Spinal Cord Regeneration

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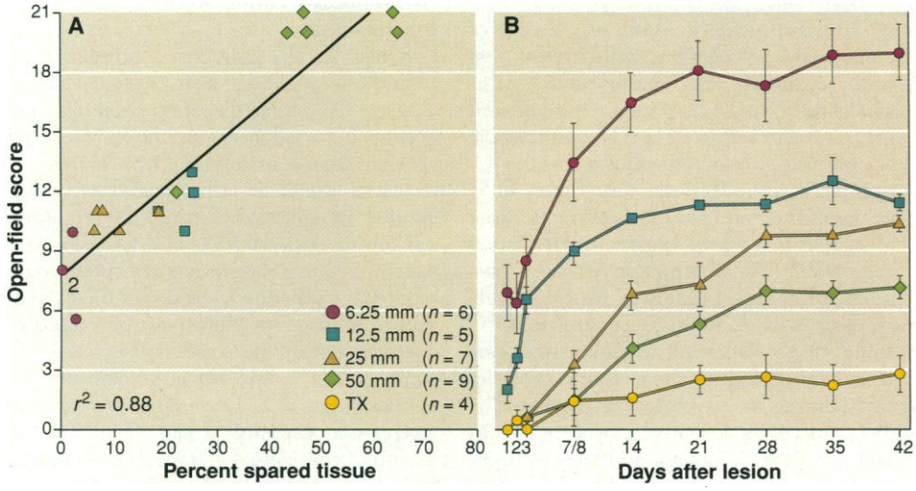
Regeneration of injured brains and spinal cords is the Holy Grail for many neurobiologists. A decade ago, such deep pessimism surrounded the prospects for spinal cord regeneration that few researchers would have attempted the audacious experiments reported by Cheng and Olson in this issue of *Science* (*1*). Now we see the first evidence that true functional regeneration can occur in the adult spinal cord.



Relearning to walk. Amount of spinal cord remaining after injury predicts locomotor ability. (**A**) The relation of white matter spared and locomotor scores, indicating that rats with only a small amount of surviving spinal cord can recover hindlimb movements and support their weight. (**B**) The time course of mean locomotor scores (±SEM) in rats after graded spinal cord contusions compared to rats with transected spinal cords (*18*). [Adapted from (*12, 19*) with permission]

Several pioneering studies provided a strong platform for these new experiments. Although the axons of injured spinal neurons cannot regrow within the spinal cord, Aguayo *et al.* (*2, 3*) showed that spinal axons will invade and grow long distances in peripheral nerves outside the cord. Schwab and co-workers discovered that the inhospitable climate in the spinal cord is a result of proteins that inhibit axonal growth (*4*) and that blockade of these proteins allows regeneration (*5*). Finally, it was shown that fibroblast growth factor (FGF) stimulates neural proliferation (*6*) and growth (*7*) and may be neuroprotective as well (*8*).

Cheng and Olson build on these findings; they completely cut (transected) rat spinal cords and used peripheral nerves to bridge individual spinal axon tracts (white matter) to areas of neuronal cell bodies (gray matter), applying FGF-impregnated fibrin glue to stabilize the bridges. Compared with untreated animals, rats with white matter–to–gray matter bridging with peripheral nerves and application of FGF-fibrin showed regeneration of axons and better behavioral recovery. This study is a major milestone. Although other investigators have shown axonal regeneration in hemisected adult rat spinal cords (*5, 9*) and transected neonatal rat spinal cords (*10*), this is the first convincing demonstration of functional regeneration in completely transected adult mammalian spinal cords.

Lest people in wheelchairs rush to have this treatment, three caveats are in order. First, clean spinal cord transections rarely occur in humans. Most spinal cord injury victims have contused (crushed) cords with residual axons crossing the injury site. The treatment would require a difficult-to-justify spinal cord transection. Second, the rats showed limited behavioral recovery. The average open-field locomotor scores of treated rats were 2 or less, suggesting that the animals were barely able to stand. None recovered coordinated locomotion. Third, more work is required to elucidate the importance of each component of the procedure. Cheng and Olson studied only two rats bridged without FGF-containing glue and two rats with white matter–to–white matter bridging. It is also unclear whether FGF is the best growth factor to apply.

Remarkably few spinal axons are required for the animal to recover some motor function. The amount of white matter remaining after injury correlates with the score on a test of walking ability [a 21-point locomotor or Basso, Bresnahan, and Beattie (BBB) scale (*11–13*), an extended version of the five-point open-field test scale (*14*) used by Cheng and Olson]. A BBB score of 8 is similar to 2 on the open-field test scale. As illustrated in the figure, the amount of remaining white matter at the injury site linearly predicts locomotion ability in rats injured by contusion of the thoracic (T8) spinal cord. The regression line had a y intercept of 8, consistent with earlier work indicating that only 10% of the original spinal axons are needed for locomotor recovery in cats (*15, 16*) and rats (*17*). Rats with completely transected spinal cords recovered to have BBB scores of 2, similar to the near-zero open-field test scores reported by Cheng and Olson in their untreated rats with transected cords.

The study by Cheng and Olson suggests that the grail has been sighted but is not yet in hand. Their findings nevertheless provide a strong basis for hope in the field. Combined with earlier studies showing that very few axons need to be preserved, restored, or regenerated to support functional recovery, the possibility of effective regenerative therapies for human spinal cord injury is no longer a speculation but a realistic goal.

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18. Each point represents a rat injured with a 10-g weight dropped 6.25, 12.5, 25.0, or 50.0 mm onto T8 cord exposed by laminectomy (the 2 by the filled circle indicates two overlapping points). Areas of spared white matter were measured from Luxol fast blue–stained cross sections of the lesion center and expressed as a percentage of total cross-sectional area. Locomotor recovery was assessed with a 21-point scale developed by Basso, Bresnahan, and Beattie (r^2 = 0.88).
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