Neuroanatomical Substrates of Functional Recovery After Experimental Spinal Cord Injury: Implications of Basic Science Research for Human Spinal Cord Injury

Human spinal cord injury (SCI) is a devastating condition that results in persistent motor deficits. Considerable basic and clinical research is directed at attenuating these deficits. Many basic scientists use animal models of SCI to: (1) characterize lesion development, (2) determine the role of spared axons in recovery, and (3) develop therapeutic interventions based on these findings. In this article, current research is reviewed that indicates: (1) most individuals with SCI will have some sparing of white matter at the lesion epicenter even when the lesion appears clinically complete, (2) even minimal tissue sparing has a profound impact on segmental systems and recovery of function, and (3) facilitatory intervention such as weight bearing and locomotor training after SCI may be more effective than compensatory strategies at inducing neuroplasticity and motor recovery. Body weight supported treadmill step training is discussed as an example of new facilitatory interventions based on basic science research using animal models. [Basso DM. Neuroanatomical substrates of functional recovery after experimental spinal cord injury: implications of basic science research for human spinal cord injury. *Phys Ther.* 2000;80:808–817.]

Key Words: *Experimental models, Flexor withdrawal reflex, Locomotion, Neuroplasticity, Treadmill training.*

D Michele Basso

Approximately 10,000 people survive spinal cord injury (SCI) each year, with the total SCI population in the United States ranging from 175,000 and 275,000 individuals.[1] The majority of these individuals experience moderate to severe motor impairment, and 60% require some assistance to function on a daily basis.[2] Few individuals with SCI recover functional ambulation, with estimates for recovery ranging from 7% to 38%.[3–6] Considerable effort by biomedical scientists has been directed toward understanding lesion development, mechanisms of natural recovery, and neuroanatomical substrates of motor recovery. In this article, I examine some of these studies.

Lesion Development After SCI

Based on the histopathology of 50 spinal cords examined post-mortem in The Miami Project, Bunge and colleagues[7–9] broadly categorized lesions into: (1) contusion injuries in which the glial limitans and spinal cord surface remain intact or (2) maceration or laceration injuries that disrupt the glial and pial interface and may directly tear the spinal cord tissue. Contusion and some maceration injuries may be present with loss of central gray and white matter, which creates a cavity that is surrounded by a rim of intact white matter at the periphery of the spinal cord.[8,9] Of particular interest to clinicians is the fact that intact, continuous central nervous system (CNS) axons traverse the lesion center in many individuals with functionally complete SCI.[8,9] Thus, a clinically complete lesion does not necessarily indicate an anatomically complete SCI. A functionally or clinically complete lesion is typically described as the absence of sensory and motor function below the level of the lesion (American Spinal Injury Association [ASIA] Impairment Scale classification A).[10] In contrast, an individual with an incomplete SCI has sensory and/or motor function below the lesion (ASIA B, C, and D).[11] Thus, tissue sparing after complete SCI suggests that the remaining axons are available to possibly mediate some recovery of function but do not appear to be recruited using traditional rehabilitation approaches such as compensation. The emergence of the full capacity of these spared axons may depend on the type of therapeutic interventions that are used.

Several experimental models of SCI have been developed in order to understand factors that may facilitate recovery of function after SCI in humans. The advantages of using an animal model rather than studying humans with SCI are: (1) the severity of the lesion can be controlled and reproduced across animals and experiments, (2) direct neuroanatomical evidence of lesion development over time can be attained using invasive procedures, and (3) effective parameters of therapeutic interventions can be established and refined before translating them for human use. One of the most clinically relevant experimental models of SCI is the contusion injury in rats, created by rapid impact of the

DM Basso, PT, EdD, Assistant Professor, Division of Physical Therapy, School of Allied Medical Professions, The Ohio State University, 306 SAMP, 1583 Perry St, Columbus, OH 43210 (USA) (basso.2@osu.edu).

Dr Basso provided concept/idea, writing, data collection and analysis, and fund procurement. Michael S Beattie, PhD, and Jacqueline C Bresnahan, PhD, contributed to the experiments and to Dr Basso's understanding of basic science research as it applies to spinal cord injury. Karen Hutchinson, PT, PhD, Lesley Fisher, and Craig Voll Jr, PT, provided data collection and analysis for the flexor withdrawal study. Lesley Fisher also provided clerical support.

The work was supported by NIH grant NS-32000, American Paralysis Association grant BB-2-9302-2, and USPHS grants NS-25095 and NS-10165.

Portions of this work were presented at the 1993–1996 Annual Meetings of the Society for Neuroscience and at the 1998 Neuroplasticity Symposium of the Section on Research, American Physical Therapy Association.

dorsal surface of the spinal cord using an electromagnetic device[12,13] or a weight-drop device.[14–16] These devices create a central core lesion and a peripheral rim of spared white matter similar to that reported in humans. The area of the cord with the greatest extent of damage is referred to as the "lesion epicenter." This review will focus on data gathered from contusion models of SCI primarily in rats.

Lesion development in SCI progresses over time and in neuroanatomical distribution. The primary phase of injury occurs during the first 18 hours and is typified by necrotic death of neurons and axons that were directly disrupted by the trauma.[17–20] The secondary phase of tissue injury can last several weeks and progresses in rostral and caudal directions, away from the lesion epicenter. Recent work suggests that the immune system plays a primary role in initiating cellular cascades that contribute to the expansion of the lesion during the secondary phase of lesion development.[21–23] In the secondary phase, immune system cells such as monocytes and macrophages are thought to emit chemical signals such as cytokines and chemokines.[22] These substances act on neurons and oligodendrocytes and appear to trigger apoptosis or programmed cell death in which DNA in the nucleus of the cell is systematically broken down into fragments.[24–26] Thus, intracellular processes in neurons and oligodendrocytes lead to destruction of their nuclei, causing cell death, despite no direct trauma to the cell. Apoptosis is known to occur after contusive SCI, especially in white matter tracts great distances away from the lesion (at least 4 spinal segments above and below the lesion epicenter).[26,27] Oligodendrocytes appear to undergo programmed cell death, which results in demyelination of axons many segments away from the lesion epicenter.[28] Thus, early after SCI, the injury is small, focal, and localized to the point of impact, but over time the lesion spreads to distant sites and may preferentially affect myelination of axons that are otherwise intact.

