Neural Plasticity after Human Spinal Cord Injury: Application of Locomotor Training to the Rehabilitation of Walking

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Recovery of locomotion has been considered unattainable following a clinically complete or severe incomplete spinal cord injury even after conventional therapy. However, the locomotion of spinal animals can be improved by training that provides complex temporal patterns of sensory information related to stepping that is interpreted by the spinal cord. This review discusses the evidence that suggests human spinal networks can integrate and interpret complex sensory signals to produce functional efferent output and adapt to repetitive training. Locomotor training, a new rehabilitative approach, is based on principles that promote the movement of limbs and trunk to generate sensory information consistent with locomotion to improve the potential for the recovery of walking after neurologic injury. NEUROSCIENTIST 7(5):455–468, 2001

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The adult mammalian lumbosacral spinal cord can relearn to step in the absence of supraspinal input when sensory information associated with weight-bearing stepping occurs periodically (Lovely and others 1986; Barbeau and Rossignol 1987; Barbeau and others 1993; de Leon and others 1998b). The ability to hindlimb step over a range of speeds after complete spinal transection is attributed to intrinsic oscillating spinal neural networks capable of central pattern generation interacting with sensory input associated with locomotion (Grillner and Zangger 1979; Grillner 1981; Grillner 1985; Gossard and Hultborn 1991). Evidence for locomotor spinal central pattern generation has been derived from studies in a variety of vertebrates, including adult cats and marmosets, which have undergone spinal cord transection and lumbosacral afferent denervation and produced fictive locomotion (rhythmical flexor and extensor motor output) (Edgerton and others 1976; Grillner 1985; Fedirchuk and others 1998). The specific pathways for central pattern generation in mammals remain obscure.

The locomotion of spinal animals can be improved by providing repetitive stepping, that is, by training for the specific motor task (de Leon and others 1998b). The neuronal pathways responsible for motor learning in the spinal cord in response to training also remain undefined. The pathways that adapt to motor training presumably differ depending on the practiced motor task. Training complete spinal transected animals to stand by weight bearing bilaterally or unilaterally demonstrated that the mammalian spinal cord can learn a task other than stepping (de Leon and others 1998a). The afferent signaling during stepping and standing is interpreted by the spinal cord as unique patterns of sensory input for a given phase of the particular motor task. This ability to interpret these task-specific afferent inputs effectively can be improved by repeated presentations, that is, practicing the motor task (de Leon and others 1998a, 1998b, 1999). The mammalian spinal cord has the ability to process complex temporal patterns of sensory information related to a specific motor task and to relearn the practiced task in the absence of supraspinal input.

This review addresses whether the human spinal cord also has similar neuronal properties including central pattern generation and the ability to relearn when provided with sensory information related to a specific motor task. Locomotor training, a new rehabilitative approach suggested to improve the potential for the recovery of walking after neurologic injury, is based on principles derived by the studies of animal models discussed previously. This review presents locomotor training after human spinal cord injury and then directly addresses properties of the human spinal cord including 1) central pattern generation, 2) integration and interpretation of complex sensory information, and 3) relearning to step and stand.

LocomotorTraining Using Body Weight Support on a Treadmill with Manual Assistance

Barbeau and colleagues (1987) described a body weight support and treadmill (BWST) system and an approach for locomotor rehabilitation based on animal models demonstrating the recovery of hindlimb stepping following complete spinal transection (Lovely and others 1986; Barbeau and Rossignol 1987). Subsequent variations of

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BWST systems and approaches to locomotor training have developed and include the individual suspended over a treadmill in a harness and an overhead support system (Fung and others 1990; Barbeau and Blunt 1991; Stewart and others 1991; Wernig and Müller 1991; Wernig and others 1992; Visintin and Barbeau 1994; Dietz and others 1995; Dobkin and others 1995; Norman and others 1995; Wernig and others 1995; Harkema and others 1997; Dietz, Curt, and others 1998; Dietz, Wirz, and others 1998; Wernig and others 1999; Behrman and Harkema 2000; Gordon and others 2000). BWST systems provide an environment in which one can facilitate balance control and manually assist trunk and leg movement during weight-bearing stepping and standing. Locomotor training is based essentially on principles that promote the movement of the limbs and trunk to generate sensory information consistent with locomotion. In conjunction with the application of the locomotor training principles using BWST, these principles must also be translated to overground ambulation to obtain a meaningful level of recovery of walking after neurologic injury.

Locomotor training principles have been described that are fundamentally based on providing specific sensory cues that provide patterns of information related to locomotion (Behrman and Harkema 2000). Some important principles include 1) generating stepping velocities approximating normal walking speeds; 2) providing normal load patterns on the stance limb; 3) maintaining an upright and extended trunk and head; 4) approximating hip, knee, and ankle kinematics within normative ranges; 5) synchronizing the extension of the hip in stance and unloading of one limb with simultaneous loading of the contralateral limb; 6) avoiding or minimizing weight bearing on the arms and facilitating reciprocal arm swing; and 7) maintaining symmetrical interlimb kinematics and kinetics. Each of these principles is designed to maximize sensory stimulation that matches the kinetic and kinematic properties associated with the phases of stepping. Several other researchers have described similar principles with the primary difference being significantly lower velocities of stepping (Fung and others 1990; Barbeau and Blunt 1991; Wernig and others 1992; Visintin and Barbeau 1994; Dietz and others 1995; Wernig and others 1995). Although the studies presented in the following sections have provided important results that are being used in some clinics, the development of locomotor training is still evolving.

Central Pattern Generation within the Human Spinal Cord?

Some investigators concluded that the "spinal central pattern generator for locomotion depends more heavily on the presence of supraspinal influences in primates" (Stewart and others 1991), a conclusion also reached by Eidelberg and colleagues (1981) after they were unable to produce locomotion with step training in spinally transected nonhuman primates. However, others suggested that this finding was unexpected and warranted further research (Vilensky and others 1992). The possibility of conservation of spinal central pattern generation for locomotion in primates became somewhat more compelling after fictive locomotion was demonstrated in nonhuman primates (Fedirchuk and others 1998). However, it was more difficult to activate pharmacologically compared with other mammals.

Bussel and others (1989) suggested that humans may have a spinal locomotor circuit similar to other mammals such as a central pattern generator. The early flexor reflex and the long-latency reflex were observed in clinically complete spinal cord injured (SCI) subjects and were attributed to spinal reflexes (Roby-Brami and Bussel 1987). Early and long latency reflexes were well documented in the acute and chronic spinal cat with pathways identified that were linked to alternating stepping movements and central pattern generation (Jankowska and others 1967a, 1967b). Bussel and colleagues (1989) noted the following similarities in these reflexes from the chronic spinal cats and from humans with SCI: long spinal delay of the late flexor reflex, the late flexor reflex response to cutaneous and muscle low threshold stimulation, and an increase in the latency with stimulus intensity. These results led the authors to conclude that at least some of the circuitry for central pattern generation is evident in the human spinal cord.

Rhythmic, alternating electromyographic (EMG) activity of the lower limbs in the absence of supraspinal afferent input also has been interpreted as evidence for central pattern generation in the human spinal cord. In one study, continuous epidural spinal cord stimulation induced rhythmic, alternating locomotor-like EMG activity in the lower limbs of six clinically complete SCI subjects (Dimitrijevic and others 1998). Bilateral stimulation of the dorsal surface of the lumbar spinal cord elicited step-like EMG activity in the quadriceps, adductors, medial hamstrings, tibialis anterior, and triceps surae with extension and flexion movements of one limb in four clinically complete subjects. Bilateral EMG activity and lower limb oscillations occurred with lumbosacral spinal cord stimulation in two clinically complete SCI subjects. The amplitude, duration, and rhythmicity of the EMG activity were modulated by stimulus strength and depended on the frequency of stimulation. Similarly, continuous electrical stimulation of the lumbosacral enlargement induced fictive stepping in acutely spinal transected cats (Grillner and Zangger 1975; Edgerton and others 1976; Grillner and Zangger 1979). However, these experiments differ from the human experiments in that there was no activation of afferents synchronized with the alternating movement because the muscles were paralyzed with curare. Therefore, the locomotor-like patterns demonstrated in the cat model can clearly be attributed solely to central pattern generation.

