Box 13.3 Genetics and Genomics
Artificial Selection of House Mice

For hundreds of years, humans have used artificial selection to tailor the locomotor physiology of animals to suit our needs for agricultural animals and sports. For instance, thoroughbred horses and greyhounds, both remarkable runners, are the products of centuries of artificial selection. Only recently have researchers designed artificial selection experiments specifically to explore the mechanisms by which locomotor systems evolve, exploring the links between physiological systems.

In the early 1990s, Ted Garland set up a long-term selection experiment with house mice, with the goal of exploring the evolution of aerobic exercise levels. Each mouse was given free access to a running wheel, with the number of revolutions monitored by computer. Mice that ran the furthest were allowed to become the parents for the next generation. After only 16 generations of such selection, the selected mice typically ran about 2.7 times further and twice as fast as randomly bred controls. Although the initial focus of the experiment was on the respiratory and musculoskeletal systems, these studies also revealed how other physiological systems coevolved with activity levels, often in surprising ways.

The goal of these selection studies was to assess relationships between locomotor propensity and ability. The characteristic used as the basis of selection was a behavioral trait: how much mice ran of their own free volition. The reason for the variation in voluntary running among individual mice in the original population remains unclear. More active individuals may have a greater sensitivity to the positive, euphoric benefits of running or alternatively, a lower sensitivity to the negative, painful effects of prolonged activity. In any case, several other behavioral traits correlated with the voluntary activity levels. Mice in the selected lines showed much greater levels of aggressive predatory behavior toward crickets. Subsequent studies showed that the region of the brain that controls predatory behavior, the lateral hypothalamus, was also more active in the selected mice. The underlying differences in CNS activity were reflected in the response to neuropharmacological agents. When mice from each of the lines were injected with Ritalin, a drug used to reduce hyperactivity in children, the differences between lines greatly diminished. Although the researchers recognized that the variation in voluntary activity levels was ultimately attributable to the motivation to run, the selection experiments also provide insight into the underlying locomotor physiology required to support high levels of aerobic activity. Although the *impetus* to run may reflect processes in the central nervous system, the *ability* to run is met by the locomotor physiology, in association with other physiological systems.

If you examined two closely related species that differed in activity levels, it would be reasonable to predict differences in indices of exercise performance and muscle metabolism. Surprisingly, the selected and control mice were indistinguishable in terms of basal metabolic rate, maximal respiratory rate (V_{max}), maximal sprint ve-

locity, or endurance capacity. Selected mice had differences in some respects: muscle glucose transport, bone dimensions, heat shock protein expression, and liver antioxidant capacities. Also, the activities of the mitochondrial enzymes that support muscle energy metabolism were somewhat higher in muscles of selected animals. At first, it was unclear which of these differences between the selected and control lines were due to genetic variation versus simple training effects. For example, were the mitochondrial enzymes higher in the selected animals because their muscles had been remodeled in response to the higher activity levels? This question was resolved in an experiment where mice were prevented from running. Under these conditions, the selected lines maintained higher enzyme activities than the control lines. This is one indication that real genomic differences, as opposed to training effects, underlie the variations seen in muscle physiology between lines.

One of the most interesting findings from these selection studies was the variability among replicate lines. When the experiments began in the early 1990s, the researchers first divided the mice into eight populations, resulting in four selected for high running and four bred randomly to serve as control lines. While the selected lines evolved similar levels of voluntary wheel running, the replicate lines differed in several ways. For example, two of the four lines of selected mice showed a high frequency of small gastrocnemius muscles. These "mighty minimuscles" had the same enzyme capacity of a larger muscle packed into a smaller muscle that is more resistant to fatigue. The minimuscle phenotype was rare in all four control lines and two of the selected lines. The gene(s) responsible for this unusual phenotype remain unknown, but the difference among lines reveals two important concepts in evolutionary physiology. First, genetic variation within populations represents a pool of alternate solutions to problems not yet encountered. The minimuscle phenotype was relatively rare in the original populations, and only underwent positive selection in the context of this experiment. However, it is not difficult to imagine how a change in the natural environment could also reward this phenotype of a smaller, more fatigue-resistant muscle. Second, these studies illustrate that genetically similar (though not identical) animals can solve physiological challenges in different ways.

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