One critical issue in SCI research is whether lesion size and tissue sparing are important determinants of final functional outcome after contusion injury. If the size of the lesion is an important determinant of final functional outcome in patients with SCI, then interventions that attempt to bridge the central lesion or limit the secondary progression of the lesion would appear to be quite beneficial. The action of methylprednisolone, the standard treatment after SCI, is to reduce the inflammatory response and inhibit the immune system.[29,30] Methylprednisolone, therefore, could limit lesion expansion, which might explain the marked improvement in functional outcome of those treated.[29,30] As other pharmaceutical interventions are developed that limit or prevent the secondary lesion cascade, it is likely that the incidence of functionally complete lesions will decline.

Relationship of Lesion Size and Behavioral Outcome

Sensitive Anatomical and Behavioral Measures

Lesion severity can be measured in 2 ways: size of the injury and severity of residual deficits in function. In order to determine the relationship between lesion severity and motor deficits, sensitive, reliable, and quantifiable measures of neuropathology in the spinal cord and gross behavioral performance are needed. Several researchers[12,15,31–35] have developed standardized measures of lesion size in experimental animals. Once the region of spinal cord containing the lesion has been recovered and histologically prepared, it is cut serially into transverse cross sections, mounted on slides, and stained. In my laboratory, we use Luxol fast blue to stain myelin in the peripheral rim of spared tissue and measure those areas that stain blue. Through light microscopy and computer processing, we calculate the percentage of spared tissue per cross-sectional area at the lesion epicenter (for details, see Behrmann et al[12]).

As a gross behavioral outcome measure for use with animal models, my collaborators and I[31] recently developed the semiquantitative Basso, Beattie, and Bresnahan (BBB) Locomotor Rating Scale to assess overground locomotion in the open field. The measure is a sensitive,[31] reliable[36] measure of overall locomotor performance. The ratings of the BBB Locomotor Rating Scale range from 0 to 21 and distinguish between locomotor features such as flaccid paralysis, isolated hind-limb joint movements, weight-supported plantar stepping, coordination, and fine details of locomotion (eg, toe clearance, paw position).

Does Tissue Sparing Mediate Behavioral Recovery?

In a series of experiments, my collaborators and I[15,31] analyzed locomotor outcomes after mild, moderate, or severe spinal cord contusion in rats with extensive (>40%), intermediate (15%–40%), or minimal (1%–14%) tissue sparing at the lesion epicenter. We found differences in BBB Locomotor Rating Scale scores across groups. In general, locomotor recovery was extensive after mild SCI with extensive axonal sparing (>40%) but was quite limited after severe SCI with little sparing (as low as 1%–2%).[15] The BBB Locomotor Rating Scale scores predicted the extent of underlying neuropathology, as indicated by a positive correlation between BBB Locomotor Rating Scale score and percentage of spared tissue at the epicenter (replicated across studies: $r^2=.79$,[15] $r^2=.88$[31]; $P<.001$). Although there was a causal relationship between the extent of sparing and the extent of recovery, correlational data were insufficient to

conclude that the spared axons directly mediated the recovery. Perhaps spinal cord systems below the level of the lesion were responsible for the locomotor recovery. Therefore, we took 2 groups that had recovered for 9 weeks after moderate and severe SCIs and transected the spared axons at the lesion epicenter.[31] If functional recovery was due to segmental systems in the lumbar spinal cord, then transection of the spared tissue would have no behavioral effect. However, we found that severing the spared axons eliminated the behavioral recovery. The secondary transection resulted in a loss of locomotion such that the animals with SCI and spinal cord transection performed no differently within the first 5 days after transection than animals with spinal cord transection alone, based on BBB Locomotor Rating Scale scores. These findings suggest that tissue sparing at the lesion epicenter is responsible for behavioral recovery after experimental spinal cord contusion.

Can Minimal Sparing Improve Motor Function?

The study of rats with SCI and spinal cord transection[31] yielded important information about reorganization within the spinal cord. We were surprised by our observation that the rats with SCI and spinal cord transection appeared to demonstrate some motor recovery 2 weeks after complete transection of the spinal cord, a finding that rarely or never occurs after complete transection alone in adult rats.[12,31] Although the ability to locomote remained lost, the rats with SCI and spinal cord transection demonstrated more extensive hind-limb joint movements than the rats with transection alone, as measured by the BBB Locomotor Rating Scale scores. On closer examination of videotaped performance in the open field, we found that the rats that recovered from SCI and spinal cord transection performed more hind-limb movements than the rats that had recovered from a transection alone.[31] This is an important finding because it shows that animals that recover in the presence of relatively few spared axons (<2% in some cases) have altered organization of systems below the lesion. This reorganization, presumably of segmental systems, is evident when the lumbar spinal cord functions in isolation of supraspinal systems after the transection. Reorganization of caudal segments may be in the form of anatomical changes such as synaptogenesis of primary afferent fibers into vacated synaptic sites,[37] physiological changes that lower the threshold of postsynaptic neurons and render them more likely to produce an action potential,[38] or loss of axo-axonic presynaptic inhibition.[39,40] In summary, tissue sparing directly mediates recovery of function after experimental SCI, and sparing of as little as 1% to 2% is sufficient to facilitate reorganization within the lumbar spinal cord.