In another study, involuntary rhythmic, locomotor-like activity was observed in a chronic clinically incomplete SCI subject and attributed to central pattern generation (Calancie and others 1994). EMG activity from the soleus, quadriceps, and hamstrings was coactivated during the extension phase of alternating lower limb move-

ments (0.3 Hz). The iliopsoas and tibialis anterior were continuously activated throughout the cycle, with increases at the end of extension and during the flexion phase with reciprocity between the two limbs. These locomotor-like patterns occurred when the subject was supine and the hips and knees were fully extended and diminished if the subject's hips were flexed. Flexion of the neck could also abolish the rhythmic activity. Surface electrical stimulation of the sole of the foot would interrupt the lower limb rhythmic pattern. The subject could not volitionally initiate or interrupt these movements, and they did not occur when the subject was upright and full weight bearing or completely suspended but did occur with partial body weight support. During stepping using BWST without manual assistance at slow velocities (0.05 m/s–0.3 m/s), alternating EMG patterns were observed with some modulation occurring with the presentation of lower limb weight bearing. Although voluntary activation did not appear to mediate the locomotor-like lower limb activity, supraspinal input and concurrent afferent feedback synchronized with the lower leg movements available to the spinal cord are likely to have contributed significantly to the locomotor-like patterns.

Another study described rhythmic lower limb movements in a clinically complete SCI subject, and these movements were attributed to the activation of central pattern generation (Bussel and others 1988). Rhythmic EMG activity synchronized among the soleus, hamstrings, and longissimus thoracis muscles were recorded at 0.6 Hz in both limbs, with no activity observed in flexors. The rhythmic EMG activity was sensitive to peripheral stimulation given below but not above the level of lesion. Trunk movements and unilateral hip flexion could modulate the activity, and bilateral hip flexion would abolish the movements. A sustained soleus stretch and cutaneous or thermal stimulation reduced the EMG frequency. Flexor reflex afferent stimulation during the rhythmic activity would induce flexor activity that always occurred between two bursts of extensor activity and persisted for several cycles generating an alternating pattern of extensors and flexors. Occasionally, after flexor afferent stimulation, alternating activity between the two limbs was observed for one cycle. The observations of rhythmic EMG activity modulated by peripheral stimulation in the absence of detectable supraspinal input indicate that the spinal networks can process afferent input and generate coordinated movements across joints.

Dietz and others (1999) also suggested that neuronal circuits for "locomotor pattern generation" exist and extend from the thoracic to cervical level and the strength of the pattern depends on the level of lesion. These conclusions were based on analyses of EMG activity from the gastrocnemius and tibialis anterior during manually assisted stepping using BWST from 13 clinically complete and 5 clinically incomplete SCI subjects. EMG amplitudes averaged over 20 step cycles from both legs of all subjects were directly compared with the level of lesion (from thoracic 12 to cervical 5). Significant correlations were found between EMG amplitude and the level of the cord lesion for the tibialis anterior during swing and the gastrocnemius during stance ($r = 0.35$, $r = 0.48$, respectively). Also, the modulation of the tibialis anterior and gastrocnemius was assessed by calculating a variance ratio from data from each SCI subject pooled with data from 16 nondisabled subjects (Erni and Colombo 1998). This ratio was then compared with the level of lesion, with a significant correlation only in the gastrocnemius ($r = 0.33$). Based on the low correlation ratios, a more comprehensive evaluation of the lower limb muscle activities will be necessary to be conclusive on the functional link between the level of lesion and the EMG modulation.

None of the studies above represents a sufficient test of whether central pattern generation can occur in the human spinal cord. Although there can be reasonable assurance that some studies eliminated supraspinal input, none has eliminated afferent input to the lumbosacral spinal cord. These studies, however, clearly demonstrate that after cervical and thoracic lesions, locomotor-like EMG patterns and lower limb movements can occur in the absence of supraspinal input and can be modulated in a phase-dependent manner. In the context of the recovery of locomotion in humans after neurologic injury, it may not be critical to provide clear evidence for intrinsic neural circuits that oscillate in the absence of oscillatory supraspinal or peripheral input. The more critical question clinically is whether the spinal networks can process remaining descending input and the proprioceptive inputs derived from stepping and standing to facilitate the generation of effective and functional motor patterns.

Sensory Processing at the Level of the Human Spinal Cord

Several studies have addressed the role of the spinal cord in processing sensory information by assessing the motor output from clinically complete SCI subjects. Stewart and others (1991) reported that the primary efferent responses observed during stepping with manual assistance using BWST could be attributed to stretch reflexes in clinically motor-complete SCI subjects (sensory function but not motor function detectable below the lesion). The medial hamstrings' EMG activity observed during passive flexion and extension of the knee and during stepping was coincident with stretch of the hamstring and was abolished after administration of clonidine. Furthermore, gastrocnemius and tibialis anterior EMG activity was characterized as clonic during stepping and this property was diminished after clonidine. These results suggested to the investigators that the spinal cord sensory processing might be limited to mediating reflexes. However, in effect these results may simply illustrate that stretch reflexes can be manifested in SCI subjects as they can be in nondisabled individuals. Furthermore, there is clear evidence from clinically complete and clinically incomplete SCI subjects that clonic EMG activity observed during stepping cannot be attributed solely to stretch reflexes (Beres and others 2001).

Harkema and others (1997) suggested that the human lumbosacral spinal cord can interpret complex sensory information related to stepping not confined to simply reflexive responses such as the stretch reflex. The efferent patterns from two clinically complete SCI, two clinically incomplete SCI, and two nondisabled subjects were studied during varied levels of lower limb weight bearing. The level of loading, EMG activity, and kinematics were studied during manually assisted or unassisted stepping (0.54 m/s) using BWST. The soleus, medial gastrocnemius, and tibialis anterior EMG mean amplitudes were directly related to peak limb load, and the response was similar in all subjects independent of level of available supraspinal input (Fig. 1). The modulation of the EMG amplitude of all muscles was more closely associated with peak limb load than muscle-tendon stretch or muscle-tendon velocity as shown by exemplary data from the soleus (Figs. 2 and 3). Although sensory information associated with muscle-tendon stretch (Fig. 2*C* and 2*D*) and velocity of muscle-tendon stretch (Fig. 2*E* and 2*F*) during stepping had some effect on the efferent motor patterns of the lower limbs, the EMG amplitudes were less coupled to length factors than limb peak load per step (Fig. 2*A* and 2*B*) in clinically complete SCI subjects. Furthermore, representative data from two consecutive steps with different limb peak load levels show that the highest EMG activity and limb load occurred during the second step, whereas the greatest stretch occurred in the first step in both nondisabled (Fig. 3*A–C*) and clinically complete subjects (Fig. 3*E–G*). In addition, in both subjects, the EMG amplitude within a step was dependent on the phase of the step cycle regardless of the level of load (Fig. 3). These results suggest that the human lumbosacral spinal cord interprets limb loading during stepping in a phase-dependent manner. Furthermore, the EMG activity from the soleus, medial gastrocnemius, and tibialis anterior could not be solely attributed to stretch reflexes during stepping in clinically complete SCI subjects.

Further examples of complex processing mediated at the level of the human spinal cord can be observed when comparing EMG activity at different stepping velocities (Patel and others 1998). The amplitudes of EMG activity in the lower limb muscles increased at faster treadmill speeds in both clinically incomplete and complete SCI subjects. Figure 4 shows representative EMG activity from a clinically complete SCI subject, a treadmill speed of 0.81 m/s (a moderate walking speed) compared with 0.36 m/s. EMG amplitudes were higher at the faster treadmill speed at functionally appropriate phases of the step cycle. For example, during stance at the faster speed, the EMG amplitude of the soleus and medial gastrocnemius were significantly higher. During the swing phase, higher EMG amplitudes of the hip flexor, iliopsoas, and the knee flexor, medial hamstring, occurred at the faster treadmill speed. Tibialis anterior EMG bursts, however, often occurred throughout the stance phase in the SCI subjects as observed previously in SCI subjects (Conrad and others 1985; Stewart and others 1991). Both clinically complete and clinically incomplete SCI subjects routinely executed the swing phase without physical assistance from the trainer at faster treadmill speeds.

Clinically complete and incomplete SCI subjects also demonstrated similar temporal and amplitude modulation of iliopsoas EMG patterns in response to changes in speed (Fig. 5) (Harkema and others 2000). Regardless of the speed of stepping, the onset of the iliopsoas EMG burst and initiation of swing were tightly coupled and always occurred during the phase of limb unloading and were dependent on hip position in SCI subjects similar to that which has been detailed in studies of locomotion in cats (Grillner and Rossignol 1978; Duysens and Pearson 1980; Andersson and Grillner 1983; Lovely and others 1986; Conway and others 1987). These results suggest complex processing of sensory information related to the velocity of limb movements within the human spinal cord that can modulate EMG activity in a functionally appropriate, that is, phase-dependent manner during stepping.

