the private equity firms home in on management controls and invest in R&D during the holding period—evidence, says Lerner, that the goal is to make companies not just leaner, but better organized.

Sometimes this entails cutting jobs, he notes, but the notion of buyout firms taking an ax to employment rolls doesn't hold water. In fact, the study found that companies were more likely to cut back in the two years *before* a buyout; takeover targets had 4 percent lower job growth than similar firms that were not bought out. In the two years following a buyout, the targeted corporations did cut jobs—7 percent more than comparable firms—but they added employment in other U.S. locations. In fact, new facilities opened by the bought-out companies grew 6 percent *faster* than comparable firms in terms of jobs created. (The study did not look at jobs created outside the United States, and did not count them as offsetting domestic shrinkage.) "Buyouts," says Lerner, "increase the pace of 'creative destruction'—the pace of job creation and destruction both accelerate."

News accounts mostly cover public-to-private deals, partly because investors care about companies in which they hold stock, and partly because public companies are easier to cover due to the financial statements they must file. But the average buyout involves a private, rather than public, company; Lerner and his colleagues found that the vast majority of the deals in their database—more than 93 percent—affected companies that were not publicly held. Even accounting for the fact that the public-to-private transactions typically involve bigger companies, such transactions were less than 30 percent of the total by value.

The study also found that quick flips (companies that went public again less than a year after a buyout) make headlines—but the average holding time was far longer. Lerner's study found that only 12 percent of the private-equity firms exited within two years; 58 percent took more than five years to exit. Another headline-grabbing situation, the company that collapses in the wake of a buyout, is also not the norm. Among firms that were bought out, the five-year failure rate—6 percent—was actually *lower* than the rate for all U.S. companies that issue public debt.

Although Lerner teaches a course on venture capital and private equity, and has spent much of his career studying those sectors, he says even he was surprised by the findings. "If you read something in a business magazine a hundred times," he says, "you sort of begin believing it."

—ELIZABETH GUDRAIS

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CHAPERONING GENETIC CHANGE

What Stress Reveals

Evolution, the fossil record shows, sometimes proceeds in sudden leaps. Millions of years of stasis can end abruptly with multiple changes in forms and functions. To distinguish this evolutionary process from Darwin's gradualism, the late Harvard professor Stephen Jay Gould famously described it as "punctuated equilibrium." (Gould's detractors, he was fond of pointing out, called it "evolution by jerks.") But one of the great scientific challenges of punctuated equilibrium has been explaining how—if mutations are random—multiple, interdependent mutations can occur all at once, giving the appearance of coordination.

A living example of this mystery is found in monkey flowers from the Rocky Mountains, explains Radcliffe Institute fellow Susan Lindquist, Ph.D. '77, a professor of biology at MIT. One form of the plant has a long trumpet suited to pollination by hummingbirds; the other, with a conventionally shaped flower, is pollinated by bumblebees. The two forms don't interbreed in nature, but scientists can pollinate the plants by hand to generate hybrid offspring. The offspring aren't likely to do well in the wild, though, says Lindquist: because they "don't have the right genes coming together," they are not easily pollinated by bumblebees *or* hummingbirds.

How *do* four or five different changes, which work together, happen simultaneously—in evolutionary time, in an individual organism—when having only two or three of those changes generates functions and forms that don't survive? Lindquist, a Howard Hughes investigator, has discovered and elucidated during the last decade an extraordinary molecular mechanism that allows organisms to do precisely this—by revealing during times of stress the accumulated genetic variation lying dormant in their genomes. Selective pressures such as heat or drought, she has shown, then act upon the revealed variation, so the mutant organisms best adapted to the new stress become widespread and the beneficial traits they carry become enriched and subsequently fixed in a population.