In another experiment, in which my collaborators and I studied the locomotion of opossums after spinal cord transection,[41] we found further evidence that an incomplete complement of descending or ascending axons induced marked reorganization below the level of the lesion. The study was designed to examine the effects of complete spinal cord transection made early in development on adult motor function.[41] Opossums are born 12 days after conception, crawl into the mother's pouch, and continue developing.[42,43] Therefore, lesions can be made extremely early in development without using high-risk, *in utero* techniques. Previous work by Martin and colleagues[44,45] established that, if the transection is made at postnatal day 26 in development, then at least a few axons from some supraspinal systems (primarily rubrospinal axons) grow across the lesion and travel into the lumbar spinal cord. However, in those studies, there was no examination of the behavioral effects of these axons.

In our study,[41] a group of opossums had midthoracic transection on postnatal day 5 and grew to adulthood; a procedure that results in only a partial complement of axons growing across the lesion into the lumbar spinal cord. Despite less input to the lumbar spinal cord, these opossums developed nearly normal locomotion, as measured by the BBB Locomotor Rating Scale in adulthood. Three animals from this group were then given spinal cord retransection to determine whether supraspinal axons reaching the lumbar spinal cord contributed to the locomotor effects. At the end of the experiment, we used one of the most sensitive silver staining methods[46] to detect axons as small as 1 μm in diameter that may have been spared after retransection. Based on our post-mortem findings that the cut ends of the spinal cord separated 5 to 10 mm and that no axons traversed the lesion site, we confirmed that the retransection was complete. Thus, any hind-limb motor function would be mediated solely by the isolated lumbar spinal cord after retransection.

As observed in the study of rats with SCI and transection,[31] severing the partial complement of axons that reach the lumbar spinal cord in the opossum eliminated locomotion immediately and hind-limb movements were similar to those exhibited by opossums that had spinal cord transection in adulthood.[41] More importantly, the opossums with retransection demonstrated dramatic rebound in hind-limb motor function over time, a pattern seen in rats with SCI and transection. By 6 weeks following retransection, each of the animals was able to take several bouts of consecutive weight-supported stepping with the hind limbs. The hind limbs often stepped in a rhythmic, alternating manner. In contrast, it is well documented that complete transection of the spinal cord in adult animals (rat,[12,47] cat,[48,49] opossum,[50] review[51]) results in hind-limb paralysis during overground locomotion. Thus, the only difference between

opossums with spinal cord transection in adulthood and those with retransection in adulthood is that the lumbar spinal cord of the animals with retransection developed in the presence of an incomplete complement of descending systems. The remarkable stepping exhibited by the animals with retransection is evidence of substantial reorganization of lumbar systems during development.

In summary, the rat and opossum studies present dramatic evidence in both adult and developing animals that a great deal of reorganization of lumbar circuits takes place in the presence of a partial complement of descending systems. In terms of clinical application, it remains to be seen whether this reorganization can be shaped or molded through therapeutic interventions such as exercise training or constraint-induced movement of the affected extremities.

Are Segmental Reflexes Modified According to the Amount of Tissue Sparing?

In our studies, we determined that tissue sparing facilitates recovery of locomotion after contusion but we did not know whether the amount of sparing would differentially affect other motor behaviors such as reflexes. In another set of experiments, my collaborators and I[52] compared the performance of the flexor withdrawal reflex in animals with substantial sparing (mild SCI) or minimal sparing (moderate SCI). The flexor withdrawal reflex was elicited by pinching the intrinsic muscles of the paw with our fingers, which elicited rapid flexion of the hip, knee, and ankle. By using our fingers rather than an implement, we were able to release the paw immediately at the onset of movement so that the motion was not impeded. We rated the pressure of the pinch on a scale from 1 to 3, with 1 being almost no pressure, 2 being the pressure necessary to elicit a response in an animal without a lesion, and 3 being a large amount of pressure. In order to assess the movement characteristics of the hind limb after stimulation, we videotaped the performance and used frame-by-frame kinematic analysis. We focused our analysis on the ankle because it appeared to have greater deficits than the other joints during locomotion.

Examination of stimulus threshold for the animals with moderate SCI showed an initial increase above normal 1 week after SCI, which decreased to below-normal levels by 4 weeks after SCI. Over time, very little pinch pressure was required to elicit a robust flexor withdrawal response. Given the manner in which we measured stimulus intensity, we have recently replicated these findings in animals with moderate SCI under blinded conditions and found a decrease in stimulus threshold compared with animals with laminectomy that served as controls.[53] Due to technological problems in which verbal statements of stimulus intensity recorded on videotape were erased, no stimulus data could be recovered for the animals with mild SCI. Therefore, we quantified the stimulus intensity after mild SCI (n=12) in several other studies in our laboratory and present these data as representative of animals with mild SCI (unpublished observation). One week after mild SCI, the stimulus intensity was slightly less than normal but had returned to normal levels by 4 weeks after SCI. In summary, animals with less sparing required a much lower stimulus intensity to elicit the reflex than animals with more tissue sparing and animals without lesions.

The reflex response was more robust after moderate SCI but not after mild SCI, as was evident by: (1) incorporation of pronounced trunk flexion and rotation, (2) rapid, repetitive hind-limb flexion to a single stimulus, and (3) brisk, full extension of the unstimulated hind limb. These qualitative observations suggest that hyperreflexia may have developed after moderate SCI, an interpretation also supported by precise quantitative measurements of hind-limb movement. Although flexor excursion of the ankle was unchanged for the animals with mild and moderate SCI, we found that movement speed and timing were different between groups. There was a trend that peak angular velocity of the ankle was consistently higher for animals with moderate SCI than for animals with mild SCI at 2, 3, and 4 weeks after SCI. We also found that the animals with moderate SCI had faster movement times and reached peak flexion sooner than the animals with mild SCI (Figure). Our data suggest that pronounced hyperreflexia of segmental systems in the lumbar spinal cord developed when the lesion was extensive and tissue sparing was minimal.