Sensory processing of afferent locomotion was also suggested by Wernig and Müller (1991) and Wernig and others (1992, 1995) when the recovery of walking in clinically incomplete subjects was not correlated with recovery of voluntary control of the lower limbs. Four clinically incomplete subjects with some voluntary motor function in one limb and none present in the other limb regained the ability to walk overground after locomotor training but did not appreciably improve in voluntary movements of the most severely paralyzed limb. These results suggested that the afferent information associated with locomotion facilitated the activation of lower limb motorneurons sufficiently to produce walking. Although these studies cannot distinguish clearly the relative contribution of spinal versus supraspinal centers in the recovery of ambulation, the bilateral stepping achieved in subjects with no voluntary control on one side emphasizes the importance of the spinal circuitry and proprioception in generating the stepping with severely compromised supraspinal input.

Maegele and others (2001) provided more direct evidence that sensory processing by the human spinal cord plays a significant role in the motor output during stepping. Soleus, medial gastrocnemius, tibialis anterior, medial hamstrings, vastus lateralis, and rectus femoris EMG activity from seven clinically incomplete and three clinically complete SCI subjects was recorded during voluntarily attempted non-weight-bearing single-joint movements, multijoint movements approximating stepping in a supine position, and stepping using BWST. The EMG mean amplitudes were significantly higher during stepping using BWST than during voluntary movements in 50/60 muscles studied, and some muscles were activated during stepping but not during voluntary attempts. In the clinically incomplete SCI subjects during attempts at isolated knee or ankle single-joint movements, significant coactivation of agonists and antagonists occurred as well as multijoint flexion or extension movements of the entire limb. However, stepping produced more reciprocal patterns of activity between agonists and antago-

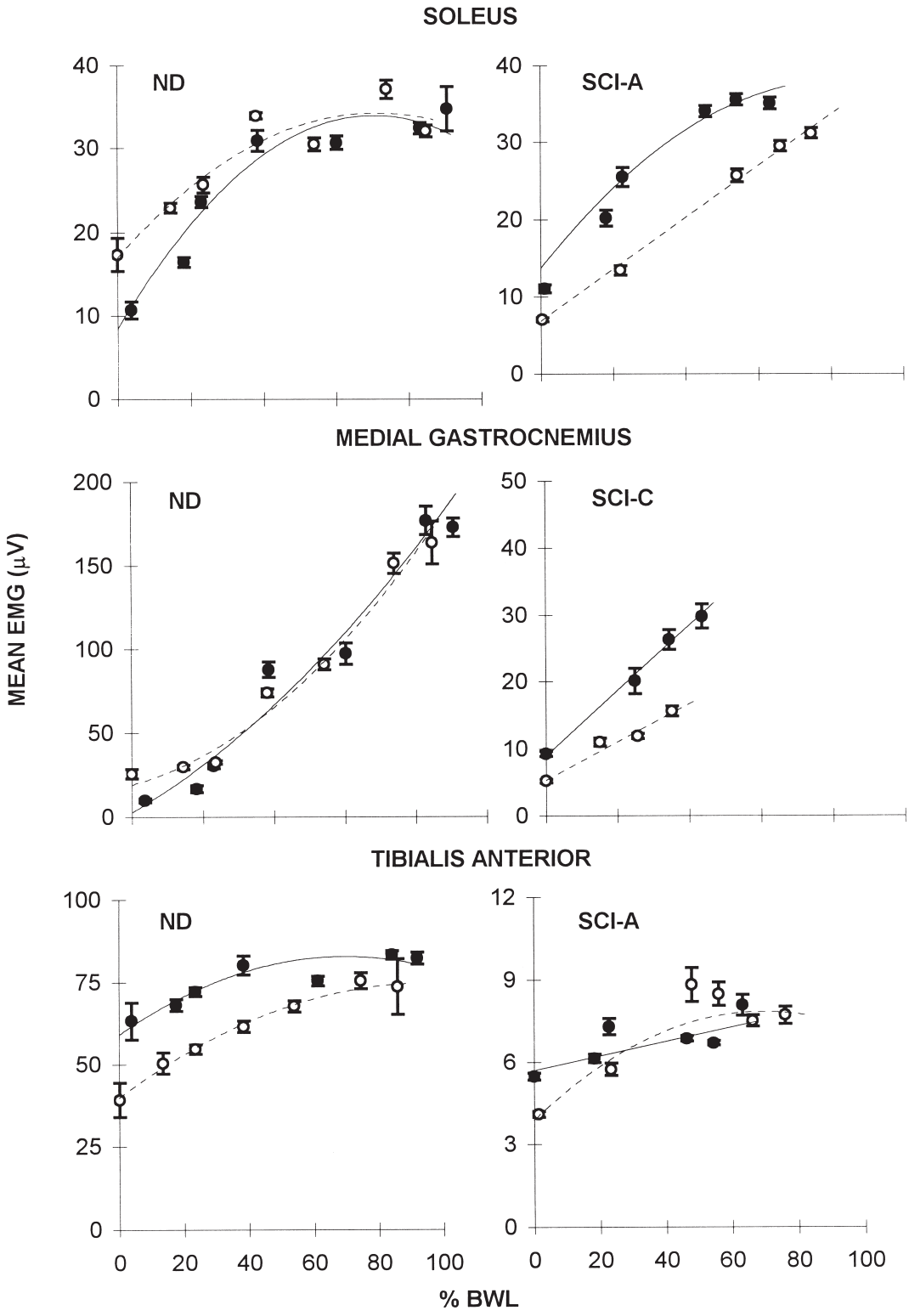

Fig. 1. Extensor and flexor electromyographic (EMG) activity increased with higher peak limb loading conditions independent of the level of available supraspinal input as shown by exemplary data from nondisabled (ND) and spinal cord injured (SCI) subjects. Averaged soleus (SOL), medial gastrocnemius, and tibialis anterior EMG mean amplitude per burst (μV; rectified, high-pass filtered at 32 Hz) versus limb peak load (percentage of body weight load, % BWL) from nondisabled (ND), clinically incomplete (SCI-C), and clinically complete (SCI-A) subjects. Each point represents the average of SOL EMG mean amplitudes (± SE) within a 10% interval of the BWL range (i.e., 0%–10%, 10%–20%, etc.). Data from the right limb (open symbols) and left limb (closed symbols) of each subject are shown separately. Data were not available for every BWL interval. The regression line was based on individual data points from each step cycle and drawn for each muscle when there was a significant relationship ($P < 0.05$).

