Teaching the Spinal Cord to Walk

A flurry of recent work suggests that, with proper training, some patients with spinal cord injuries can regain at least a limited ability to walk

Two years ago, 27-year-old Thorsten Sauer grabbed a therapist's hand and took his first steps in 6 years. At the time, he had been confined to a wheelchair since the 1989 motorcycle accident that had partially torn his spinal cord, leaving him almost totally paralyzed from the ribs down. But in 1995, prompted by a television news program, Sauer traveled from his hometown of Erlangen, Germany, to participate in an experimental program run by neurophysiologist Anton Wernig of the University of Bonn. At Wernig's clinic, located near Karlsruhe, a therapist hoisted Sauer and helped him walk slowly on a treadmill for 3 meters while grasping parallel bars. "It was amazing," Sauer recalls.


ANTON WERNIG/UNIVERSITY OF BONN

On the move. With his weight partially supported by a harness, a spinal cord patient undergoes training on a treadmill.

Today, after completing Wernig's 10-week program, in which patients step on treadmills assisted by specially trained therapists and a harness that can support part of their weight, Sauer pushes a wheeled walker around his apartment, stopping to grab books off shelves formerly out of reach. With help, he can even climb a few stairs. And Sauer is not alone. Dozens of other spinal cord–injury patients once confined to wheelchairs can now walk, although in a limited way, thanks to Wernig's program.

The idea that training can restore some walking ability is buttressed by a growing body of evidence in cats and now in humans. It shows that, contrary to dogma, the adult mammalian spinal cord can perform on its own, largely independent of the brain, many of the functions necessary for walking. What's more, recent data show that neural circuits governing locomotion in the spinal cord can "learn," by altering their connections, in a way that may help explain some of the improvements Wernig is seeing (see sidebar). "There is a flurry of activity and a pretty upbeat mood. People think that training procedures can enhance the abilities of [those] with spinal cord injuries," says Keir Pearson, an expert on the neurophysiology of walking at the University of Alberta in Edmonton, Canada.

More work will be needed to confirm these encouraging, but early, results. Indeed, even supporters caution that no one knows how much improvement individual patients can expect from the treatment. Furthermore, many patients with spinal cord injuries—who number 200,000 in the United States alone—will not benefit from the approach. In particular, notes Sten Grillner, a neurophysiologist at the Karolinska Institute in Stockholm, Sweden, training is unlikely to produce useful walking in patients whose cords are so badly damaged that no connections survive between their brains and the region below their injury. These people would have a lot of trouble voluntarily keeping control of when their legs started or stopped walking. In addition, he says, locomotor training does not restore balance. As a result, quadriplegics like actor Christopher Reeve, who can't use their arms to hold onto walkers and other devices for stability, could not learn to walk without being held upright.

But if the approach does someday prove successful in larger clinical tests, it might ultimately change the way many individuals with spinal cord injuries are treated. Today, doctors often leave such patients alone, except for therapy to strengthen healthy muscles or maintain flexibility. Current rehabilitative techniques such as helping patients stand or having them cycle their legs in the air have not proved consistently helpful.

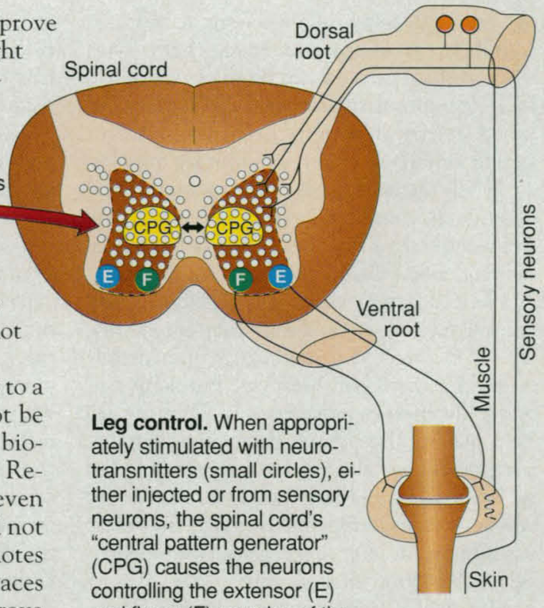
The new work, however, "is saying to a person in a wheelchair: 'This may not be your lot,' " says J. Thomas Mortimer, a biomedical engineer at Case Western Reserve University in Cleveland. And even though he concedes that training will not restore normal walking, Mortimer notes that merely being able to walk a few paces and climb a few stairs could vastly improve such a person's life, enabling him to enter a friend's home, a movie theater, or a narrow bathroom that would otherwise be off limits to him.