In summary, tissue sparing after contusion-type SCI appears to directly mediate recovery of function in experimental models. Although the extent of locomotor recovery is related to the amount of tissue sparing, even minimal sparing induces marked reorganization of neural systems below the level of the lesion. This reorganization appears to increase segmental reflex responses and may or may not be sufficient to facilitate locomotor recovery in animals. Given the relative dependence of recovery of motor function on tissue sparing, it seems important to identify which supraspinal systems are spared after spinal cord contusion and to determine whether training in motor skill development after SCI will promote even more extensive recovery.

Identification of CNS Systems Spared After SCI

To date, the focus of research in my laboratory has been on identifying the source and extent of sparing in descending systems after spinal cord contusion in the rat. Using anatomical techniques, my collaborators and

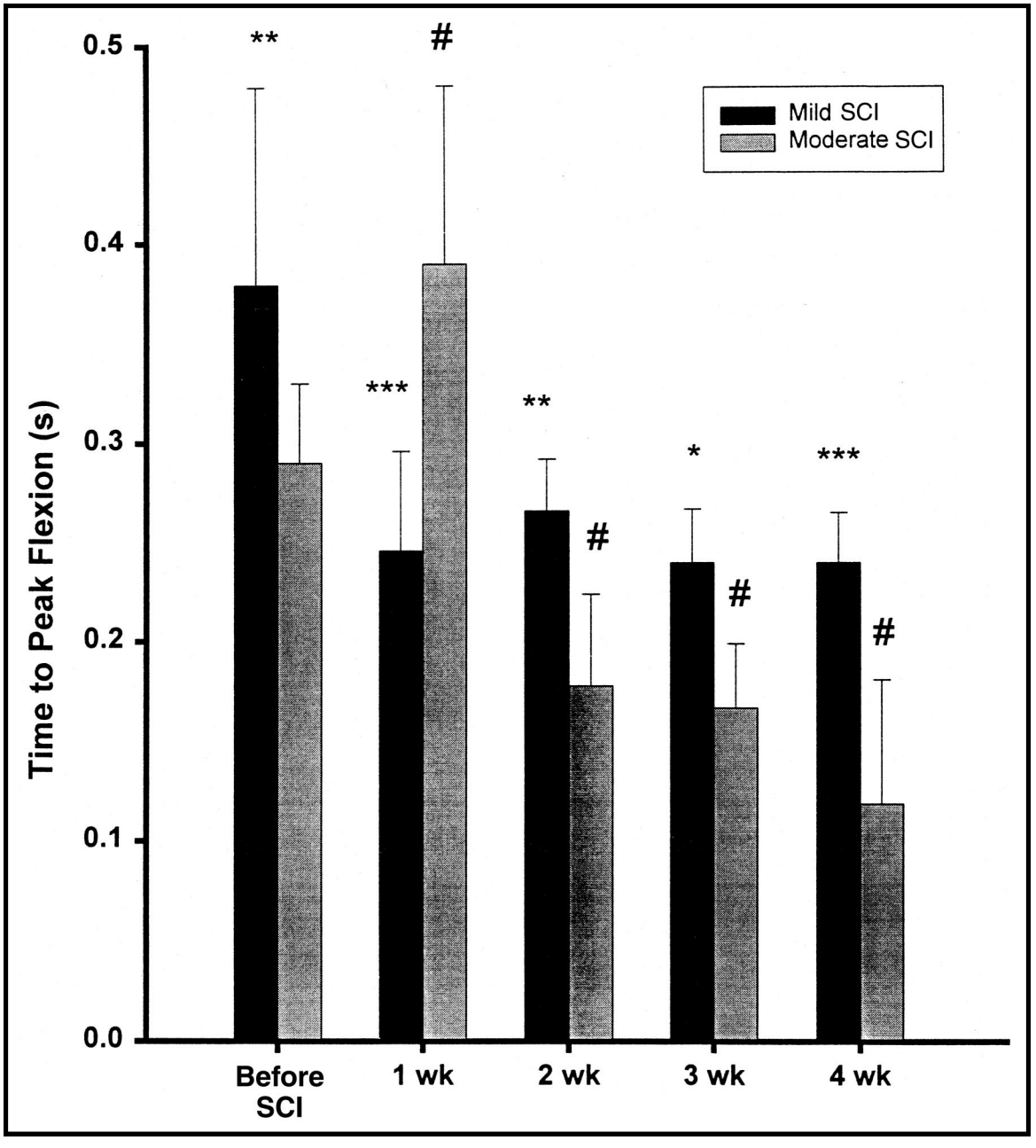

Figure.
Mean (±SD) movement times in animals with mild spinal cord injury (SCI) and in animals with moderate SCI. Time to peak flexion was recorded before SCI and at 1-week intervals for 4 weeks after SCI. Number sign (#) indicates $P < .05$, significantly different than before SCI values; asterisk (*) indicates $P < .05$, significant difference between groups; double asterisk (**) indicates $P < .01$, significant difference between groups; triple asterisk (***) indicates $P < .001$, significant difference between groups.