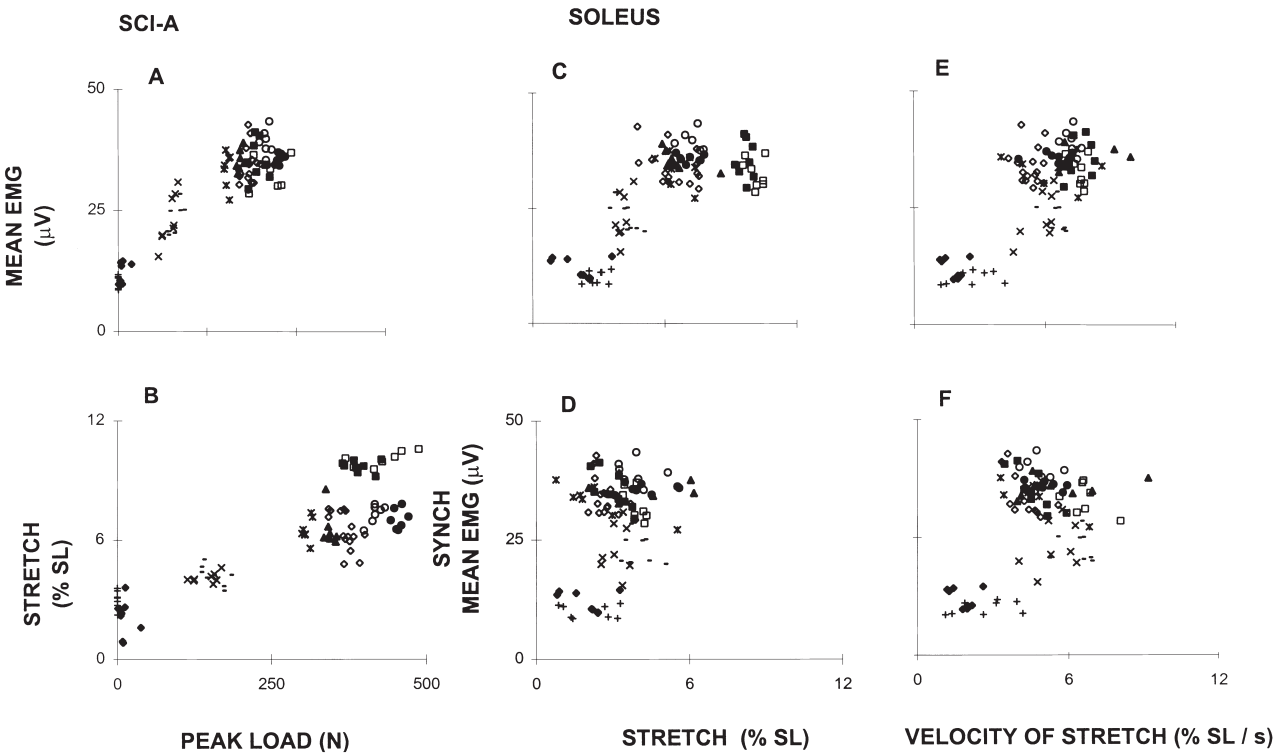

Fig. 2. Relationships among soleus (SOL) electromyographic (EMG) mean amplitude (μV), limb peak load (N), SOL muscle-tendon stretch (percentage shank length, % SL), and velocity of SOL muscle-tendon stretch (percentage shank length/lengths, % SL/s) from a clinically complete spinal cord injured subject (SCI-A) over a range of loading conditions are shown. Muscle-tendon stretch and velocity of muscle-tendon stretch were measured during an entire step cycle (*C* and *E*) and also during the period synchronized with SOL EMG activity (SYNCH mean EMG; *D* and *F*). Each data point represents one step and each symbol represents a series of consecutive steps at one level of body weight support. There was a significant relationship between SOL muscle-tendon stretch and limb peak load (*B*, $r = 0.86$).

nists. These results suggest that the residual motor input in incomplete SCI subjects had a limited capacity to selectively activate individual muscles and simultaneously inhibit antagonists, resulting often in coactivation and/or generalized motor patterns. In clinically complete SCI subjects, EMG activity and movement was not detectable. However, stepping produced alternating, rhythmic EMG patterns similar to those observed in the clinically incomplete and complete SCI subjects. These results support that stepping with alternating lower limb loading provides proprioceptive inputs to the spinal cord that increase motor recruitment and more reciprocity between agonists and antagonists compared with voluntary efforts.

Further evidence of phase-dependent sensory modulation was reported by Yang and others (1991) when they observed soleus H-reflex modulation during stepping in clinically incomplete SCI subjects with varied ambulation abilities. Some of the 14 SCI subjects stepped unilaterally and some bilaterally at a range from 0.1 to 0.8 m/s. Three different patterns of modulation were observed among the clinically incomplete SCI subjects, including 1) soleus H-reflex was low in early stance and increased progressively to peak during the push-off phase and low during swing phase similar to nondisabled subjects (although a prolonged elevation can occur at the beginning of the swing phase); 2) a generally elevated H-reflex is present throughout the stance phase, with a slight inhibition during the swing phase; or 3) little or no H-reflex amplitude differences between stance and swing with elevated H-reflex amplitudes even at a very low stimulus intensity. There were several confounding factors in this study including varied speeds and in most cases very slow speeds of walking, unilateral versus bilateral stepping, and different levels of anti-spasticity medication across subjects. The authors suggested that because phasic modulation was observed in some subjects, either the remaining descending fibers modulated the reflex or that source of modulation could be from spinal neurons. These studies do suggest that phase-dependent reflex modulation as reported in nondisabled subjects (Capaday and Stein 1986; Crenna and Frigo 1987; Duysens and others 1990) can also occur even after supraspinal input is compromised. Similar studies in clinically complete SCI subjects could distinguish the role of the human spinal cord versus supraspinal input in modulating these reflexes.

Activity-Dependent Plasticity of the Human Spinal Cord

The first comprehensive study of the efficacy of locomotor training was completed in 44 chronic clinically incomplete and 45 acute clinically incomplete SCI sub-

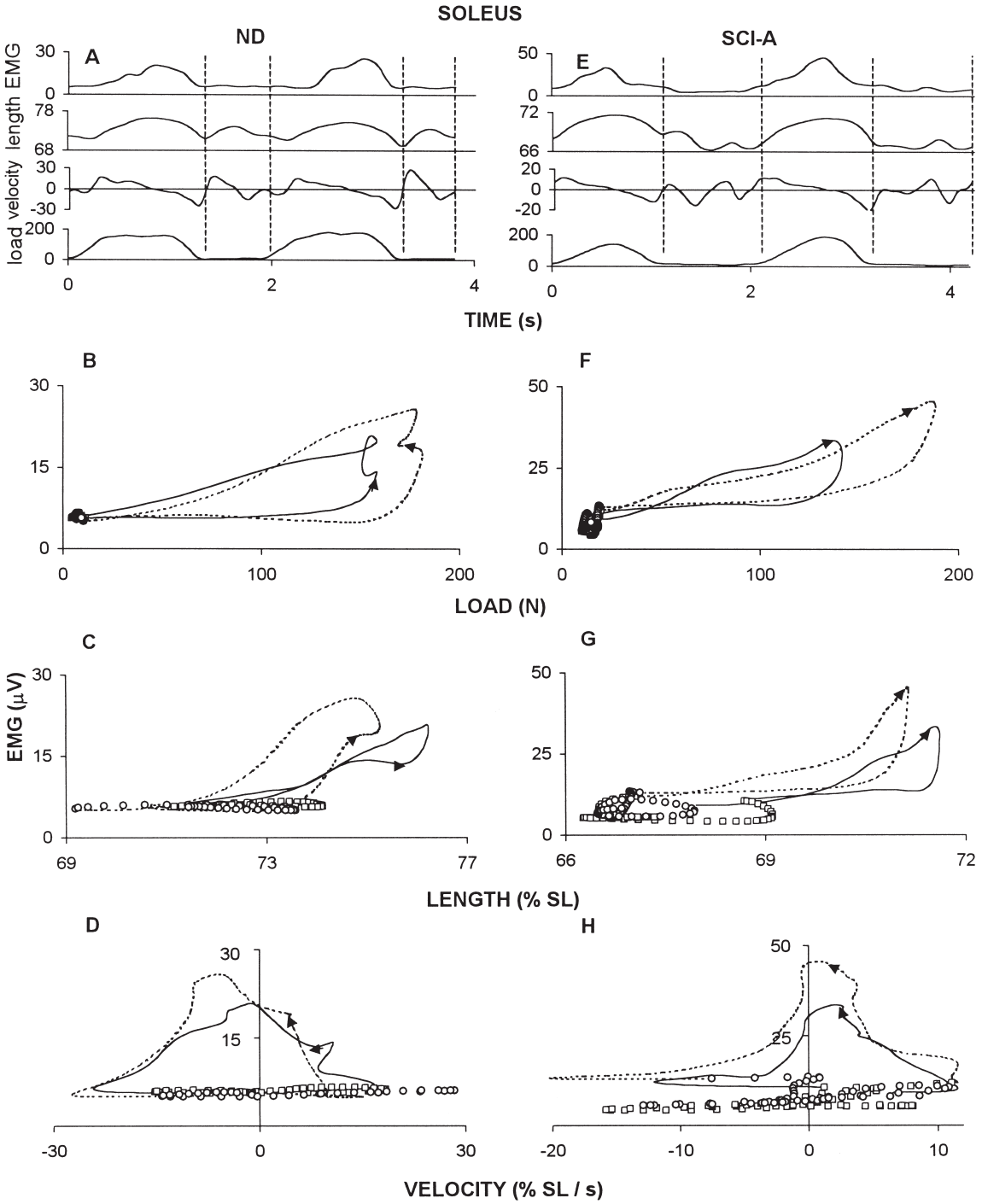

Fig. 3. Within a step, the relationships among soleus (SOL) electromyographic (EMG) activity, level of load, and muscle-tendon length were similar in clinically complete spinal cord injured (SCI-A) and nondisabled (ND) subjects. The response of the SOL EMG activity to load was dependent on the step cycle phase because the EMG amplitude was modulated differently, at the same absolute load level, during loading and unloading phase of stance. SOL EMG amplitude (μV; rectified, high-pass filtered 32 Hz, low-pass filtered 5 Hz), limb load (N), SOL muscle-tendon length (% SL), and velocity of SOL muscle-tendon length change (% SL/s) from two consecutive steps with inadvertently different limb loads from ND (*A–D*) and SCI-A (*E–H*) are shown. All data are shown relative to the phase of the step cycle (seconds) in *A* and *E.* The vertical dashed lines denote the transitions between stance and swing phases. SOL EMG amplitude versus limb load (*B* and *F*), SOL EMG amplitude versus muscle-tendon length (*C* and *G*), and SOL EMG amplitude versus velocity of muscle-tendon length change (*D* and *H*) are illustrated. The stance phase of the steps is represented by a dashed line (high load) and solid line (low load). The swing phases of the steps are represented by open symbols (O-high load; □-low load). Arrows indicate the direction of the step cycle and are located at the time point that represents 50% of the stance phase.

