

# What Controls Organ Regeneration

Unlike automobiles, humans get along pretty well for most of their lives with their original parts. But organs do sometimes fail, and we can't go to the mechanic for an engine rebuild or a new water pump—at least not yet. Medicine has battled back many of the acute threats, such as infection, that curtailed human life in past centuries. Now, chronic illnesses and deteriorating organs pose the biggest drain on human health in industrialized nations, and they will only increase in importance as the population ages. Regenerative medicine—rebuilding organs and tissues—could conceivably be the 21st century equivalent of antibiotics in the 20th. Before that can happen, researchers must understand the signals that control regeneration.

Researchers have puzzled for centuries over how body parts replenish themselves. In the mid-1700s, for instance, Swiss researcher Abraham Trembley noted that when chopped into pieces, hydra—tubelike creatures with tentacles that live in fresh water—could grow back into complete, new organisms. Other scientists of the era examined the salamander's ability to replace a severed tail. And a century later, Thomas Hunt Morgan scrutinized planaria, flatworms that can regenerate even when whittled into 279 bits. But he decided that regeneration was an intractable problem and forsook planaria in favor of fruit flies.

Mainstream biology has followed in Morgan's wake, focusing on animals suitable for studying genetic and embryonic development. But some researchers have pressed on with

studies of regeneration superstars, and they've devised innovative strategies to tackle the genetics of these organisms. These efforts and investigations of new regeneration models—such as zebrafish and special mouse lines—are beginning to reveal the forces that guide regeneration and those that prevent it.

Animals exploit three principal strategies to regenerate organs. First, working organ cells that normally don't divide can multiply



**Self-repair.** Newts reprogram their cells to reconstruct a severed limb.

and grow to replenish lost tissue, as occurs in injured salamander hearts. Second, specialized cells can undo their training—a process known as dedifferentiation—and assume a more pliable form that can replicate and later respecialize to reconstruct a missing part. Salamanders and newts take this approach to heal and rebuild a severed limb, as do zebrafish to mend clipped fins. Finally, pools of stem cells can step in to perform required renovations. Planaria tap into this resource when reconstructing themselves.

Humans already plug into these mechanisms to some degree. For instance, after surgical removal of part of a liver, healing signals

tell remaining liver cells to resume growth and division to expand the organ back to its original size. Researchers have found that when properly enticed, some types of specialized human cells can revert to a more nascent state (see p. 85). And stem cells help replenish our blood, skin, and bones. So why do our hearts fill with scar tissue, our lenses cloud, and our brain cells perish?

Animals such as salamanders and planaria regenerate tissues by rekindling genetic mechanisms that guide the patterning of body structures during embryonic development. We employ similar pathways to shape our parts as embryos, but over the course of evolution, humans may have lost the ability to tap into it as adults, perhaps because the cell division required for regeneration elevated the likelihood of cancer. And we may have evolved the capacity to heal wounds rapidly to repel infection, even though speeding the pace means more scarring. Regeneration pros such as salamanders heal wounds methodically and produce pristine tissue. Avoiding fibrotic tissue could mean the difference between regenerating and not: Mouse nerves grow vigorously if experimentally severed in a way that prevents scarring, but if a scar forms, nerves wither.

Unraveling the mysteries of regeneration will depend on understanding what separates our wound-healing process from that of animals that are able to regenerate. The difference might be subtle: Researchers have identified one strain of mice that seals up ear holes in weeks, whereas typical strains never do. A relatively modest number of genetic differences seems to underlie the effect. Perhaps altering a handful of genes would be enough to turn us into superhealers, too. But if scientists succeed in initiating the process in humans, new questions will emerge. What keeps regenerating cells from running amok? And what ensures that regenerated parts are the right size and shape, and in the right place and orientation? If researchers can solve these riddles—and it's a big "if"—people might be able to order up replacement parts for themselves, not just their '67 Mustangs.

—R. JOHN DAVENPORT

R. John Davenport is an editor of *Science's* SAGE KE.

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