I[54] filled the lumbar spinal cord with dye (Fluorogold*) in animals without lesions as well as in animals that had recovered from mild or moderate SCI. The tracer is taken up at the axon terminals and retrogradely transported back to the cell body, where it accumulates. Thus, cell bodies with intact axons extending to the lumbar cord will be positively labeled with tracer. We examined several areas of the brain, brain stem, and cervical spinal cord known to contribute to movement. For locomotion in animals without lesions, the rubrospinal tract has been shown to control hind-limb flexion during the swing phase of locomotion[55,56] and the vestibulospinal tract has been shown to control hind-limb extension during stance.[57] Likewise, the reticulospinal system appears to be important for both flexion and extension of the hind limb during the swing and stance phases of normal locomotion, respectively.[58,59] There is also evidence that coordination of the forelimbs and hind limbs

* Fluorochrome, Englewood, CO 80110.

is mediated by long-descending propriospinal neurons connecting the cervical and lumbar enlargements.[60]

In general, retrograde tracing demonstrated greater cell labeling after mild SCI than after moderate SCI. Despite differential sparing, both groups had labeled neurons in most of the movement-related nuclei in the CNS, including the red nucleus, medullary reticular formation, raphe nuclei, and lateral vestibular nucleus. However, there were 2 areas that had little or no labeling in either group: the sensorimotor cortex and lamina 8 of the gray matter of the cervical spinal cord. Thus, it appears that corticospinal and long-descending propriospinal tracts to the anterior horn are lost after spinal cord contusion, regardless of lesion severity. It is likely that the central position of these tracts in the rat spinal cord rendered them more susceptible to damage after contusion than tracts located at the peripheral edge of the spinal cord. Although the human corticospinal tract runs in the anterior and lateral funiculi of the spinal cord, the corticospinal tract in the rat travels in the base of the dorsal funiculus.[61]

In summary, the spared tissue at the lesion center following mild or moderate spinal cord contusion is composed of at least rubro-, reticulo-, vestibulo-, and raphe-spinal tracts. Given that locomotor recovery depends on tissue sparing, these descending brain-stem systems must play an important role, whereas corticospinal and propriospinal tracts probably play little or no role. Anatomically intact axons may not be physiologically active. However, in our model, at least some of these intact axons appear to be functional, given that transection of the spared axons results in a loss of previously recovered locomotion. Further studies are being conducted to determine whether individual descending pathways contribute to the recovery of specific features of locomotion. Alternatively, the spared systems may function as a unit, modulating descending drive to the reorganized spinal cord systems below the injury.

Justification for Locomotor Training After SCI

In the clinic, the goal of rehabilitation after SCI is re-entry into the community, functional independence, and energy conservation. Traditionally, the treatment of choice to achieve these goals has been to train the patient to perform compensatory strategies. Although these strategies effectively accomplish the essential goals of rehabilitation, they may not have taken advantage of spared descending systems or the inherent neuroplasticity of the spinal cord. Given our knowledge about SCI through basic science research, the physical therapy profession is now challenged to adapt current interventions and to create new, effective therapeutic approaches for individuals with SCI according to these scientific principles to test whether they are beneficial.

One of the first attempts to convert neuroanatomical principles from the laboratory into a therapeutic treatment approach is based on evidence of central pattern generators (CPGs) in the spinal cord. Central pattern generators produce rhythmic, oscillating activity of limb flexor and extensor muscle groups independent of any supraspinal or afferent input.[62–64] Thus, CPGs appear to be interneuron-motoneuron circuits within the spinal cord of vertebrates. It is widely held that such CPGs are located in the lumbar segments of the spinal cord in rats, cats, and dogs.[62–65] These CPGs are multifunctional and can produce a variety of locomotor behaviors. Normally, CPGs that produce overground locomotion are activated by descending supraspinal input; however, in the absence of this input, the CPGs can be triggered by an external stimulus such as a moving treadmill belt. Thus, the neural control of overground locomotion is distinct from the control of reflex locomotion on a treadmill. Animals that are unable to locomote overground after complete transection of the spinal cord perform nearly normal stepping on the treadmill.[48,49,66]

Scientists have taken advantage of the principles of CPG activation to examine the capacity of the isolated lumbar spinal cord to learn. Edgerton and colleagues[67,68] have carried out a series of studies in which animals with complete, low-thoracic transection of the spinal cord were trained to step or stand with their hind limbs and their performance was compared with the spontaneous recovery of untrained animals with SCI that served as controls. The animals in the experimental group were placed in a body support sling on a treadmill and underwent extensive training to either stand in a stationary position with the treadmill turned off or to step with their hind limbs on the moving treadmill belt. Initially, the hind limbs of the animals in the step training group were manually assisted, when necessary, to complete the step. During training, the amount of body weight supported by the hind limbs and treadmill speeds were varied.

The animals in the standing group were trained by increasing afferent input to the spinal cord via cutaneous stimulation of the tail or paw. By 3 months, the animals in the standing group could stand independently and support their full body weight for 30 minutes, whereas the untrained animals were unable to stand. The animals in the stepping group were able to walk on the treadmill at relatively high speeds without assistance. Although the untrained animals had some spontaneous recovery of treadmill stepping, these animals could only tolerate treadmill speeds nearly 3 times lower than the treadmill speeds tolerated by the trained animals. Thus,

each group of animals learned to perform the task on which they were trained to a higher competency than animals relying on only spontaneous recovery. More importantly, these findings demonstrate that the isolated lumbar spinal cord has the capacity to "learn" and execute motor tasks in quadrupedal animals.

In further research, Edgerton's group set out to determine whether this learning was task-specific or more generalized and could improve motor performance on other behavioral tasks.[69] Animals with complete transection of the spinal cord were trained to step or stand until performance plateaued, then they were tested on the opposite task (eg, step training followed by stand training). Animals that were trained to step could not stand in a manner similar to that of animals that were trained to stand. They were unable to support themselves for any length of time without a large amount of cutaneous stimulation. Likewise, most animals that were trained to stand could not step. Two animals took only a few aberrant steps at extremely low treadmill speeds. Thus, the general observation that animals trained to step could not stand and animals trained to stand could not step is powerful evidence of task-specific learning. Further evidence was gleaned by cross-training these animals. Animals that learned to step or stand were later trained to perform the opposite task, although they lost the ability to perform the first task. That is, the isolated spinal cord acquires complex motor skills in a context-dependant manner and requires extensive training.

