body mass is used as a covariate in the analysis (see Fig. 1B and Table 4).

Directional selection on a polygenic trait should increase the number of dominant alleles for a trait in the direction of increasing fitness (5, 12, 25). Thus the presence and direction of dominance may indicate the direction of past selection. If so, then the wild mice we studied may have experienced directional selection for high activity (as indicated by the running wheel tests), high sprint speed, high $\dot{V}O_{2\max}$, large ventricles, and possibly high swimming endurance. [Interestingly, Brueell (5) also documented substantial directional dominance for high voluntary wheel running in a study of inbred strains of mice.] These results are consistent with the idea that wild mice have generally faced directional selection for enhanced locomotor abilities, perhaps as related to foraging, dispersal, or escape from predators. Lab mice, on the other hand, may have faced relaxed selection for such traits. The foregoing arguments must be taken with caution, however, because the breeding design employed here cannot rule out the possibility of additional sources of nonadditive genetic effects, such as epistasis.

Differences between the two reciprocal hybrid groups (wild dam vs. lab dam) would be indicative of maternal

effects. Cytoplasmic inheritance, intrauterine effects, and behavioral or physiological (e.g., milk production) differences associated with maternal care can all affect the development of physiological traits (8). For the mice studied here, the only evidence we found for potential maternal effects was for sprint speed and BMR (see Ref. 31), and we have no information bearing on their origin. Hybrid offspring from wild dams had higher forced sprint speeds and lower BMR values than did hybrid offspring from lab dams.

Several authors have proposed that, in response to the altered selection caused by domestication, behavioral traits should respond first or at least more rapidly than associated traits at lower levels of biological organization (30 and references therein). Our results are generally consistent with this idea, because the magnitude of differences between lab and wild mice was greater as a whole for the behavioral than for the physiological traits. Behavioral differences between wild and domestic house mice have been reported many times, with wild mice consistently showing higher activity levels than lab mice in a variety of behavioral tests (e.g., 7, and reviews in Refs. 29, 30).

Our study was motivated initially by empirical observations that wild house mice tested within a few days of capture showed substantially higher sprint speeds than laboratory mice (see below). Because mammalian exercise physiology is relatively plastic and responds to physical conditioning (4), differences between field-fresh wild mice and lab mice could be environmentally based, genetic, or both. Wild mice, because of the need to forage, must generally be more active than lab mice, which typically are restricted to small cages. Thus field-fresh wild mice could have higher exercise capacities because they are more active and hence in a "naturally trained" state (19 and references therein).

Our common garden experimental design reduced the likelihood that differences between wild and lab mice could be caused by differences in activity, but it did not eliminate this possibility (see also Ref. 17). We did not measure activity of the wild and lab mice in their cages, and so we cannot absolutely rule out training effects as the cause of differences between lab and wild house mice. Given the small size of the housing cages, however, we consider it unlikely that differences in activity levels alone could account for our results. As a further check, we also measured the forced sprint speeds of 19 wild mice of both sexes, from the same Wisconsin population, within 2 days of capture. The mean value for these mice [3.17 ± 0.246 (SD), range 2.77–3.64 m/s; no significant difference between sexes; mean mass = 14.40 g] was not significantly different from the mean value for the 12 wild mice born and raised in captivity (see Table 1).

Comparisons such as those presented here may be useful for predicting the outcome of artificial selection experiments. For example, as noted above, common sense suggests that wild animals, including house mice, have generally been selected for high levels of physical fitness. Domestic forms, and especially laboratory forms, on the other hand, should have experienced relaxed

selection for exercise capacities. Thus, if one were to select artificially a laboratory form for high exercise abilities, a reasonable prediction would be that a selection limit might eventually be reached that would correspond roughly with the levels of performance exhibited by the wild form (cf. Refs. 18 and 25). Our laboratory is currently conducting such experiments.

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