Moving to the beat

The first inklings that the mammalian spinal cord houses the sophisticated neural machinery needed for walking emerged in 1910, when Charles Sherrington, a neurophysiologist at Oxford University in the United Kingdom, found that cats whose spinal cords had been completely cut could perform limited stepping motions. But it was decades before anyone could conclusively pin the engine of locomotion to the spinal cord.

In 1967, Anders Lundberg and his colleagues at the University of Göteborg in Sweden isolated the spinal cord in adult cats by cutting its link to the brain and also paralyzing all the muscles to deprive the cord of movement-related sensory cues. The researchers then activated the animals' spinal neurons with an injection of L-dopa, a precursor for one of the cord's main neurotransmitters, noradrenaline. They found that the neurons that flex the legs and those that extend them fired in an alternating pattern.

The researchers concluded that the spinal cord holds a "rhythm generator" for locomotion that beats like the heart and is independent of both sensory cues and the brain. In the 1970s, Grillner and Peter Zangger, then also



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Leg control. When appropriately stimulated with neurotransmitters (small circles), either injected or from sensory neurons, the spinal cord's "central pattern generator" (CPG) causes the neurons controlling the extensor (E) and flexor (F) muscles of the leg to fire alternately.

Watching "Walking" Nerves Learn

Researchers have long known that in the brain, learning goes with subtle changes that strengthen or weaken the connections between neurons. As a result, they've assumed that similar neuronal "plasticity" also underlies the ability of the spinal cord to learn how to control walking after an injury destroys connections to the brain (see main text). But while plasticity had been seen in other motor systems, no one had directly seen it in the spinal cord's walking circuits—until now, that is.

Working with cats, neurobiologist Keir Pearson of the University of Alberta in Canada and his colleagues Patrick Whelan and Gordon Hiebert have shown that the influence of sensory nerves in the spinal locomotor system can adapt to compensate for an injury. "If you want any motor system that involves reflexes to work precisely, those reflexes must be modifiable. Our work provides the first glimpse of this type of thing in the locomotor system," says Pearson, whose team's results were published in 1995 and 1997 in the *Journal of Neurophysiology*.

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—Keir Pearson

The Pearson team members made the discovery serendipitously while studying the way sensations from the leg muscles influence walking in the cat. In 1994, while conducting those experiments, they cut a sensory nerve in a calf muscle called the lateral gastrocnemius (LG). When this nerve is stimulated, the signals it sends to the spinal cord elicit in the leg's motor neurons responses that prolong stance—keeping a walking animal's leg extended and on the ground. This helps calibrate the timing of each step.

But a few days after the researchers cut the nerve, they noticed that stimulating it didn't keep the leg on the ground as long as usual. At the same time, the cats began walking more normally again. So Whelan and Pearson began to wonder whether some change in the spinal cord might be compensating for the damage to the LG sensory neuron.

To find out, Pearson's team cut the LG nerves in one hind leg on each of 10 adult cats. Then, after 3 to 28 days, team members stimulated both the LG nerve and a sensory nerve in another calf muscle—the medial gastrocnemius (MG)—while the cats walked on a treadmill. Within 5 days, the researchers found, the ability of the severed LG nerves to prolong stance was much lower than that of the controls, while the stance-prolonging ability of the MG nerves in the injured legs had increased. Thus, the neuronal circuitry had changed to compensate for an injury-induced deficit.

To prove that the changes had taken place in the cord and not the brain, Pearson and Whelan repeated the experiment in another group of cats, this time cutting the spinal cord in nine of them. With the cord now isolated from the brain in those animals, the researchers found the same decreased influence of the LG nerve in all of the cats that could be evaluated; in some of them, they also saw an increased effectiveness of the MG nerve. This showed that at least part of the plasticity occurred in the cord.

The mechanism underlying this plasticity is so far unknown. But Pearson speculates that walking may produce "activity-dependent competition," in which two sensory nerves with similar functions compete for influence in the spinal cord. If one neuron is then cut, its connections to spinal neurons will weaken, allowing the competing nerve to exert greater influence.

If sensory feedback from walking does influence the strength of spinal connections, this type of plasticity could underlie the improved walking that can be induced in some paraplegics by locomotor training, Pearson suggests. By helping to compensate for a sensory or motor weakness—in this case, from a spinal cord rather than peripheral lesion—it could help a patient improve the rhythm of his or her walk as the cord learns when to bend an extended leg to start the next step. –I.W.

