The New York Times
nytimes.com

April 11, 2006

Regrow Your Own

By NICHOLAS WADE

Stem cell therapy has long captured the limelight as a way to the goal of regenerative medicine, that of repairing the body with its own natural systems. But a few scientists, working in a relatively obscure field, believe another path to regenerative medicine may be as likely to succeed. The less illustrious approach is promising, in their view, because it is the solution that nature itself has developed for repairing damaged limbs or organs in a wide variety of animals.

Many species, notably amphibians and certain fish, can regenerate a wide variety of their body parts. The salamander can regenerate its limbs, its tail, its upper and lower jaws, the lens and the retina of its eye, and its intestine. The zebra fish will regrow fins, scales, spinal cord and part of its heart.

Mammals, too, can renew damaged parts of their body. All can regenerate the liver. Deer regrow their antlers, some at the rate of 2 centimeters a day, said to be the fastest rate of organ growth in animals. In many of these cases, regeneration begins when the mature cells at the site of a wound start to revert to an immature state. The clump of immature cells, known as a blastema, then regrows the missing part, perhaps by tapping into the embryogenesis program that first formed the animal.

Initiation of a blastema and the formation of the embryo are obviously separate biological programs, but "the processes must converge at some point," says Jeremy Brockes, a leading regeneration researcher at University College London.

The blastema seems to derive its instructions from the wound-site cells from which it was formed, and is quite impervious to cues from new surrounding tissue if it is transplanted. If a blastema made by sectioning a salamander's limb at the wrist is transplanted elsewhere in the body it will still grow just a wrist and paw, while a shoulder blastema will regrow the whole limb. People, of course, cannot regrow their limbs like newts, and do not form blastemas, so the relevance of regeneration to medicine has long seemed remote. But the capacity for regeneration exists in such a wide variety of species that it is unlikely to have evolved independently in each, regeneration researchers believe.

Rather, they say, the machinery for regeneration must be a basic part of animal genetic equipment, but the genes have for some reason fallen into disuse in many species.

In support of this notion, people are not wholly lacking in regenerative powers.

There are reports that the tip of the finger can occasionally be regenerated, if the cut is above the last joint. And people can vigorously repair damage to the liver. Even after 75 percent has been removed in surgery, the liver regains its original mass in two to three weeks. It is not certain why other organs and limbs have lost this useful capacity, but perhaps only the liver was damaged often enough during its owner's lifetime to make a repair system worth the cost. "I believe that the reason is the extensive and recurring injury that the liver was exposed to in evolution: rotten food, plant toxins, viruses," says Markus Grompe, a liver expert at the Oregon Health and Science University.

The liver can regenerate itself, when all else fails, from stem cells, the versatile cells that produce the mature cells of many organs and tissues. But usually it relies on its own mature cells, which, like those of a blastema, possess a remarkable power to divide and multiply, even though they can only restore the organ's mass, not its original structure.

A more specific reason for thinking regeneration is not a wholly lost ability comes from genes. Last December, Mark Keating, who studies regeneration in zebra fish, identified a gene that is essential for initiating blastema formation when the fish's fin is cut. Both this gene, called fgf20, and another he has found, hsp60, also exist in people, suggesting the genetic basis for regeneration may still be in place even though the body can no longer evoke it.

Dr. Keating, a vice president at the Novartis Institutes for Biomedical Research in Cambridge, Mass., believes stem cells can ordinarily undertake only very limited repairs of organs like the liver and heart, and that the scarring often seen in these tissues is a fallback mechanism put in place when the stem cells' capacities are exceeded.

If the genes that boot up the zebra fish blastema also exist in people but are not switched on, perhaps some drug might be developed that goads them into action. Once a blastema had been induced at some wound site in the body, regeneration researchers suggest, it might regrow the missing limb or organ with no further intervention required. "Maybe there are residual abilities that could be enhanced" in mammals, says Shannon Odelberg, a researcher at the University of Utah. He studies regeneration in the newt, with the eventual goal of inducing blastemas to form in mammals.

Regeneration is studied in only a few laboratories. It was not even on the agenda of the research planning meeting held last October by the California Institute of Regenerative Medicine, which was dominated by stem cell biologists.

One reason for this orphan status is that the model animals used by most biologists, like the roundworm, the fruitfly and the mouse, happen to be ones that do not regenerate.

