Despite the interruption in communication between the brain and lower centers by spinal cord injury, many of the neurons engaged in generating locomotion survive. Several strategies have been used to activate spinal cord circuitry independent of the higher centers, including direct electrical stimulation, pharmacological agents, and training programs that involve moving the legs through the motions of walking. Ambulatory leg movements are achieved by these interventions, leading to substantial functional improvements in the subset of patients with incomplete spinal cord injury. The neurobiological basis for these phenomena likely involves activity-dependent reconfiguration of synaptic connections within the spinal cord. Fostering this process may lead to further benefits for individuals with spinal cord injury.

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Within the realm of mindless activities, only breathing rivals walking. Conscious control can be superimposed, but munching on a muffin and glancing at a newspaper while walking is routine. Compensatory minor adjustments for surface irregularities, balance, speed, and rhythm essentially proceed by autopilot. The neuroanatomical system that subserves this remarkable ability is widely distributed, involving neurons in the cerebral cortex, brainstem, cerebellum, and spinal cord. Perhaps because of its presence in even the most primitive of chordates, the spinal cord is often thought to receive instructions passively from higher centers. A consortium of neurons within the upper lumbar cord termed the central pattern generator (CPG) plays a fundamental role by interpreting descending and segmental afferent signals and patterning the firing of motor neurons. This network of neurons drives the rhythmic activation and relaxation of groups of leg muscles and coordinates the movement of one leg with the other.

Studies of laboratory animals and, to a lesser extent, human beings have provided insight into the structure and function of the spinal cord circuitry underlying walking. The following 2 features bear highlighting: (1) even when disconnected from supraspinal inputs, the isolated spinal CPG can generate ambulatory alternating leg movements, and (2) the isolated CPG circuitry can be trained to learn specific tasks. These 2 key properties have captured the imagination of researchers in the spinal cord injury (SCI) field. If the neuronal ensemble within lumbar enlargement can be stimulated to generate ambulatory leg movements, could this form the basis for walking by individuals with SCI? Evidence now exists that this approach can lead to important functional benefits for individuals with SCI.

To begin to determine the utility of various methods for stimulating the spinal CPG, it is important to identify and quantify the deficits that exist in individuals with clinically incomplete SCI. The characteristic abnormalities seen on gait evaluation of individuals with SCI include a reduction in walking speed, a longer swing-stance cycle duration, and a shorter stride length. Angular displacements of leg joints during walking deviate substantially from those seen in healthy individuals. Specific therapeutic interventions may lead to amelioration of particular walking deficits. It seems likely that if a series of small improvements in these


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measures can be achieved, the aggregate benefit will lead to the most important outcome, an improvement in function.

Several methods have been used to stimulate the isolated human lumbar spinal cord and have met with variable success in eliciting walking. Beyond the intrinsic efficacy of individual stimulation paradigms, a number of other factors have an impact on the utility of these approaches, including the age of the patient, the interval between injury and stimulation, and the severity of the SCI. The major approaches tried include (1) direct electrical stimulation of the lumbar spinal cord, peripheral nerves, or muscles; (2) pharmacological activation of specific subtypes of neurotransmitter receptors; and (3) activation of segmental afferent nerve fibers in the leg by moving paralyzed limbs through the trajectory of normal walking.

In the intact nervous system, descending inputs from brainstem neurons from the pedunculopontine nucleus and the mesencephalic locomotor region provide a tonic drive to the spinal CPG that is needed for locomotion. In an attempt to mimic this input, epidural stimulation at the T10 through L1 vertebral levels was provided to selected individuals with a complete SCI. One of the justifications for this invasive approach is that epidural spinal cord stimulation is an accepted means of reducing spasticity. Epidural stimulation led to steplike movements of the leg with organized flexion/extension of multiple groups of muscles. By changing stimulation variables, such as the strength of the electrical input and the frequency and location along the dorsal spinal cord, investigators were able to convert tonic leg extension into rhythmic and well-coordinated steplike movements. Although this work is a remarkable achievement, there are some caveats. First, although steplike movements could be elicited in a single leg, alternating leg movements proved to be more difficult, if not impossible, to achieve. Second, although visible leg movements were observed (and could be recorded by means of surface electromyography), they were feeble. It is questionable whether electrically stimulating the spinal cord engenders sufficient leg strength to permit weight bearing and walking. Despite these limitations, the demonstration of a human lumbar spinal cord CPG is important. The generation of inchoate walking movements in individuals with complete SCI has significant implications, as will be described herein.