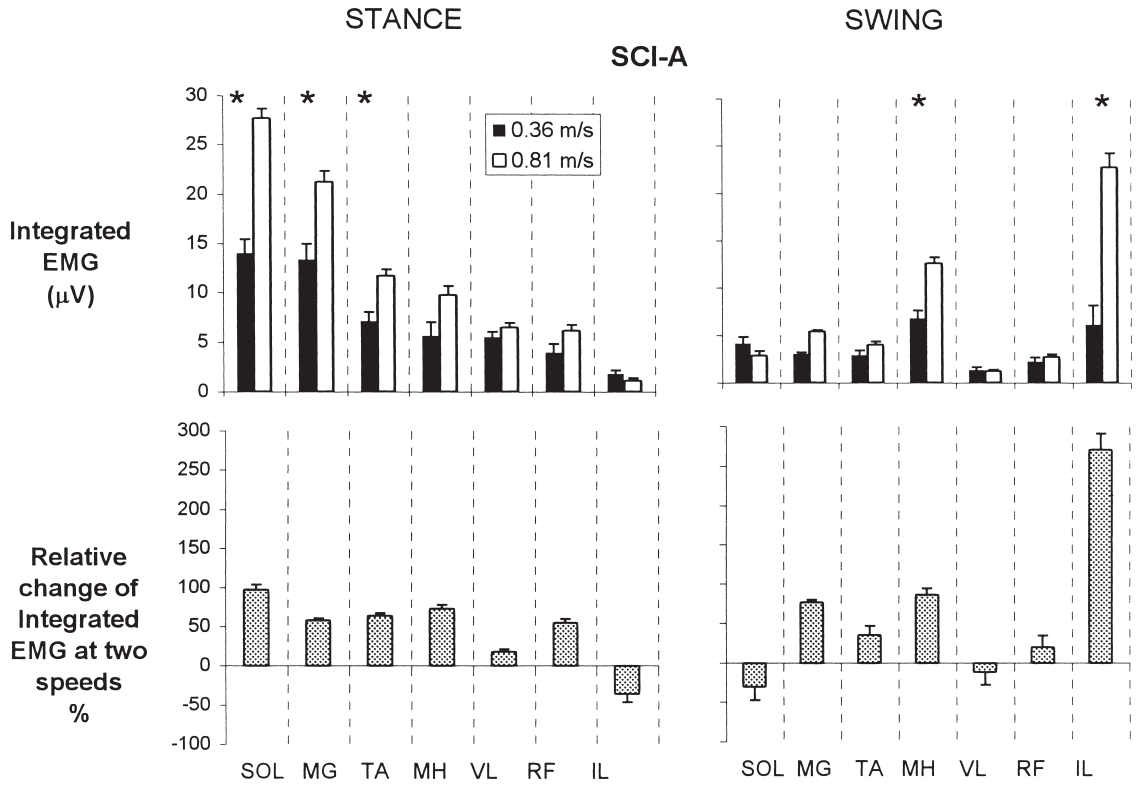

Fig. 4. Extensor electromyographic (EMG) activity during stance and flexor EMG activity during swing is higher at greater stepping speeds in a clinically complete spinal cord injured (SCI-A) subject. EMG activity (rectified, high-pass filtered at 32 Hz) from the soleus (SOL), medial gastrocnemius (MG), tibialis anterior (TA), medial hamstrings (MH), vastus lateralis (VL), rectus femoris (RF), and iliopsoas (IL) within a session of stepping with body weight support and treadmill (BWST) from an SCI-A subject. The limb movements of the SCI subject were assisted when necessary. Integrated EMG and mean ± SE at 0.36 m/s (white bars) and 0.81 m/s (black bars) during the stance and swing phases of seven consecutive step cycles are reported in the *top* panel. Differences between 0.81 and 0.36 m/s are reported in the *bottom* panels. Stance = phase of step cycle from the onset of foot contact to the point of transition of the hip from extension to flexion. Swing = phase of the step cycle from the transition of the hip from extension to flexion to the onset of foot contact. For each muscle, the integrated EMG was normalized to the step cycle duration. A mixed model *F* test was used to determine a significant change in EMG amplitude at different speeds. $^{*}P < 0.05$.

jects who underwent locomotor training using BWST and manual assistance (Wernig and others 1995). Recovery of locomotion was assessed using a functional class assessment ranging from 0 to 5 (0–2 wheelchair bound; 3–5 ambulatory, with the higher score indicating less assistance required for ambulation). After locomotor training, 25 subjects moved from wheelchair-bound to ambulatory categories. The majority of those subjects that were able to ambulate prior to training improved in their functional classification. Twenty-nine of those subjects were compared with a retrospective conventional group of 24 chronic clinically incomplete subjects matched by functional class and type of lesion. In the conventional group, 14 subjects moved from wheelchair-bound to ambulatory categories as compared with only 1 subject in the conventional group. In the acute population, 33 of 36 subjects moved from the wheelchair-bound to ambulatory categories as compared with 12 of 24 in the conventionally treated group. There was no significant difference in the recovery of voluntary muscle activity determined by manual muscle testing between the conventional versus the locomotor training groups. In a follow-up study, it was reported that all subjects retained and in some cases further improved their ability to walk over ground (Wernig and others 1998).

These studies provide the best evidence to date that locomotor training can improve the potential for recovery of locomotion over conventional gait therapy in individuals after clinically incomplete SCI. The enhanced recovery with locomotor training could not be attributed to only increases in voluntary muscle activation or muscle strength. The authors suggested that the improved recovery after locomotor training was attributed to the repetitive alternating limb loading in an upright posture attained using BWST and manual assistance even in severely paralyzed individuals. Conventional therapy approaches did not provide these key elements in the rehabilitation process. A limitation of the studies was that the subjects were not randomized to an intervention; rather, a matched group of subjects were selected from historical records from the same clinic and used for the acute and chronic conventional therapy groups. However, these results do demonstrate relevant changes in locomotor recovery that appear to be attributed specifically to locomotor training using BWST and manual assistance.

