SCIENCE ●http://www.sciencemag.org

EDITORIAL

New Tissues from Old

The annual cost of injured or failed human tissues and organs runs into billions of dollars, to say nothing of the loss of quality of life that often accompanies compromised tissue function. Over the past 50 years, we have made remarkable progress in restoring the structure and function of damaged and dysfunctional tissues through bionic devices and organ transplants. Such replacement parts, however, still pose significant biological problems, and they are not useful in all situations. What we really want is a minor version of the Lazarus miracle—to regenerate damaged tissues in vivo. That wish is closer to becoming reality because of research in the emerging field of regenerative biology, several aspects of which are reviewed in this issue of *Science*.

In most vertebrates, the capacity for regeneration is limited to a few tissues, such as liver, bone, and skeletal muscle. Regeneration of these tissues partially recapitulates their embryonic differentiation from multipotential stem cells. In mammalian bone and muscle, subpopulations of stem cells are set aside during embryonic and fetal life for use in juvenile growth stages and for regeneration throughout life. In the regenerating mammalian liver, cells undergo partial dedifferentiation, allowing them to reenter the cell cycle while maintaining all critical differentiated functions. The divas of dedifferentiation are the urodele amphibians (salamanders and newts), which can regenerate many tissues by this mechanism, including the neural retina, cardiac muscle, limbs, and tails. Urodeles can also regenerate the spinal cord by a reversible epithelial-mesenchymal transformation that restores the ependyma while providing an environment favorable to the regrowth of severed axons.

The general approach of regenerative biology is to identify the cellular and molecular differences that distinguish tissue embryogenesis from wound repair (scarring) and then to recreate an embryonic (regenerative) environment in an injured adult tissue. Limited success in stimulating the regeneration of mammalian bone, skin, blood vessels, and spinal cord has been achieved by bridging lesions with artificial or natural biomaterial scaffolds that promote the migration, proliferation, and differentiation of cells or the growth of severed axons. But achieving a wider range and greater degree of regeneration will require a deeper understanding of the cellular and molecular differences between wound repair and embryogenesis. There are two major reasons, not mutually exclusive, why our tissues might scar rather than regenerate. First, they might contain regeneration-competent cells but lack the stimulatory signals to effect regeneration and might also produce signals that suppress regeneration and favor repair. Thus, a major research direction in regenerative biology is to identify the signals that regulate the proliferation and differentiation of tissue precursor cells during embryogenesis and in regenerating adult tissues as well as those that suppress these activities in nonregenerating adult tissues.

Alternatively, most of our tissues might lack stem or progenitor cells for regeneration. However, multipotential stem cells have now been identified in some nonregenerating adult tissues, such as the brain, and it has been postulated that stem cells might lie dormant in many or all tissues of the adult body. The function in vivo of these cells is unknown, but their presence could mean that converting repair to regeneration may be "simply" a matter of activating these cells by supplying the correct stimulatory signals or neutralizing suppressor signals, or both. If cells for regeneration are not ubiquitous in adult tissues, they could be provided in other ways, such as transplantation of embryonic stem cells into the body, either by themselves or after being seeded into polymer scaffolds that promote their differentiation. A longer-term but ultimately more satisfying approach would be to learn from the mammalian liver and from the urodeles how to induce regeneration via dedifferentiation.

Many basic research and technical challenges remain to be addressed before tissue regeneration becomes a clinical reality, but the major approaches to solving the problem are now in place. I believe that, not too far into the next century, we will be able to regenerate a number of vital tissues. Regenerative biology promises not only to substantially reduce health care costs but to prevent potential losses in personal freedom, quality of life, and productivity. That will be miracle enough.

David L. Stocum

The author is professor of biology and dean of the School of Science, Indiana University–Purdue University, Indianapolis, IN.