An alternative electrical stimulation approach has been used in individuals with incomplete SCI. Functional electrical stimulation (FES) involves direct stimulation of peripheral nerves and/or muscles, in an attempt to augment motor abilities that were curtailed by the initial injury. Some devices simply stimulate leg flexors when a hand switch is pressed and stimulate leg extensors when released. More sophisticated multichannel devices with tilt sensors providing feedback are also available. Mastery of the FES-assisted ambulation requires a prolonged training period under the attentive guidance of a skilled therapist. In a multicenter Canadian study, application of FES to individuals with incomplete SCI led to significant improvement of walking speed, stride length, and cycle duration. The effects on walking could be attributed to the FES and training per se. Improvement in gait was seen in all individuals, regardless of the severity of the initial deficit. The relative importance of FES vs training varied as a function of the initial deficit. Individuals who began this program with the smallest deficits experienced the most improvement, and the increase in walking speed was entirely attributable to the training, not FES.

It has long been recognized that spasticity can be a significant impediment to walking for individuals with SCI. The pharmacotherapeutic mainstays for individuals with SCI include the antispasticity medications such as  \( \gamma \)-aminobutyric acid, serotonin receptor antagonists, and \( \alpha \)-adrenergic receptor agonists (a complete list of antispasticity medications is given in the Table). On the other hand, some degree of increased leg tone is helpful for these individuals by enabling upright posture and promoting walking. Increasing antispasticity medications past a threshold dose leads to worsening of gait in ambulatory individuals with SCI. Titration of therapy with these drugs to achieve an optimal level of reflex tone in legs must be tailored to meet individual needs.

More recent attention has turned to the idea that some of the drugs used to control spasticity might be capable of triggering or facilitating patterned leg movements. Studies of laboratory animals indicate this approach could be very promising. For example, when the \( \alpha \)-noradrenergic agonist clonidine hydrochloride is administered to cats with an acute spinal cord transection, normal-appearing walking and hind-limb weight support can be elicited. In addition, when animals with chronic SCI are trained to walk, the administration of clonidine had significant additive effects that increased the maximum speed of walking. Even untrained cats with chronic SCI benefited from clonidine administration.

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**Medications Used to Alleviate Spasticity**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>GABAergic</td>
<td>Dantrolene sodium, Baclofen, Propranolol hydrochloride, Clonidine hydrochloride, Tizanidine hydrochloride, Cyproheptidine hydrochloride, GABAergic</td>
</tr>
<tr>
<td>Noradrenergic</td>
<td>Clonidine hydrochloride, Propranolol hydrochloride, Clonidine hydrochloride</td>
</tr>
<tr>
<td>Serotonergic</td>
<td>Prozac, Fluoxetine, Sertraline, Fluvoxamine, Serotonin receptor antagonists</td>
</tr>
<tr>
<td>Other</td>
<td>Morphine sulfate, Lidocaine hydrochloride (Xylocaine)</td>
</tr>
</tbody>
</table>
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**Abbreviation:** GABAergic, directing  \( \gamma \)-aminobutyric acid.

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In a placebo-controlled trial in individuals with clinically complete SCI, clonidine showed no beneficial effect on walking. In contrast, when administered to individuals with a partial SCI, clonidine led to improvements in walking.11 These clinical studies involved oral clonidine, and preliminary work has also been undertaken using intrathecal clonidine. The improvements in walking speed and the duration of the effects were more pronounced with intrathecal clonidine.12

Precisely how clonidine works to improve walking is not clear. However, it is likely not simply due to its antispasticity actions. Other drugs are equally effective in reducing spasticity yet do not trigger ambulatory leg movements. For example, the serotonergic antagonist cyproheptadine hydrochloride effectively reduces clonus and spontaneous spasms in individuals with SCI.13 Administration of cyproheptadine to individuals with markedly increased tone derived important functional benefits. Cyproheptadine had no beneficial effects on individuals with partial SCI who did not have clonus or spasticity. An important goal will be to understand the relationship between the circuitry underlying spasticity and that driving ambulation. If these two can be dissociated, the development of drugs that specifically stimulate the spinal cord CPG may occupy an important niche in the therapy for individuals with SCI.

The above-described methods for engaging spinal cord CPGs involve the application of exogenous (electrical or chemical) stimuli. Except in the case of complete anatomic spinal cord transection, the locus of action may involve activation of sites in addition to the lumbar spinal cord. An alternative method that enlists the participation of endogenous afferent systems within the segmental spinal cord is termed exercise therapy or interactive locomotor training. In humans and experimental animals with SCI, a significant functional benefit is derived from a training program of repeatedly moving paralyzed limbs through the normal trajectory taken when walking.