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at the University of Göteborg, confirmed Lundberg's results and extended them. They showed that the cord can produce not only a basic locomotor rhythm but also a more detailed electrical pattern in which different neural signals are sent to different leg muscles.

While researchers were picking up electrical activity in severed spinal cords, various labs were seeing signs that it might have functional consequences. Grillner's team found, for example, that kittens whose spinal cords had been cut walked well, as could adult cats temporarily, if they were given certain drugs immediately after their cords had been cut. But adult cats with older injuries walked poorly. They needed help placing their paws, balancing, and supporting their weight. And few experts believed such animals could improve. The mature cord was seen as too inflexible to make the subtle adjustments in its wiring required for independent locomotion after an injury.

But two neurophysiologists, Reggie Edgerton and Serge Rossignol, leading separate teams at the University of California, Los Angeles (UCLA), and the University of Montreal in Canada, weren't so pessimistic. Indeed, both teams showed, in a series of studies in the 1980s, that chronic "spinal cats," as the animals with severed spinal cords are called, can relearn the locomotor pattern of a normal cat.

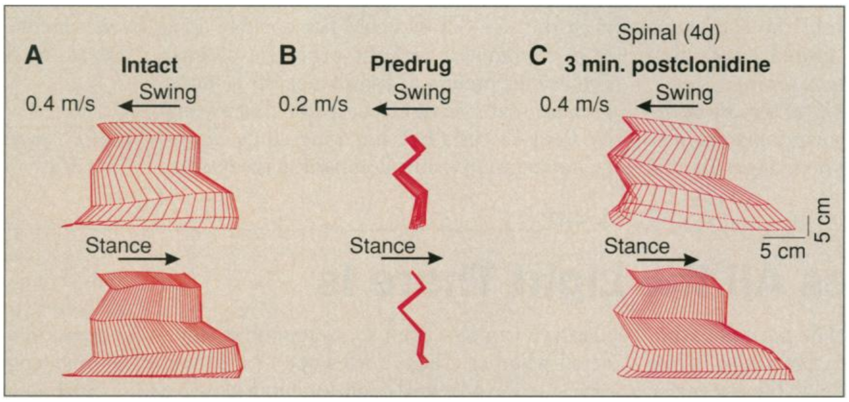
In one study published in 1987, for instance, Rossignol and his former postdoctoral student Hughes Barbeau, now at McGill University in Montreal, demonstrated dramatic improvements in the walking abilities of three spinal cats after two to three sessions a week, during which they were trained to walk with their hindlimbs on a treadmill. The animals at first had to be held up by their tails, but they eventually became able to support their hindquarters while they stepped. They also learned to place their paws sole-first on the treadmill and to take longer, more natural-looking steps. At the same time, mathematical measurements constructed from video images of the cats walking showed that their joint angles and leg movements began to mirror those of intact walking felines. In addition, the cats' leg muscles also began to exhibit more normal patterns of electrical activity.

Then, in the early 1990s, Edgerton's team members discovered that what an injured spinal cord learns can be surprisingly specific. They compared the walking abilities of three groups of spinal cats: untrained animals, those trained to step, and others trained only to stand. The team showed that the step-trained cats could, after 5 months, walk more naturally and rapidly than the untrained cats. By contrast, the cats that had practiced standing could hardly step at all. This shows, Edgerton says, not only that the cord can learn but that what it learns depends on the exact sensory input it receives. "If you teach a cat to step, it learns to step. If you teach it to stand, it learns to stand, but it can't step," Edgerton concludes.

Despite these encouraging results, most experts dismissed the idea that humans with spinal cord injuries might also learn to walk if trained properly. They had never seen it happen before in people, who after all are not cats. One exception was Barbeau at McGill. In a pilot study completed in 1989, his team had trained 10 patients on a treadmill, using a harness that could support up to 40% of their body weight. After 6 weeks of training, the researchers saw significant improvements—both on the treadmill and on the ground—in either the amount of weight a patient could support while walking or in walking speed, depending on whether a patient could walk without support when the study began. By 1990, Wernig's team in Bonn also had results with 12 patients showing that treadmill training had positive effects.

Small steps for man

Few researchers paid attention to these early studies because they were small, lacked controls, and were as yet unsupported by other evidence that the human spinal cord contains the neural machinery needed for locomotion. In 1994, however, such evidence emerged when Blair Calancie of the Miami Project to Cure Paralysis published a case study of a man who had partially severed his spinal cord 17 years before.