The genetics of regenerating animals, like the salamander, are largely unknown. Hence the process of regeneration has received little attention from research biologists. But there is a group of vertebrates that can regenerate very successfully, said Dr. Brockes. "It would be rather surprising if there weren't some interesting and important lessons one could learn from them."

"Regeneration is the result of an evolutionary experiment that nature has already done for us," said Alejandro Sánchez Alvarado, a Hughes Institute researcher who studies flatworm regeneration at the

University of Utah The blastema, he notes, performs the difficult task — one not faced by the embryo — of integrating new and existing tissues.

Many proponents of regeneration, while conceding they have a great deal more to learn, believe stem cell therapy too may not be as close to clinical use as its advocates sometimes suggest. Dr. Brockes noted that the blastema's reliance on internal information contrasts with a principal assumption of stem cell therapy, that stem cells inserted into a damaged tissue will use local cues to behave appropriately and integrate into the surrounding tissue.

Stem cell therapists assume that injected cells can replace missing tissue with guidance from the invisible template supplied by chemical signals from nearby cells. That is the solution a human engineer might logically think of, Dr. Brockes said, but evolution has chosen a different one.

The basic biology of regeneration is not yet fully understood, but nor is that of stem cells. Indeed, it may be premature to start thinking about how to use stem cells therapeutically, said Dr. Sánchez Alvarado.

"Translating a biological process you don't understand into technology is like trying to translate hieroglyphs without a Rosetta Stone," he said.

Dr. Grompe, the expert on liver regeneration, said that getting stem cells to behave properly in a patient's body "is a very, very difficult problem." With transplanted stem cells, the usual outcome is "nonfunctional at best and cancerous at the worst because the local environment is not able to modulate the behavior," he said. "I think that cell therapy of the nervous system will be extremely difficult because of that. So much for stem cells curing Alzheimer's."

Dr. Keating believes that the expense of stem cell therapy, should it work, is a major consideration. "I would never begin to guess that the whole stem cell approach has no chance of working," he said. But even if it does, developing cells for every patient who needs them would be very expensive. Switching on the regenerative process with drugs, should that prove possible, would be cheap by comparison, he said.

Scientists who work on stem cells reject the idea that the blastema mechanism is the only way to repair the body's tissues. "I agree that blastema regeneration models might have something to tell us, but I wouldn't give up on normal stem cell regeneration," said Irving Weissman, a leading expert on blood stem cells at Stanford University. The stem cells involved in bone marrow transplants "can regenerate drastic loss of tissue," he said.

Bone marrow transplantation is the big success story on which much of the hope for stem cell therapy is based. But regeneration researchers believe the bone-marrow example may be misleading because blood is not an organized tissue, and the marrow's blood-making stem cells are not required to do anything much beyond their usual function.

In disagreement with this view, Dr. Weissman said that blood-making stem cells are highly versatile and have the ability to home in on the marrow and set up shop in their proper niche there, and that neural stem cells appear to have a similar degree of versatility. Human neural stem cells, when put into embryonic mice, will migrate through the mouse's brain and add insulation to mouse neurons that lack it.

Robert Weinberg, a biologist at the Whitehead Institute in Cambridge, said therapeutic regeneration was "decades away" because the cells of animals that regenerate are so different from those of people.

But there is great hope of taking embryonic stem cells, he said, and making them yield primitive adult stem cells that still possess regenerative capability. He placed less confidence in using fully mature adult stem cells, which may have lost the ability to build new tissue. "I think the notion of trying to extract adult stem cells from adult tissues is possibly a fool's errand," he said.

In the light of new knowledge, some stem cell biologists are making more guarded predictions about the imminence of stem cell therapy. Ron McKay, an expert on neural stem cells at the National Institutes of Health, noted that stem cells inserted into the developing brain of a fetal animal "become incorporated in an extraordinary way, as if local cues were controlling their behavior."

But in the adult brain, he said, nothing happens, suggesting that the concept of using stem cells to treat Alzheimer's disease is illusory.

Stem cells head the hierarchy of cells with which nature organizes animal tissues, but so much remains to be understood that it is hard to tell which aspect of their biology may hold therapeutic promise. "I think the idea of cell therapy per se will not be that powerful a tool for most diseases," Dr. McKay said. "But stem cell biology will be a hugely important tool."

Regeneration and stem cell therapy are promising aspects of regenerative medicine but both are still at the research stage. "I'm very bullish on regenerative medicine," said Dr. Keating, alluding to both types. "I think it's going to happen and it will be a revolution, but it will take time. It would be a mistake to oversell it and promise too much too early."