Discoveries

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Repairing broken spines

Regeneration of damaged nerves in rats raises hope for humans

By Margie Patlak

NEUROSCIENCE

Teri Berdine is an energetic 31-year-old woman who loves to dance, jog and play softball — but who can move across a room only in a wheelchair.

Four summers ago, a fall from a second story porch injured her spine and left her paralyzed from the bust down.

"Now that it's been four years since the accident, my doctors tell me I'll never walk again," says Berdine, of Milwaukee, Wis.

But some researchers aren't so sure that people with injuries like Berdine's will never walk again. In various laboratories, the possibility of spinal cord repair is being studied seriously.

"Although there's no cure immediately in hand," says Paul Reier, a neuroscientist at the University of Florida in Gainesville, "people used to think injured adult spinal cord nerves can't grow. Over the past 10 years we've discovered that they can grow. If we can tap into that growth potential with the right strategies, we might be able to glean something that will translate into functional recovery. There's a contagious feeling of optimism these days."

That optimism is growing as new research supports the belief that repair of the spinal cord is possible. Among the latest findings:

■ Cell bridges coaxed rat nerve cells to grow past severed nerves in the thigh and into the spinal cord, where they made enough proper connections to restore sensation in the big toe.

■ A weak electrical current prompted the healing and return of function to severed nerves in the spines of guinea pigs.

■ Compounds in laboratory studies prevented scar tissue from hampering recovery and prompted nerve cells to grow and connect with other nerve cells.

These findings are modifying the pessimism that has dominated the field of spinal cord repair in the past. As Reier indicated, for more than 80 years, animal studies and human experience showed that adult brain and spinal cord cells called neurons generally did not have the ability to regrow and repair damaged nervous system circuits after injury.

In contrast, fetal central nervous system neurons can regenerate with ease. Reier capitalized on that fact by bridging injured spinal cords in rats with fetal spinal cord nerves. The fetal nerves of most mammals cannot only grow when cut, but effectively seek out the correct or "target" neurons with which to connect. Correct connections in the nervous system are the key to proper functioning.

Although Reier was unable to coax neurons to grow through his fetal bridge to the other side,he was able to get neurons to venture into the entrance of the bridge and connect to neurons within the bridge. These neurons then connected to neurons on the bridge's exit side. This neuron relay system enabled "one end of the spinal cord to talk to the other," said Reir, who has published some of his findings in the *Journal of Comparative Neurology.*

"We used to wonder how we were ever going to get nerves to find their right targets," Reier said. "Turns out they sniff out the targets pretty well with the aid of fetal transplants."

Using a different type of cell bridge, neuroscientist Jerry Silver of Case Western Reserve University in Cleveland was able to restore sensation in the big toe of rats whose nerves connecting the toe to the spinal cord were crushed. Silver made his bridges from fetal spinal cord cells called astrocytes that were latched onto filters. He chose immature astrocytes because these cells are known to prevent scarring, prompt nerve cell growth, and provide a "roadway" for growing neurons that directs them to their targets.

In Silver's experiment, reported last fall at a scientific meeting in New Orleans, nerves in a control group of rats were crushed and allowed to heal without the aid of a fetal bridge. Those neurons regrew up the leg but made dramatic U-turns when they reached the scar tissue that blocked the entrance to the spinal cord. In contrast, neurons in several of the rats given fetal bridges continued to grow into the spinal cord and connect to target cells within the cord. This regrowth of nerve appeared to be linked to restored function, because in these animals sensation of the big toe returned but was then lost when the new connections were cut.

"These findings tell us there's hope for repair inside the spinal cord," Silver says, "because the problems encountered at the entrance to the spinal cord are similar to those within the spinal cord."

The key to the bridge's success, according to Silver, is that compounds or growth factors secreted by the young astrocytes aid spinal cord repair. "In the future we may be able to stick in these growth factors and forget the bridges," he said.

Several researchers are pursuing that avenue, and so far growth factors have been uncovered that prevent the death of neurons following spinal cord injury, promote the growth of neurons, and hamper scar tissue formation. Compounds have also been created that block an inhibitor of neuron growth that is found in parts of the spinal cord.

But several more factors affecting spinal cord repair still need to be pinned down. This sort of chemical detective work is difficult to do because the compounds are present in such minute quantities.

Once all the critical growth factors are isolated, their use in the repair of spinal cords still won't be easy, because the timing and dosage of all the various factors is likely to be complex.

"We won't be able to create some magic pill that will get people walking again," says University of California at Irvine neuroscientist Manuel Nieto-Sampedro, a pioneer in research on growth factors and spinal cord repair.

A different approach that shows promise in spinal cord repair is electrical stimulation. Electrical fields generated naturally by cells or tissues are known to control the growth and development of a