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Speeding recovery. As the lines indicate, before clonidine treatments, a cat with a severed spinal cord can barely move its hind legs (B), but afterward (C), the movements approach those of a normal cat (A).

A week after the man began an intense physical therapy regimen that included some walking, he reported that his legs suddenly began "walking" one night when he was lying on his back. Because the walking was involuntary, it suggested, Calancie says, that the man's leg movements were not controlled by his brain but had arisen largely in the spinal cord. Indeed, when Calancie and his colleagues measured the electrical activity of the leg muscles, which reflects that of the nerves controlling them, they found that, as in cats, the extensor and flexor nerves were firing alternately with clocklike regularity.

Since then, several groups have added to the evidence that the human spinal cord can generate steplike electrical patterns when exposed to sensations associated with walking. In 1995, for example, Volker Dietz and his colleagues at the University Hospital Balgrist in Zurich, Switzerland, induced elements of stepping in 10 paraplegics whose spinal cords were completely disconnected from their brains by placing them on moving treadmills with each one's weight supported in a harness. They found that the patterns of leg-muscle activity in these patients were similar to those in healthy subjects during treadmill walking.

In that same year, Wernig and his team in Germany published the first strong documentation that the spinal cord's walking program can be trained after an injury. In their study, published in the *European Journal of Neuroscience*, the researchers compared results with partially paralyzed patients whom they trained on the treadmill for 3 to 20 weeks with those of matched controls treated conventionally with other forms of exercise. Of 36 patients with recent cord injuries who were wheelchair-bound at the start of the study, 33 learned to walk independently, at least with the aid of walkers or canes, after treadmill training. By comparison, only 12 of 24 wheelchair-bound controls became independent walkers with conventional therapy. And 25 of another 33 patients with older injuries who had been wheelchair-bound learned to walk independently with Wernig's program, compared to just one of 14 controls.

Just last year, in the *Journal of Neurophysiology*, Susan Harkema, Bruce Dobkin, Edgerton, and their UCLA colleagues reported detailed evidence from the human spinal cord that helps explain how a program of exercise walking might help paraplegics. While four patients with complete cord injuries walked with assistance on a treadmill, the researchers recorded the electrical activity in three leg muscles and the instantaneous load on each leg. They did the same in two able-bodied people, who walked unassisted.

In both sets of subjects, the researchers found that the spinal cord's output, as measured by muscle activity, depended greatly upon the load on the legs. The greater the load, the higher the activity. What's more, the activity was timed to the phase of the step cycle so that it rose just when appropriate to facilitate stepping. The results provide "excellent evidence," Edgerton says, that the human spinal cord relies on complex sensory information, including load, to orchestrate walking.

Someday such data will help optimize training regimens by giving researchers a better idea of exactly what kinds of sensory cues the spinal cord needs to govern walking most effectively. But it may take years before most clinicians adopt locomotor training as part of their rehabilitation programs. For one thing, experts schooled in other approaches are not convinced that treadmill walking is better—in part because they may be unfamiliar with the evidence, and in part because no large-scale comparison study has yet been done. "I don't think any of these newer techniques have been proven superior to conventional treatment," says John Ditunno, a rehabilitation specialist at Thomas Jefferson University Hospital in Philadelphia.

Even proponents of the new approach urge caution. "A lot more studies need to be done to show that training makes a significant difference," notes Edgerton. "We're confident that it does, but we need to be careful, because that's an important conclusion."

Some of these studies may not be long in coming. Calancie's team at the Miami Project has already begun testing locomotor training with both a treadmill and a ceiling-mounted circular track to which patients are harnessed, allowing them to step forward something like a shirt sliding on a rack at a dry cleaning shop. The track enables somewhat more realistic walking than a treadmill because patients move over the ground instead of having the ground move under them, Calancie says.

And there may be other, very different improvements on the way. In a paper to appear this month in the *Journal of Neurophysiology*, Rossignol, Barbeau, and their graduate student Connie Chau showed that the drug clonidine, which they knew helped turn on the cord's locomotor pattern, can speed the recovery of cats from spinal cord transection when combined with locomotor training. "Within a week," Rossignol says, "the cats are walking with their hindlimbs" without needing more of the drug. Without clonidine, similar recovery in cats takes 3 to 4 weeks. Thus, in the future, patients might be treated with a combination of medication and walking workouts.

For now, pioneering patients such as the young, good-natured Thorsten Sauer, who once relished the freedom of a motorcycle, bask daily in the small freedom afforded by walking a few paces on their own. "The human body is not built for sitting," Sauer declares. "Sometimes it should walk."

–Ingrid Wickelgren