Lindquist stumbled into evolutionary biology by accident. As a graduate student at Harvard, she began studying the stress, or "heat-shock," response in yeast. "If you take a cell doing one thing," she says, "and expose it to high temperature, it immediately switches on a new set of genes." At the time, biologists didn't understand how cells did this. Eventually, however, they were able to connect what was happening at the level of the gene (a

DOUGLAS SCHEMSKE

One form of the Rocky Mountain monkey flower has a long trumpet suited to pollination by hummingbirds; the other is pollinated by bumblebees. Their hybrid offspring don't do well in the wild, however, because they are not easily fertilized by the birds or the bees.

TODD SANGSTER

Inhibiting a "protein chaperone" in the cress plant, *Arabadopsis thaliana,* mimics the effect of an environmental stress, revealing the hidden variation in the plant's genome. On the left, the unmodified control plant; on the right, a mutant reveals succulent-like characteristics.

unit of DNA that codes for a protein) to the different kinds of proteins cells make.

"The code for life—DNA—is linear," explains Lindquist. "It is like a tape; it doesn't do anything interesting by itself. But when you put it in a tape recorder and press 'PLAY,' music comes out." Similarly, proteins, when first made, appear as long, linear strings of amino acids. "But they do nothing when they are linear," Lindquist notes. In order to perform their functions, they must fold into complicated shapes. For example, hemoglobin, which carries oxygen in the blood, must fold properly in order to bind the iron groups that then bind to oxygen. If a protein's long string of amino acids doesn't fold just right, it won't bind to its targets.

Just as there are mutations in DNA, so there are situations in which proteins misfold, or fold only partially. That is where protein chaperones, Lindquist's particular area of expertise, step in. The chaperone's job is to "keep other proteins out of trouble while they are still immature and haven't finished folding properly," a condition in which they might "make inappropriate liaisons with other proteins," she says. A protein chaperone called HSP90 (heat-shock protein 90) plays a key role in the stress response.

HSP90 regularly works on a small but critical subset of proteins called signal transducers, which are involved in cell growth and development. It binds to these proteins in their vulnerable, unfolded state, keeping them neutralized and latent, but safe, until the right signal—from a hormone, for example—comes along, at which point the HSP90 releases them so they can bind to their proper targets.

But HSP90 plays another role, as well: it rescues mutant proteins. Many proteins fold just fine without chaperones. But when there is a mutation, the resulting protein often doesn't fold properly and becomes relatively unstable. HSP90 binds to such unstable proteins, allowing them to survive in a latent state in which the genetic variation they represent is neutralized rather than physically manifested. Major environmental stress, such as heat or drought, however, produces so many unfolded proteins that they can overwhelm HSP90's buffering capacity, which simultaneously reveals numerous mutations that have accumulated over generations.

Lindquist first observed this effect a decade ago when she genetically inhibited HSP90 production in fruit flies. A few of them developed malformed wings, legs, or bristles. Given the protein's important role in cellular circuity, this was not surprising. "But what was interesting about it," she reports, "was that,...depending on where we had gotten the flies, they had different kinds of morphologies. Flies from England had funny-looking legs. Flies from California had funny-looking eyestalks." The Lindquist lab's tinkering had not randomly interfered with development; instead, it had revealed "hidden variations in the genome that were not having an effect before, but were revealed when the organism was stressed."

In February, in the *Proceedings of the National Academy of Sciences,* Lindquist described further HSP90 experiments with the cress plant, *Arabadopsis thaliana,* which is separated from fruit flies by a billion years of evolution. Starting with a normal population of the plants, Lindquist's student Todd Sangster '00 inhibited HSP90 and showed that the underlying variation thus revealed is common. Focusing on the rare individuals with beneficial traits that might actually confer an evolutionary advantage, such as the tendency to develop succulent-like leaves (which could help the plant survive a drought), she and her colleagues showed that these traits could be enriched and made stable in just 10 to 15 generations of cross-breeding. Lindquist says this is probably just one of several mechanisms that facilitate rapid evolution. But the work is important because it shows that in the face of changing environmental conditions, HSP90 is likely to play a central role in the translation of genetic variation into physical changes in all kinds of organisms.

—JONATHAN SHAW

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