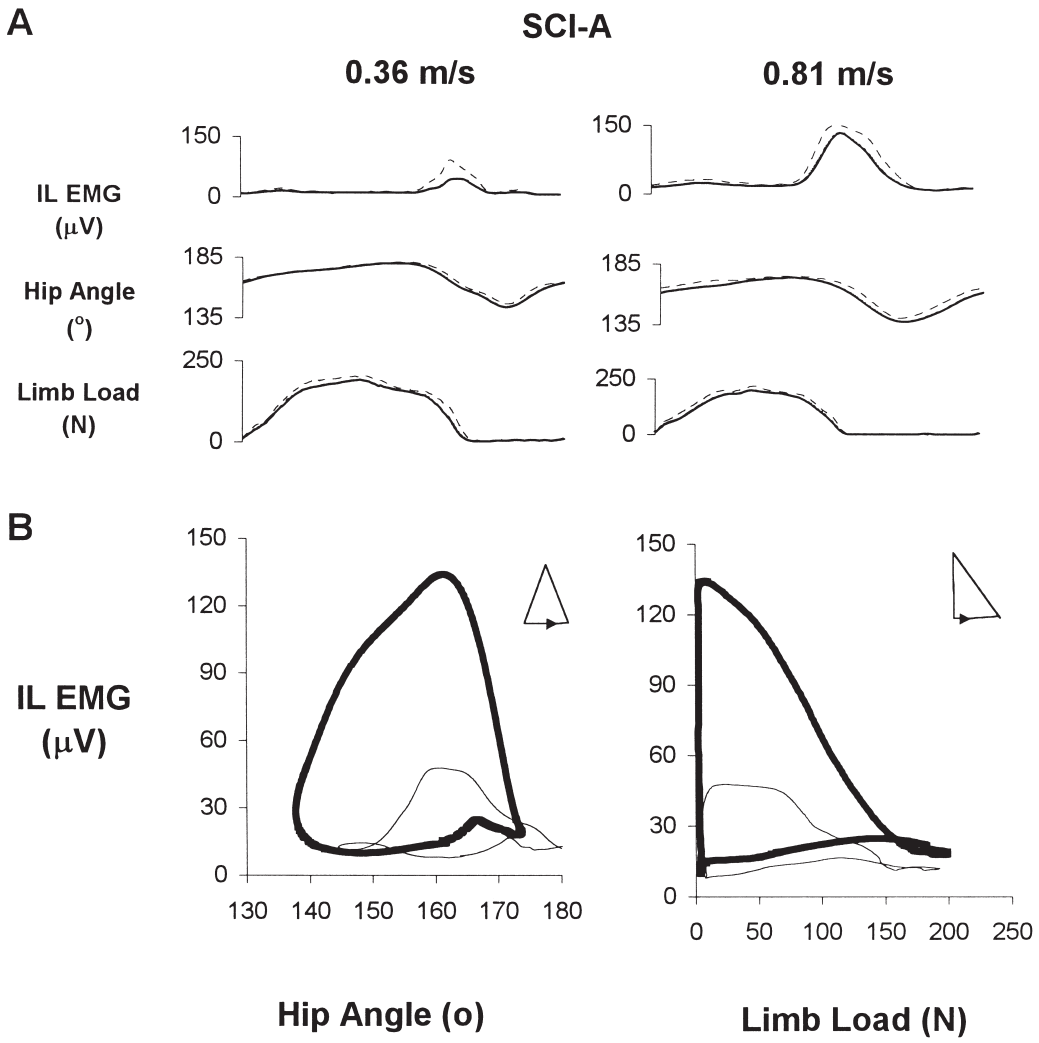

Fig. 5. The iliopsoas (IL) electromyographic (EMG) amplitude from a clinically complete spinal cord injured (SCI-A) subject increases in a phase-dependent manner at different speeds. Regardless of the velocity of stepping, the initiation of the swing phase occurred at the same extended hip position and only when the limb was unloaded. *A*, The IL EMG amplitude (rectified, high-pass filtered at 32 Hz, low-pass filtered at 5 Hz), hip angle (degrees), and limb load (Newtons) from seven consecutive steps at 0.36 and 0.81 m/s from an SCI-A subject are normalized to a common step cycle duration and represented by the average (thicker lines) and average ± SD (thinner lines). When the limb load is greater than zero, the foot is in contact with the treadmill belt. *B*, *left* panel, The relationship between IL EMG amplitude and hip angle throughout the step cycle is shown at 0.36 m/s (thinnest line) and 0.81 m/s (thickest line). Each line represents an average of seven consecutive step cycles of same step cycles as panel *A*. *B*, *right* panel, The relationship between the IL EMG amplitude and level of limb load of same step cycles as panel *A* are shown. Insets in the top right corner display the temporal direction of each relationship with an arrow placed at the point of initial foot contact and a circle at toe-off.

Two chronic clinically incomplete SCI subjects that were wheelchair bound and had minimal voluntary lower limb activity were studied after a plateau stage of recovery following conventional therapy (Fung and others 1990). Both SCI subjects were assessed after receiving placebo, followed by a combination of both cyproheptadine and clonidine administered over 4 weeks and continued during locomotor training for 2 months using BWST and manual assistance. After clonidine and cyproheptadine, both subjects gained the ability to walk unassisted, independently on the treadmill at 0.26 m/s, with reduced excessive flexion of hip and knee in swing toward normal. Following training, both subjects walked independently, with less knee flexion, and one subject showed an improvement in the hip, knee, and angular displacement profiles. EMG activity, assessed using the index bin analyses as a measure of levels of coordination of motor pools (Fung and Barbeau 1989), showed trends toward normal activation patterns in the medial hamstrings and medial gastrocnemius with the combination of clonidine and cyproheptadine and locomotor training. However, the vastus lateralis and tibialis anterior showed no improvement and the EMG activation patterns got worse in one subject. The effects of the drug administration versus locomotor training on recovery of walking in these two subjects cannot be determined from this study.

Other studies in SCI subjects have addressed neural changes associated with locomotor training. In one

study, EMG activity (gastrocnemius, tibialis anterior, rectus femoris, medial hamstrings) from 3 acute clinically incomplete and 10 clinically complete SCI subjects was studied before and after several months of locomotor training using BWST and manual assistance (Dietz and others 1994, 1995). In one clinically incomplete subject, EMG activity was coactivated during stance with a clonic-like pattern observed prior to locomotor training. A more reciprocally organized pattern was reported after training. The root mean square (RMS, μV) of EMG amplitudes of the gastrocnemius was calculated for a defined interval representing 20% of the step cycle when gastrocnemius activation was expected to occur for all SCI subjects. The gastrocnemius RMS amplitudes were plotted versus time of training (up to 200 days). A statistically significant increase was reported for gastrocnemius from the three clinically incomplete subjects (slope = 0.44%/day; $r = 0.52$) with a 60.5 ± 20.1 μV difference reported with training. A group of four clinically complete SCI subjects showed a significant increase in RMS (slope = 1.38%/day, $r = 0.74$) with a 26.0 ± 17.4 μV difference attributed to training. However, the other six clinically complete SCI subjects showed no changes in gastrocnemius RMS amplitude modulation as a result of locomotor training. In all subjects, the body weight support decreased and loading of the limbs increased with training. The investigators concluded that the increase in medial gastrocnemius was related to a greater weight-bearing function of these muscles. Although these investigators interpreted this singular increase in EMG amplitude as a training effect and evidence for spinal cord learning, the changes in medial gastrocnemius amplitudes could have been attributed to a greater level of weight bearing in the legs (Harkema and others 1997).

In a subsequent study, seven clinically incomplete SCI subjects and five clinically complete subjects were studied before and after locomotor training (Dietz, Wirz, and others 1998). One of the subjects categorized in this article as clinically complete did have detectable sensory function below the level of lesion. In the seven clinically incomplete SCI subjects, gastrocnemius RMS increases were reported in both limbs of two subjects (r = 0.87-right, 0.88-left; 0.68-right, 0.42-left) and in one limb of two subjects (r = 0.65-right, 0.68-left). In a group analysis of all seven subjects with body weight support considered, a significant increase of normalized RMS amplitude was calculated based on a correlation with time of training ($r = 0.52$). For clinically complete SCI subjects, there was a statistically significant increase in gastrocnemius RMS amplitude in one limb of two subjects (0.59-right, 0.49-left) and a decrease in one limb of one subject (r = –0.43-right). A statistically significant correlation was observed after group analyses of the five clinically complete SCI subjects, with body weight support also considered (r = 0.37). American Spinal Injury Association scores (Ditunno and others 1994; Maynard and others 1997), sensory-evoked potentials, and motor-evoked potentials did not change throughout the locomotor training period for any of the 12 SCI subjects. The authors concluded that the MG modulation with locomotor training could be attributed to increases in loading of the limbs with a significant effect of training that was not attributable to concurrent changes in limb loading. Based on the low correlation ratios and the variability of the results within and among subjects, further studies are warranted. The authors also concluded that the effects of locomotor training can be separated from spontaneous recovery based on no improvement in the clinical assessments. However, these clinical assessments do not necessarily identify all measures of changes that could occur spontaneously and could contribute to the recovery independent of the locomotor intervention.

Independent stepping, that is, full weight bearing without manual assistance, has not been elicited even after several weeks of locomotor training with BWST and manual assistance in acute (Dietz and others 1995; Dietz, Curt, and others 1998; Dietz, Wirz, and others 1998) or chronic (Stewart and others 1991) clinically complete SCI human subjects. Another report also did not observe significant improvement in the independence of stepping from the therapist's assistance at the lower limbs after 4 to 9 weeks of locomotor training using BWST in seven clinically complete SCI subjects (Wernig and others 1995). However, locomotor-like EMG patterns from clinically complete SCI subjects when stepping with manual assistance using BWST have been demonstrated (Stewart and others 1991; Dietz and others 1994, 1995; Dobkin and others 1995; Harkema and others 1997; Dietz, Curt, and others 1998; Dietz, Wirz, and others 1998). There have been a few qualitative reports of a substantial level of independence during some phases of the step cycle from chronic clinically complete subjects (Behrman and Harkema 2000; Maegele and others 2001).