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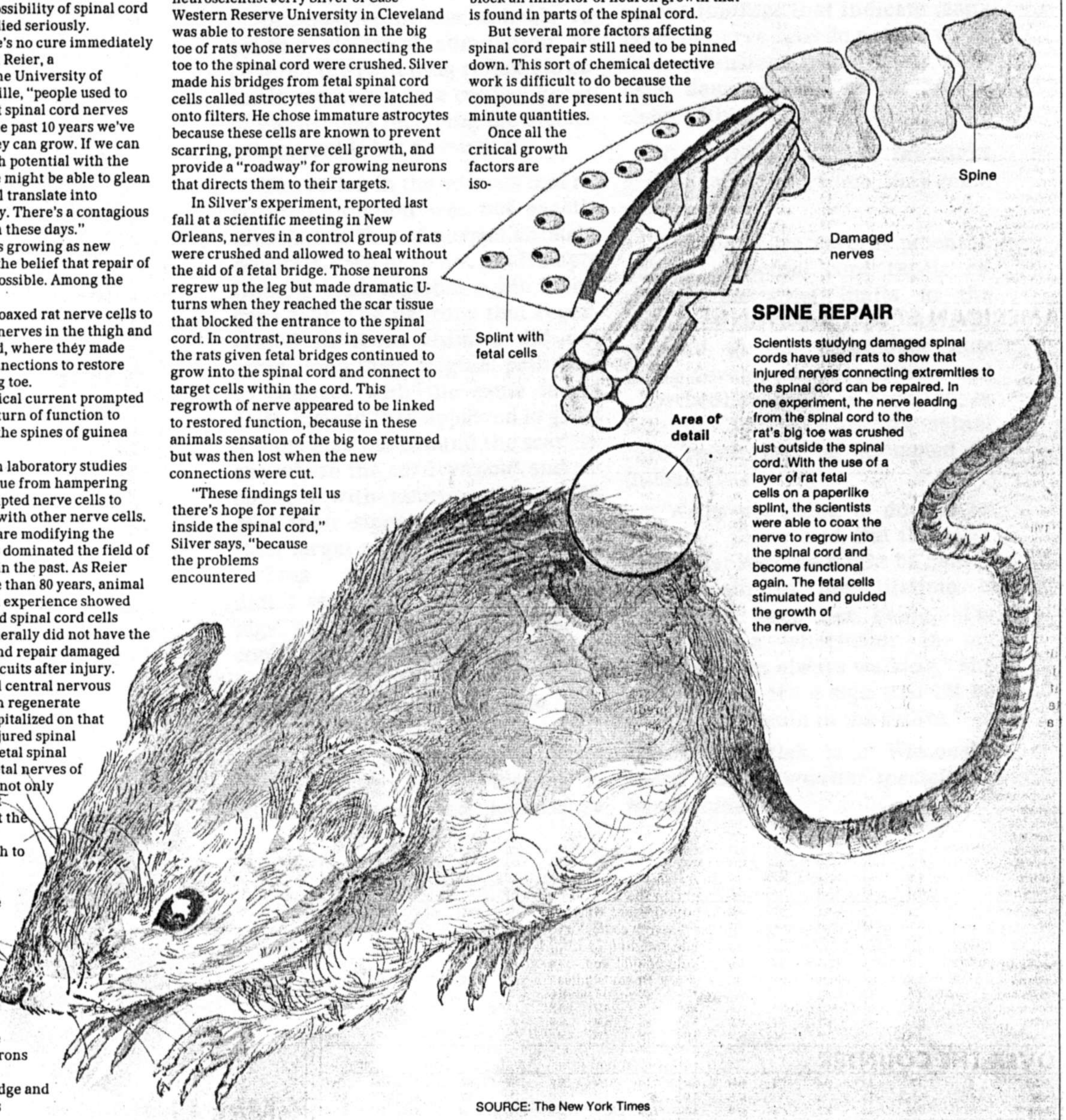

SPINE REPAIR

Scientists studying damaged spinal cords have used rats to show that injured nerves connecting extremities to the spinal cord can be repaired. In one experiment, the nerve leading from the spinal cord to the rat's big toe was crushed just outside the spinal cord. With the use of a layer of rat fetal cells on a paperlike splint, the scientists were able to coax the nerve to regrow into the spinal cord and become functional again. The fetal cells stimulated and guided the growth of the nerve.

SOURCE: The New York Times

Spinal cord research shows positive signs

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variety of animals and influence their recovery from injury.

Banking on that fact, Richard Borgens, director of Purdue University's Center for Paralysis Research in West Lafayette, Ind., applied weak electrical currents to guinea pigs whose nerves controlling a particular twitching reflex were severed in the spinal cord. Batteries were implanted in the animals, and electrical current flowed between electrodes placed on either side of the injury for about a month.

One-quarter of the animals receiving electrical stimulation recovered the twitching reflex. No animals recovered in a control group of guinea pigs receiving the electrical apparatus but no current.

The reflex in the animals that recovered function was not exactly identical to that of normal animals, however. "We have not put Humpty Dumpty back together again," Borgens said. The neurons that regenerated in these animals did not grow along their original pathways to connect with the same target cells. Instead they appeared to grow a short distance around the scar tissue where the cord was cut and reconnect with neurons that mediated their signal transmissions to their target cells.

This replacement circuitry didn't seem to hamper the guinea pigs' functioning, but whether it could be used to rewire the complex nervous system circuitry that governs human movements and sensations is questionable.

Of prime importance to paralyzed people like Berdine is whether any of the techniques being pursued to overcome spinal cord injuries can be applied to people whose spinal cords were injured several years ago. Repair of the spinal cord has not yet been shown to be possible in animals similar to humans like primates, let alone in humans. But if the bridging, growth factor and electrical stimulation techniques continue to show promise, few researchers see problems in using them to counter paralysis in a person whose spinal cord injury is several years old.

Their optimism is supported by recent findings that indicate many types of nerve cells do not die when their extensions, called axons, have been damaged, but rather "go to sleep," Silver said.

"Give those neurons the right growth factor and boom, they come right back."

But there are several potential pitfalls in spinal cord repair research, including limits to the wound or nerve cell types that will respond to the techniques now being developed. A lot of time and effort will probably be required, in addition, before work on spinal cord repair can be attempted in humans.

"We're not going to do this tomorrow," Silver said. But the possibility that Berdine might be able to walk again in her lifetime is enough to keep her going. "I'm never in a wheelchair in my dreams — I'm always walking," she said. "Maybe it's a sign that I'll be able to walk again in the future."

Margie Patlak is a Wisconsin-based free-lance writer specializing in medicine.