Recently, treatments based on CPGs have been successfully transferred to human subjects with SCI by several researchers.[70–76] The methods of intervention are based on the principles identified in animals with SCI by Edgerton and colleagues.[67–69] Initially, the individual is partially unweighted over a treadmill, and the lower extremities are manually assisted to step. With training, people with SCI can progress to full weight support and stepping independently while on the treadmill.[70] Even individuals with long-standing, functionally complete lesions have been trained to step independently on the treadmill (see article by Behrman and Harkema[77] in this special series). Furthermore, training at increased treadmill speeds and greater loads across the legs over time facilitated greater angular excursion of the joints, increased amplitudes of muscle activity (measured via electromyography), and facilitated appropriate muscle activation patterns relative to other muscles and to the phases of gait.[70] These findings serve as a dramatic example of the inherent neuroplasticity of the spinal cord. In addition, training can trigger this plasticity several years after the SCI, suggesting that the potential for recovery is somehow preserved in the spinal cord over time.

Summary

The focus of this review has been to highlight current advances in basic science research that may have important implications for understanding recovery of function after SCI. Research using animal models appears to be relevant to humans and can serve as a guide for rehabilitative intervention. In summary, some key factors of SCI are: (1) the initiation of secondary immunological cascades contributes to lesion development and loss of undamaged CNS tissue, (2) anatomically incomplete lesions can exist in humans where the lesion is clinically complete, (3) sparing of tissue at the lesion epicenter can dramatically enhance motor output and is likely to facilitate reorganization of neural systems below the lesion, (4) the spinal cord has the capacity to learn complex motor skills such as locomotion, (5) training paradigms must provide specific, task-dependent experience to facilitate skill acquisition after SCI, and (6) an exercise paradigm based on rhythmic stepping under low-load conditions, developed and extensively used in experimental models of SCI, appears to produce remarkable benefits in humans with SCI as well.

Clinical Implications

Basic science research has contributed dramatically to our understanding of SCI; however, important clinical questions remain. First, we do not know whether motor skill learning after anatomically complete SCI is the same as when the lesion is incomplete, the condition most frequently encountered in the clinic. Perhaps when tissue is spared, less training specificity will be needed to induce learning because more of the CNS can participate. Second, we have a general understanding of training paradigms that facilitate skill acquisition after SCI, but we do not yet know the effect of specific components on learning. For example, there are at least 2 primary paradigms involved in body weight–supported treadmill step training: rhythmicity and loading of the limbs. We currently do not know whether one, both, or none of these paradigms play a primary role in learning to step. Third, it remains to be shown whether treadmill training can reduce the hyperreflexia that often accompanies SCI. Fourth, and perhaps most importantly, there is little data on how to transfer treadmill-induced locomotion to more functionally relevant tasks such as overground locomotion.

My list of questions is meant to illustrate the importance and necessity of clinically based studies. Some of the most important, valuable, and relevant questions concerning advances in the treatment of people with SCI may be posed by physical therapists. Therefore, it is imperative that physical therapists contribute to clinically based research and the development of new treatment approaches.

References

1 Harvey C, Rothschild BB, Asmann AJ, Stripling T. New estimates of traumatic SCI prevalence: a survey-based approach. *Paraplegia.* 1990; 28:537–544.

2 Lazar RB, Yarkony GM, Ortolano D, et al. Prediction of functional outcome by motor capability after spinal cord injury. *Arch Phys Med Rehabil.* 1989;70:819–822.

3 Daverat P, Sibrac MC, Dartigues JF, et al. Early prognostic factors for walking in spinal cord injuries. *Paraplegia.* 1988;26:255–611.

4 Ducker TB, Lucas JT, Wallace CA. Recovery from spinal cord injury. *Clin Neurosurg.* 1983;30:495–513.

5 Yarkony GM, Roth E, Lovell L, et al. Rehabilitation outcomes in complete C5 quadriplegia. *Am J Phys Med Rehabil.* 1988;67:73–76.

6 Ditunno JF, Cohen ME, Formal C, Whiteneck GG. Functional outcomes. In: Stover SL, DeLisa JA, Whiteneck GG, eds. *Spinal Cord Injury: Clinical Outcomes From the Model Systems.* Gaithersburg, Md: Aspen Publications; 1995:170–184.

7 Bunge RP. Clinical implications of recent advances in neurotrauma research. In: Salzman SK, Faden AI, eds. *The Neurobiology of Central Nervous System Trauma.* New York, NY: Oxford University Press; 1994: 329–339.

8 Bunge RP, Puckett WR, Becerra JL, et al. Observations on the pathology of human spinal cord injury: a review and classification of 22 new cases with details from a case of chronic cord compression with extensive focal demyelination. *Adv Neurol.* 1993;59:75–89.

9 Bunge RP, Puckett WR, Hiester ED. Observations on the pathology of several types of human spinal cord injury, with emphasis on the astrocyte response to penetrating injuries. *Adv Neurol.* 1997;72: 305–315.

10 Maynard FM Jr, Bracken MB, Creasey G, et al. International Standards for Neurological and Functional Classification of Spinal Cord Injury. American Spinal Injury Association. *Spinal Cord.* 1997;35: 266–274.

11 Waters RL, Adkins R, Yakura J, Vigil D. Prediction of ambulatory performance based on motor scores derived from standards of the American Spinal Injury Association. *Arch Phys Med Rehabil.* 1994;75: 756–760.

12 Behrmann DL, Bresnahan JC, Beattie MS, Shah BR. Spinal cord injury produced by consistent mechanical displacement of the cord in rats: behavioral and histological analysis. *J Neurotrauma.* 1992;9: 197–217.

13 Stokes BT, Noyes DH, Behrmann DL. An electromechanical spinal injury device with dynamic sensitivity. *J Neurotrauma.* 1992;9:187–195.

14 Gruner JA. A monitored contusion model of spinal cord injury in the rat. *J Neurotrauma.* 1992;9:123–128.

15 Basso DM, Beattie MS, Bresnahan JC. Graded histological and locomotor outcomes after spinal cord contusion using the NYU weight-drop device versus transection. *Exp Neurol.* 1996;139:244–256.