Preliminary studies (unpublished observations) have indicated a potential training effect for standing in place. Both complete and incomplete subjects became able to maintain stance on their paraplegic or severely paretic legs (Fig. 6). Additionally, after several weeks of step and stand training, clinically complete SCI subjects were able to bear weight while standing, with one subject able to stand bearing 90% of full body weight unassisted for 45 seconds. The chronic clinically incomplete subjects increased the amount of weight bearing and eventually were able to stand independently for several minutes. These results show a limited ability for individuals to bear weight after step and stand training with little or no supraspinal input that was not achieved prior to training.

Implications

Conventional views of the human motor system maintain a hierarchal approach to the nervous system, with the primary role of the spinal cord to serve as a conduit for supraspinal input and reflexes (Fig. 7*A*). It is also largely assumed that processing of sensory information, plasticity, and learning after spinal cord injury must be attributed largely to supraspinal structures rather than to

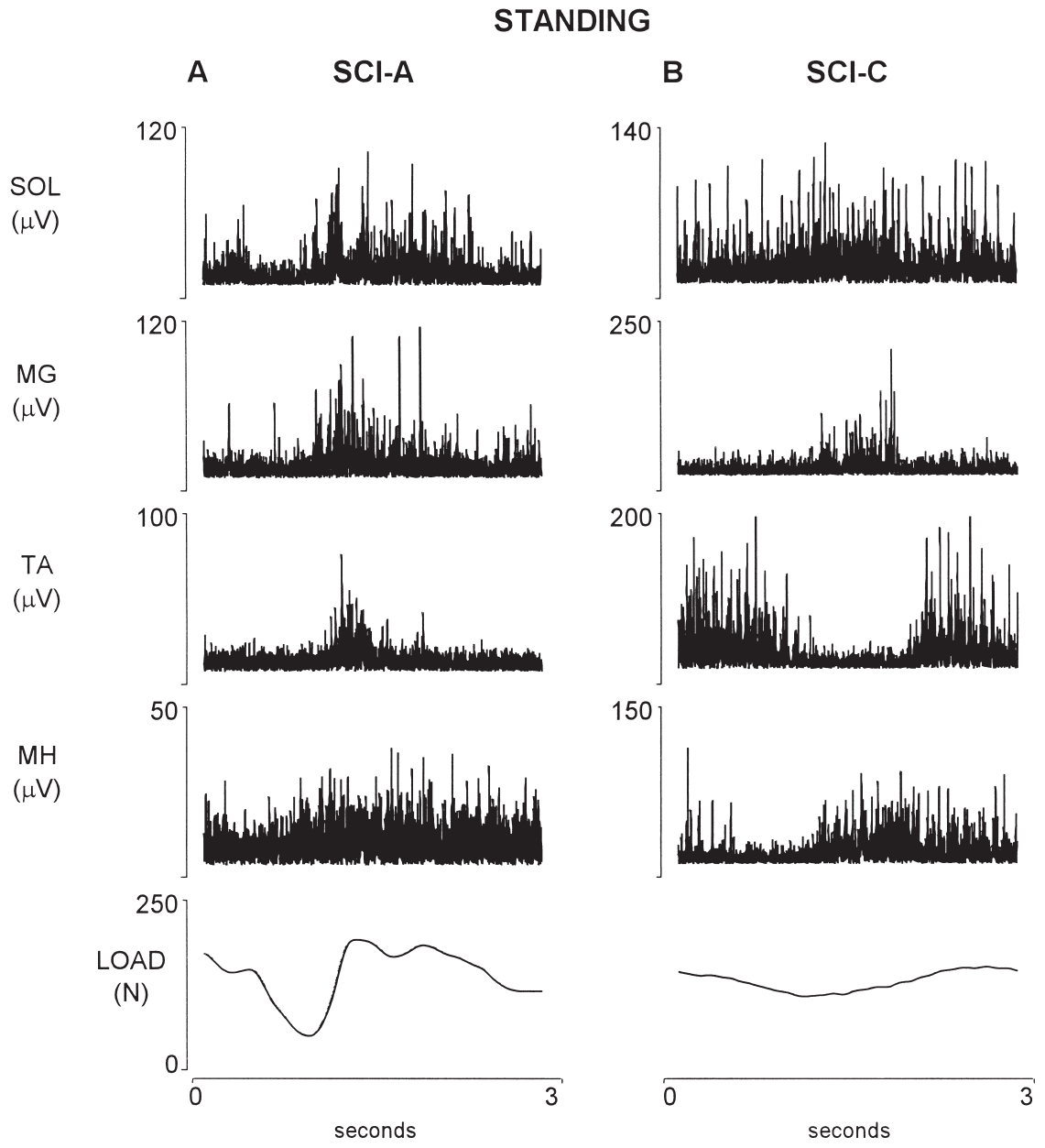

Fig. 6. During standing, the electromyographic (EMG) activity is continuously changing, illustrating the dynamic nature of the neural control that occurs when standing when supraspinal input is severely compromised or absent. EMG activity (μV; rectified, high-pass filtered at 32 Hz) from soleus (SOL), medial gastrocnemius (MG), tibialis anterior (TA), and medial hamstrings (MH) and limb load (Newtons, N) from the right limb during standing using body weight support after several months of step and stand training from one clinically complete spinal cord injured subject (SCI-A) and one clinically incomplete SCI subject (SCI-C).

the spinal cord. Consequently, with the loss of supraspinal input and no regrowth across the spinal lesion, recovery of locomotion has been considered unattainable following a severe or clinically complete spinal cord injury even after conventional therapy. However, the question remains as to the degree that spinal interneurons of humans can integrate and interpret complex sensory signals to produce functional efferent output and adapt to repetitive training like other mammals (Fig. 7*B*). Clear evidence of independent stepping has not been shown in clinically complete SCI subjects; however, studies presented in this review suggest that extensive processing of sensory information at the level of the spinal cord occurs, which can facilitate locomotion. The degree to which the human spinal cord can generate the efferent details necessary to step and stand may define the level of recovery in individuals with incomplete spinal cord injury, stroke, or other neurological disorders with limited supraspinal descending input. Several studies have indicated that individuals with very limited supraspinal input after locomotor training can achieve significant levels of recovery of locomotion not