In the 1980s, several groups investigated the beneficial effects of locomotor training on cats with SCI.14-16 Spinalized animals were suspended over a treadmill, and investigators lifted and placed the legs on the moving surface to replicate walking. These training sessions occurred daily for several weeks. Over time, several measures of functional improvement became evident. First, the amount of investigator intervention could be cut back; second, the amount of hind-limb unweighting by suspension could be reduced; and third, treadmill speed could be increased. After 3 to 4 weeks of this training program, spinalized animals were able to walk on a moving treadmill unassisted. Furthermore, spinalized cats could learn to step over and avoid a small obstruction on the moving treadmill. A distinct training program undertaken with a second set of spinalized cats achieved full-weight support standing.17 The important conclusion to draw from this body of work is that the circuitry within the lumbar spinal cord is sufficient to evoke several important behaviors such as standing and walking. What is required is a specific pattern of segmental afferent input to stimulate and instruct the network. The capacity to learn task-specific motor programs illustrates the inherent plasticity of interneuronal communication within the spinal cord.

Several centers that treat humans with SCI have applied these lessons to their patients and met with varying degrees of success.18,19 The basic approach involves supporting of body weight (unloading is accomplished with a parachute harness), stationing the patient over a treadmill, and having a physiotherapist assist leg movements (Figure). Special attention is directed toward foot liftoff and subsequent planting of the companion extended leg. A common approach involves 15- to 30-minute sessions occurring 5 times per week for approximately 3 months. Individuals with partial injuries showed improvements in walking speed, endurance, and the need for support. Quantitative electromyographic analysis showed increased activity in leg muscles such as the gastrocnemius. In some individuals, the patterns of leg muscle activation showed qualitative adjustments. Instead of the coactivation of extensors and flexors evident before therapy, a reciprocating pattern was achieved after therapy. Measurable improvements in leg movements could be achieved with the training of individuals with complete SCI, but the functional improvements were small. Stepping movements were only exhibited when body weight was reduced, although the amount of unweighting diminished with training. Although locomotor-patterned activation of leg muscles resulted from training, these effects were quantitatively smaller in comparison with those in individuals with incomplete SCI.

In studies of spinalized cats, administration of clonidine at the time of exercise therapy accelerated recovery.20 This has naturally led to the idea of combining interactive locomotive training of humans with SCI with pharmacological stimulation. Anecdotal reports use this approach, but whether this hastens and/or increases functional improvement is difficult to know.20 In individuals with SCI who have poor ambulatory leg movements with body-weight support at the treadmill, initiation of ambulation pharmacologically or by means of electrical
stimulation might be particularly useful. Pharmacological supplementation to interactive gait training should be evaluated prospectively in clinical trials.

How long do the benefits of locomotive training last? A few studies have examined this issue, and in some individuals with incomplete SCI, the functional improvements can be indefinite.\cite{21,22} A likely scenario is that once a higher level of ambulatory function is achieved, individuals use this new capability. Increased use stimulates the revised neuronal circuitry. Whatever the nature of the adaptive processes, feed-forward positive reinforcement is salubrious.

There has been relatively little inquiry into the neurobiological events occurring within the spinal cord that underlie the adaptation process. On the basis of the human and animal studies, the most likely inference is that use-dependent modifications of synaptic efficacy and remodeling of synaptic connections subserves the adaptation process. Synaptic activity-dependent growth and modification of interneuronal connectivity is a normal part of spinal cord development.\cite{23} The activity-dependent fine tuning of connectivity tailors each organism’s nervous system to the environment in which it was reared.\cite{24,25} It is plausible that this machinery can be engaged after SCI and, if appropriately stimulated, can lead to useful restructuring of synaptic organization. Insight into the molecular events driving activity-dependent spinal cord development might be profitably applied to individuals with SCI to enhance interactive training therapy.

As advances in the acute care of individuals with SCI proceed, reductions in the severity of myelopathy will surely follow. In addition, progress is being made in coaxing axons to ignore inhibitory factors (largely derived from myelin) and grow past a focal spinal cord lesion.\cite{26,27} These factors working together make it likely that, in the future, most spinal cord insults will lead to a clinically incomplete phenotype. It is reasonable to anticipate that optimizing the circuitry that survives after the initial insult will play an increasing prominent therapeutic role for individuals with SCI.

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