16 Gale K, Kerasidis H, Wrathall JR. Spinal cord contusion in the rat: behavioral analysis of functional neurologic impairment. *Exp Neurol.* 1985;88:123–134.

17 Bresnahan JC. An electron-microscopic analysis of axonal alterations following blunt contusion of the spinal cord of the rhesus monkey (*Macaca mulatta*). *J Neurol Sci.* 1978;37:59–82.

18 Bresnahan JC, King JS, Martin GF, Yashon D. A neuroanatomical analysis of spinal cord injury in the rhesus monkey (*Macaca mulatta*). *J Neurol Sci.* 1976;28:521–542.

19 Ballentine JD. Pathology of experimental spinal cord trauma, I: the necrotic lesion as a function of vascular injury. *Lab Invest.* 1978;39: 236–253.

20 Ballentine JD. Pathology of experimental spinal cord trauma, II: ultrastructure of axons and myelin. *Lab Invest.* 1978;39:254–266.

21 Schwab ME, Bartholdi D. Degeneration and regeneration of axons in the lesioned spinal cord. *Physiol Rev.* 1996;76:319–370.

22 Popovich PG, Wei P, Stokes BT. Cellular inflammatory response after spinal cord injury in Sprague-Dawley and Lewis rats. *J Comp Neurol.* 1997;377:443–464.

23 Popovich PG, Stokes BT, Whitacre CC. Concept of autoimmunity following spinal cord injury: possible roles for T lymphocytes in the traumatized central nervous system. *J Neurosci Res.* 1996;45:349–363.

24 Bergeron L, Yuan J. Sealing one's fate: control of cell death in neurons. *Curr Opin Neurobiol.* 1998;8:55–63.

25 Pettmann B, Henderson CE. Neuronal cell death. *Neuron.* 1998;20: 633–647.

26 Liu XZ, Xu XM, Hu R, et al. Neuronal and glial apoptosis after traumatic spinal cord injury. *J Neurosci.* 1997;17:5395–5406.

27 Crowe MJ, Bresnahan JC, Shuman SL, et al. Apoptosis and delayed degeneration after spinal cord injury in rats and monkeys. *Nat Med.* 1997;3:73–76.

28 Shuman SL, Bresnahan JC, Beattie MS. Apoptosis of microglia and oligodendrocytes after spinal cord contusion in rats. *J Neurosci Res.* 1997;50:798–808.

29 Bracken MB, Shepard MJ, Holford TR, et al. Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury: results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial. National Acute Spinal Cord Injury Study. *JAMA.* 1997;277:1597–1604.

30 Bracken MB, Holford TR. Effects of timing of methylprednisolone or naloxone administration on recovery of segmental and long-tract neurological function in NASCIS 2. *J Neurosurg.* 1993;79:500–507.

31 Basso DM, Beattie MS, Bresnahan JC. A sensitive and reliable locomotor rating scale for open field testing in rats. *J Neurotrauma.* 1995;12:1–21.

32 Noble LJ, Wrathall JR. Correlative analyses of lesion development and functional status after graded spinal cord contusive injuries in the rat. *Exp Neurol.* 1989;103:34–40.

33 Bresnahan JC, Beattie MS, Stokes BT, Conway KM. Three-dimensional computer-assisted analysis of graded contusion lesions in the spinal cord of the rat. *J Neurotrauma.* 1991;8:91–101.

34 Olby NJ, Blakemore WF. A new method of quantifying the extent of tissue loss following spinal cord injury in the rat. *Exp Neurol.* 1996;138: 82–92.

35 Moriarty LJ, Duerstock BS, Bajaj CL, et al. Two- and three-dimensional computer graphic evaluation of the subacute spinal cord injury. *J Neurol Sci.* 1998;155:121–137.

36 Basso DM, Beattie MS, Bresnahan JC, et al. MASCIS evaluation of open field locomotor scores: effects of experience and teamwork on reliability. Multicenter Animal Spinal Cord Injury Study. *J Neurotrauma.* 1996;13:343–359.

37 Goldberger ME, Murray M, Tessler A. Sprouting and regeneration in the spinal cord: their roles in recovery of function after spinal injury. In: Gorio A, ed. *Neuroregeneration.* New York, NY: Raven Press; 1993: 241–264.

38 Pubols LM. Characteristics of dorsal horn neurons expressing subliminal responses to sural nerve stimulation. *Somatosens Mot Res.* 1990;7:137–151.

39 Thompson FJ, Reier PJ, Lucas CC, Parmer R. Altered patterns of reflex excitability subsequent to contusion injury of the rat spinal cord. *J Neurophysiol.* 1992;68:1473–1486.

40 Skinner RD, Houle JD, Reese NB, et al. Effects of exercise and fetal spinal cord implants on the H-reflex in chronically spinalized adult rats. *Brain Res.* 1996;729:127–131.

41 Wang XM, Basso DM, Terman JR, et al. Adult opossums (*Didelphis virginiana*) demonstrate near normal locomotion after spinal cord transection as neonates. *Exp Neurol.* 1998;151:50–69.

42 Ulinski PS. External morphology of pouch young opossum brains: a profile of opossum neurogenesis. *J Comp Neurol.* 1971;142:33–58.

43 Langworthy OR. The development of progression and posture in young opossums. *Am J Physiol.* 1925;74:1–13.

44 Wang XM, Terman JR, Martin GF. Evidence for growth of supraspinal axons through the lesion after transection of the thoracic spinal cord in the developing opossum *Didelphis virginiana*. *J Comp Neurol.* 1996;371:104–115.

45 Martin GF, Ghooray XM, Wang XM, Xu XM. Plasticity of descending spinal pathways in developing mammals. *Adv Neural Sci.* 1995;2: 169–203.

