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Recipes for regenerating limbs

Researchers look to porcine bladders, salamanders, mice to regrow limbs

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Researchers are trying to find ways to regrow fingers — and someday, even limbs — with tricks that sound like magic spells from a Harry Potter novel.

There's the guy who sliced off a fingertip but grew it back, after he treated the wound with an extract of pig bladder. And the scientists who grow extra arms on salamanders. And the laboratory mice with the eerie ability to heal themselves.

This summer, scientists are planning to see whether the powdered pig extract can help injured soldiers regrow parts of their fingers. And a large federally funded project is trying to unlock the secrets of how some animals regrow body parts so well, with hopes of applying the the lessons to humans.

The implications for regrowing fingers go beyond the cosmetic. People who are missing all or most of their fingers, as from an explosion or a fire, often can't pick things up, brush their teeth or button a button. If they could grow even a small stub, it could make a huge difference in their lives.

And the lessons learned from studying regrowth of fingers and limbs could aid the larger field of regenerative medicine, perhaps someday helping people replace damaged parts of their hearts and spinal cords, and heal wounds and burns with new skin instead of scar.

Four months for a new fingertip

But that's in the future. For now, consider the situation of Lee Spievack, a hobby-store salesman in Cincinnati, as he regarded his severed right middle finger one evening in August 2005.

He had been helping a customer with an engine on a model airplane behind the shop. He knew the motor was risky because it required somebody to turn the prop backwards to make it run the right way.

"I pointed to it," Spievack recalled the other day, "and said, 'You need to get rid of this engine, it's too dangerous.' And I put my finger through the prop."

He'd misjudged the distance to the spinning plastic prop. It sliced off his fingertip, leaving just a bit of the nail bed. The missing piece, three-eighths of an inch long, was never found.

An emergency room doctor wrapped up the rest of his finger and sent him to a hand surgeon, who recommended a skin graft to cover what was left of his finger. What was gone, it appeared, was gone forever.

If Spievack, now 68, had been a toddler, things might have been different. Up to about age 2, people can consistently regrow fingertips, says Dr. Stephen Badylak, a regeneration expert at the University of Pittsburgh. But that's rare in adults, he said.

Spievack, however, did have a major advantage — a brother, Alan, a former Harvard surgeon who'd founded a company called ACell Inc., that makes an extract of pig bladder for promoting healing and tissue regeneration.

It helps horses regrow ligaments, for example, and the federal government has given clearance to market it for use in people. Similar formulations have been used in many people to do things like treat ulcers and other wounds and help make cartilage.

The summer before Lee Spievack's accident, Dr. Alan Spievack had used it on a neighbor who'd cut his fingertip off on a tablesaw. The man's fingertip grew back over four to six weeks, Alan Spievack said.

Lee Spievack took his brother's advice to forget about a skin graft and try the pig powder.

Soon a shipment of the stuff arrived and Lee Spievack started applying it every two days. Within four weeks his finger had regained its original length, he says, and in four months "it looked like my normal finger."

Spievack said it's a little hard, as if calloused, and there's a slight scar on the end. The nail continues to grow at twice the speed of his other nails.

"All my fingers in this cold weather have cracked except that one," he said.

All in all, he said, "I'm quite impressed."

'We're not smart enough …'

None of this proves the powder was responsible. But those outcomes have helped inspire an effort to try the powder this summer at Fort Sam Houston in San Antonio, on soldiers who have far more disabling finger loss because of burns.

Fingers are particularly vulnerable to burns because they are small and their skin is thin, says David Baer, a wound specialist at the base who's working on the federally funded project. The five to 10 patients in the project will be chosen because they have major losses in all their fingers and thumbs, preventing them from performing the pinching motion they need to hold a toothbrush, for example.

The soldiers will have the end of a finger stub re-opened surgically, with the powder applied three times a week.

Nobody is talking about regrowing an entire finger. The hope is to grow enough of a finger, maybe even less than an inch, to do pinching.

And it is just a hope.

"This is a real shot in the dark," says Badylak, who's participating in the project. "There's literally nothing else these individuals have to try. They have nothing to lose."

But from a scientific standpoint, he said, "this isn't ready for prime time."

For one thing, it's not completely clear what happened inside Lee Spievack's finger.

The broad outline is pretty straightforward. The powder is mostly collagen and a variety of substances, without any pig cells, said Badylak, who's a scientific adviser to ACell. It forms microscopic scaffolding for incoming human cells to occupy, and it emits chemical signals to encourage those cells to regenerate tissue, he said.

Those signals don't specifically say "make a finger," but cells pick up that message from their surroundings, he said.

"We're not smart enough to figure out how to regrow a finger," Badylak said. "Maybe what we can do is bring all the pieces of the puzzle to the right place and then let Mother Nature take its course."

But "we are very uninformed about how all of this works," Badylak said. "There's a lot more that we don't know than we do know."

No pig powder needed

Some animals, of course, can regenerate tissue without help from any powder. Badylak and other scientists are involved in a separate, Pentagon-funded project to uncover and harness their secrets. This work might someday lead to regenerating entire limbs.

One animal they're studying is the salamander, a star of the regeneration field. Chop off a salamander's arm,

and it will grow back in a matter of weeks.

Why? The short answer is that rather than making a scar to heal quickly, as people do, the salamander forms a mound of cells called a blastema. This is a regeneration factory: If you cut off a salamander hand and transplant the resulting blastema to the creature's back, it will grow out a hand there.

David Gardiner at the University of California, Irvine, is studying the secrets of the salamander by growing extra arms on the creatures. That allows for more controlled conditions than amputating arms and trying to follow what happens, he said.

So how do you make a salamander grow an extra arm? Make a shallow wound on the upper arm. Re-route a nerve to the site so it will pump out critical chemical signals that promote the creation of blastema cells. And insert a tiny piece of skin from the other side of limb you just wounded, to help provide a blueprint for what needs to be done.

The recipe sounds like "you put it in a cauldron under a full moon," Gardiner observed.

The creatures are so lethargic it's hard to tell if they can use their extra arms, he noted. But the research shows that beyond establishing a blueprint for a new arm, this mix of cells sends out a chemical SOS to attract other kinds of cells from the salamander's body to help construct a new appendage.

Just how many chemical signals are involved, and what they are, remain to be discovered.

A very special mouse

Then there's the specially bred mouse strain that befuddled Ellen Heber-Katz a decade ago, and has since become a focus of her research.

Heber-Katz, of the Wistar Institute in Philadelphia, was using the mouse strain known as MRL in a study of autoimmune diseases. Her team punched tiny holes in the animals' ears as markers. About three weeks later, Heber-Katz noticed a troubling thing.

"There were no ear holes," she recalled the other day. "We ear-punched again, and they closed up and disappeared.... We were just so shocked."

Like salamanders, the mice were growing blastemas instead of scars. They also heal damage to their hearts.

But for regrowing digits, even this mouse falls short. If a toe is cut off at some point other than the tip, the remnant produces a cell mass that looks like a small blastema, but it doesn't grow the missing part back. (An ordinary mouse just develops a scar.)

At least, the MRL mouse "looks like it's trying," Heber-Katz said.

In studying the mice and salamanders, scientists will pursue several questions. What genes rev up to produce regrowth? What biochemical signals are involved? What is the role of specific cells? Can this knowledge be used to regrow a digit on a mouse?

Scientists say it's not clear when this research might help people.

As for Spievack, the model-airplane enthusiast, he's had enough personal experience in this area.

"I don't plan on cutting anything more off to find out if I can grow that back," he said.

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