46 Sevier AC, Munger BL. A silver stain for paraffin sections of neural tissue. *J Neuropathol Exp Neurol.* 1965;24:130–135.

47 Weber ED, Stelzner DJ. Behavioral effects of spinal cord transection in the developing rat. *Brain Res.* 1977;125:241–255.

48 Howland DR, Bregman BS, Tessler A, Goldberger ME. Development of locomotor behavior in the spinal kitten. *Exp Neurol.* 1995;135: 108–122.

49 Robinson GA, Goldberger ME. The development and recovery of motor function in spinal cats, I: the infant lesion effect. *Exp Brain Res.* 1986;62:373–386.

50 Hinsey JC, Cutting CC. Reflexes in the spinal opossum. *J Comp Neurol.* 1936;64:375–387.

51 Eidelberg E. Consequences of spinal cord lesions upon motor function, with special reference to locomotor activity. *Prog Neurobiol.* 1981;17:185–202.

52 Voll CA Jr, Fisher LC, Hutchinson KJ, Basso DM. The severity of hyperreflexia is greater after moderate vs mild experimental spinal cord injury in rats. *Neurol Rep.* 1998;22:174.

53 Hutchinson KJ. *The Recovery of Function After Spinal Cord Contusion Injury in Rats: Skeletal Muscle, Neural and Behavioral Adaptations With and Without Exercise* [dissertation]. Columbus, Ohio: Ohio State University; 2000.

54 Basso DM, Bresnahan JC, Beattie MS. Incomplete recovery after spinal cord contusion is associated with a nearly complete loss of vestibulospinal system (VSS) and long descending propriospinal neurons (LDPN) in rats. *Soc Neurosci Abstr.* 1993;19:541.

55 Arshavsky YI, Orlovsky GN, Perret C. Activity of rubrospinal neurons during locomotion and scratching in the cat. *Behav Brain Res.* 1988;28: 193–199.

56 Orlovsky GN. Activity of rubrospinal neurons during locomotion. *Brain Res.* 1972;46:99–112.

57 Orlovsky GN. Activity of vestibulospinal neurons during locomotion. *Brain Res.* 1972;46:85–98.

58 Orlovsky GN. The effect of different descending systems on flexor and extensor activity during locomotion. *Brain Res.* 1972;40:359–371.

59 Perreault MC, Drew T, Rossignol S. Activity of medullary reticulospinal neurons during fictive locomotion. *J Neurophysiol.* 1993;69: 2232–2247.

60 Forssberg H, Grillner S, Halbertsma J, Rossignol S. The locomotion of the low spinal cat, II: interlimb coordination. *Acta Physiol Scand.* 1980;108:283–295.

61 Paxinos G, Watson C. *The Rat Brain in Stereotaxic Coordinates.* New York, NY: Academic Press; 1986.

62 Grillner S, Zangger P. On the central generation of locomotion in the low spinal cat. *Exp Brain Res.* 1979;34:241–261.

63 Grillner S, Wallen P. Central pattern generators for locomotion, with special reference to vertebrates. *Ann Rev Neurosci.* 1985;8:233–261.

64 Grillner S, Dubuc R. Control of locomotion in vertebrates: spinal and supraspinal mechanisms. *Adv Neurol.* 1988;47:425–453.

65 Brown TG. On the nature of the fundamental activity of the nervous centres; together with an analysis of the conditioning of rhythmic activity in progression, and a theory of evolution of function in the nervous system. *J Physiol.* 1914;48:18–46.

66 Barbeau H, Rossignol S. Recovery of locomotion after chronic spinalization in adult cat. *Brain Res.* 1987;412:84–95.

67 Hodgson JA, Roy RR, Dobkin B, Edgerton VR. Can the mammalian lumbar spinal cord learn a motor task? *Med Sci Sports Exerc.* 1994;26: 1491–1497.

68 de Leon RD, Hodgson JA, Roy RR, Edgerton VR. Locomotor capacity attributable to step training versus spontaneous recovery after spinalization in adult cats. *J Neurophysiol.* 1998;79:1329–1340.

69 Edgerton VR, de Leon RD, Tillakaratne N, et al. Use-dependent plasticity in spinal stepping and standing. *Adv Neurol.* 1997;72:233–247.

70 Harkema SJ, Hurley SL, Patel UK, et al. Human lumbosacral spinal cord interprets loading during stepping. *J Neurophysiol.* 1997;77: 797–811.

71 Dobkin BH, Harkema SJ, Requejo PS, Edgerton VR. Modulation of locomotor-like EMG activity in subjects with complete and incomplete spinal cord injury. *J Neurol Rehab.* 1995;9:183–190.

72 Wernig A, Muller S, Nanassy A, Cagol E. Laufband therapy based on "rules of spinal locomotion" is effective in spinal cord injured persons [published erratum appears in *Eur J Neurosci* 1995;7:1429]. *Eur J Neurosci.* 1995;7:823–829.

73 Visintin M, Barbeau H, Korner-Bitensky N, Mayo NE. A new approach to retrain gait in stroke patients through body weight support and treadmill stimulation. *Stroke.* 1998;29:1122–1128.

74 Norman KE, Pepin A, Ladouceur M, Barbeau H. A treadmill apparatus and harness support for evaluation and rehabilitation of gait. *Arch Phys Med Rehabil.* 1995;76:772–778.

75 Visintin M, Barbeau H. The effects of body weight support on the locomotor pattern of spastic paretic patients. *Can J Neurol Sci.* 1989;16: 315–325.

76 Dietz V, Colombo G, Jensen L, Baumgartner L. Locomotor capacity of spinal cord in paraplegic patients. *Ann Neurol.* 1995;37:574–582.

77 Behrman AL, Harkema SJ. Locomotor training after human spinal cord injury: a series of case studies. *Phys Ther.* 2000;80:688–700.