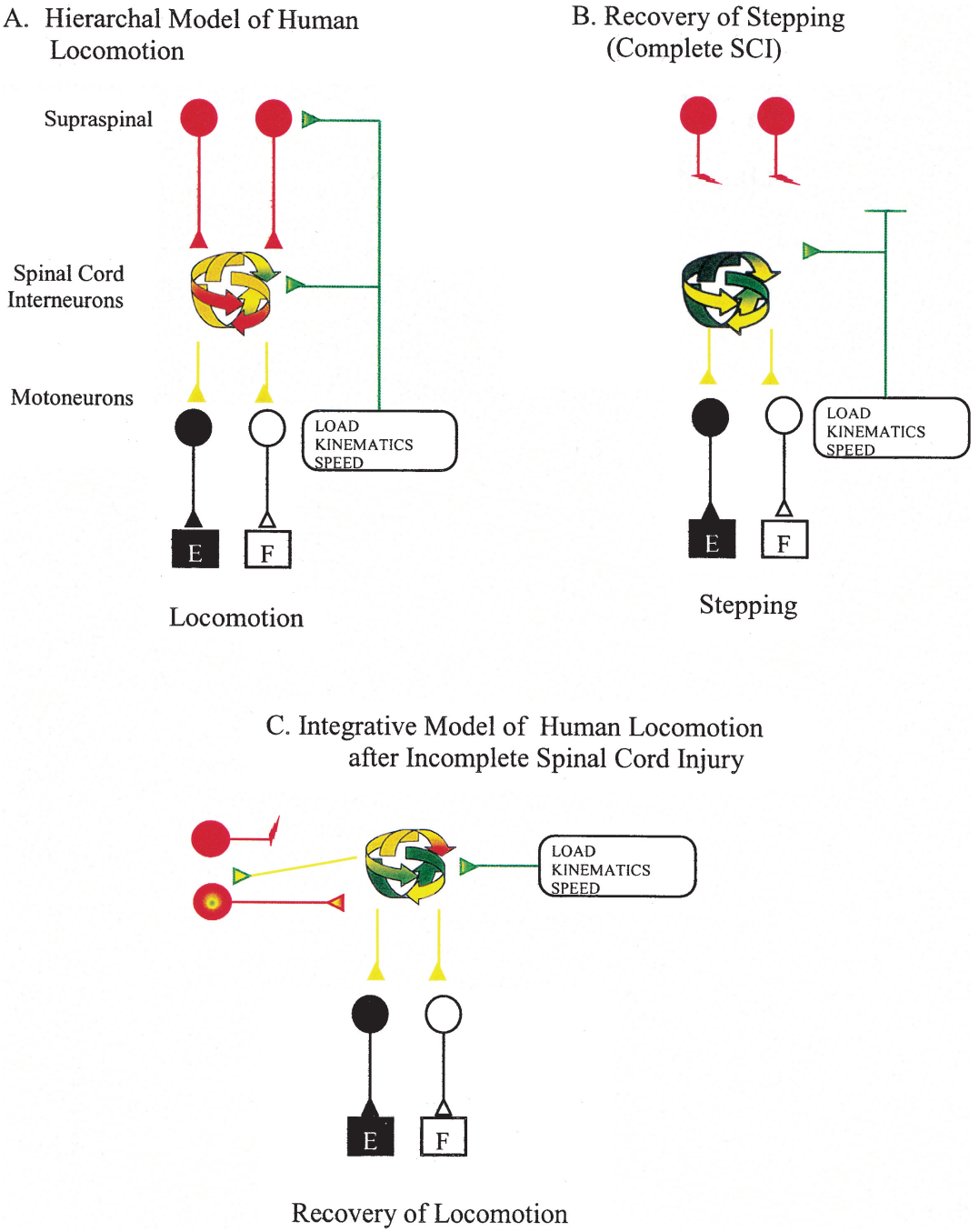

Fig. 7. Conceptual model of the neural control of locomotion. *A*, Hierarchal model: Supraspinal centers (red) receive afferent information (green) from the lower limbs related to locomotion either directly or by propriospinal connections. The spinal interneurons (yellow) primarily serve as a conduit for relaying supraspinal and afferent information generating successful alternating efferent activity in flexors and extensors in the lower limb muscles (e.g., in general when extensors are active, flexors are inhibited; black = active; white = inactive; E = extensors, F = flexors). *B*, Recovery of stepping after clinically complete spinal cord injury (SCI) successful stepping could only occur if the spinal cord had the ability to process afferent information in a complex manner and could learn by repetitive practice as observed in other mammals. Supraspinal centers (red) do not receive afferent information (green) from the lower limbs related to locomotion either directly or by propriospinal connections or provide input to the spinal cord after complete SCI. The spinal interneurons (yellow) interpret and integrate afferent information to generate successful alternating efferent activity in flexors and extensors in the lower limb muscles (e.g., in general when extensors are active, flexors are inhibited; black = active; white = inactive; E = extensors, F = flexors). *C*, Integrative model of the recovery of locomotion after incomplete SCI. Afferent information (green) is processed by spinal interneurons (yellow) and interacts with remaining supraspinal connections (red) to generate successful alternating efferent activity in flexors and extensors in the lower limb muscles (e.g., in general when extensors are active, flexors are inhibited; black = active; white = inactive; E = extensors, F = flexors). An interactive effect of activity-dependent reorganization at both the spinal cord and supraspinal centers is induced by the repetitive presentation of the appropriate afferent information related to stepping (e.g., load, kinematics, speed).

predicted by their capacity to voluntarily move the lower limbs. These results suggest that the spinal interneurons may have the ability to integrate sensory information and remaining descending input to generate successful stepping patterns (Fig. 7*C*); however, further studies are warranted. We currently have a poor understanding of the interactive reorganization potential of the spinal cord and supraspinal centers when minimal connectivity between the brain and spinal cord remains. It appears that incomplete SCI subjects can regain a higher level of locomotor function as a result of locomotor training when compared with conventional therapy. However, there is a critical need for randomized clinical trials across rehabilitation centers in both acute and chronic SCI populations to continue to explore for which individuals and to what extent improvements of locomotor capacity can be expected following SCI with locomotor training.

References

Andersson O, Grillner S. 1983. Peripheral control of the cat's step cycle: II. Entrainment of the central pattern generators for locomotion by sinusoidal hip movements during "fictive locomotion." Acta Physiol Scand 118:229–39.

Barbeau H, Blunt R. 1991. A novel interactive locomotor approach using body weight support to retrain gait in spastic paretic subjects. In: Wernig A, editor. Plasticity of motorneuronal connections. Amsterdam, the Netherlands: Elsevier Science. p 461–74.

Barbeau H, Chau C, Rossignol S. 1993. Noradrenergic agonists and locomotor training affect locomotor recovery after cord transection in adult cats. Brain Res Bull 30:387–93.

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

Barbeau H, Wainberg M, Finch L. 1987. Description and application of a system for locomotor rehabilitation. Med Biol Eng Comput 25:341–4.

Behrman A, Harkema S. 2000. Locomotor training after human spinal cord injury: a series of case studies. Phys Ther 80:688–700.

Beres JA, Johnson TD, Harkema SJ. 2001. Clonus after human spinal cord injury cannot be attributed solely to recurrent muscle-tendon stretch. J Neurophysiol. Submitted.

Bussel B, Roby-Brami A, Azouvi P, Biraben A, Yakovleff A, Held P. 1988. Myoclonus in a patient with spinal cord transection. Brain 111:1235–45.

Bussel B, Roby-Brami A, Yakovleff A, Bennis N. 1989. Late flexion reflex in paraplegic patients. Evidence for spinal stepping generator. Brain Res Bull 22:53–6.

Calancie B, Neilson T, Jacobs K, Willer G, Zych G, Green BA. 1994. Involuntary stepping after chronic spinal cord injury. Brain 117:1143–59.

Capaday C, Stein RB. 1986. Amplitude modulation of the soleus H-reflex in the human during standing and walking. J Neurosci 6:1308–13.

Conrad B, Benecke R, Meinck HM. 1985. Gait disturbances in paraspastic patients. In: Delwaide PJ, Young R, editors. Clinical neurophysiology in spasticity. Amsterdam, the Netherlands: Elsevier. p 155–74.

Conway BA, Hultborn H, Kiehn O. 1987. Proprioceptive input resets central locomotor rhythm in the spinal cat. Exp Brain Res 68:643–56.

Crenna P, Frigo C. 1987. Excitability of the soleus H-reflex arc during walking and stepping in man. Exp Brain Res 66:49–60.

de Leon RD, Hodgson JA, Roy RR, Edgerton VR. 1998a. Full weight-bearing hindlimb standing following stand training in the adult spinal cat. J Neurophysiol 80:83–91.

de Leon RD, Hodgson JA, Roy RR, Edgerton VR. 1998b. Locomotor capacity attributable to step training versus spontaneous recovery after spinalization in adult cats. J Neurophysiol 79:1329–40.

de Leon RD, Hodgson JA, Roy RR, Edgerton VR. 1999. Retention of hindlimb stepping abililty in adult spinal cats after the cessation of step training. J Neurophysiol 81:85–94.

Dietz V, Colombo G, Jensen L. 1994. Locomotor activity in spinal man. Lancet 344:1260–3.

Dietz V, Colombo G, Jensen L, Baumgartner L. 1995. Locomotor capacity of spinal cord in paraplegic patients. Ann Neurol 37:574–82.

Dietz V, Curt A, Colombo G. 1998. Locomotor pattern in paraplegic patients: training effects and recovery of spinal cord function. Spinal Cord 36:380–90.

Dietz V, Nakazawa K, Wirz M, Erni T. 1999. Level of spinal cord lesion determines locomotor activity in spinal man. Exp Brain Res 128:405–9.

Dietz V, Wirz M, Colombo G, Curt A. 1998. Locomotor capacity and recovery of spinal cord function in paraplegic patients: a clinical and electrophysiological evaluation. Electroencephalogr Clin Neurophysiol 109:140–53.

Dimitrijevic MR, Gerasimenko Y, Pinter MM. 1998. Evidence for a spinal central pattern generator in humans. Ann N Y Acad Sci 860:360–76.

Ditunno JF, Young W, Donovan WH, Creasey G. 1994. The international standards booklet for neurological and functional classification of spinal cord injury. Paraplegia 32:70–80.

Dobkin BH, Harkema SJ, Requejo PS, Edgerton VR. 1995. Modulation of locomotor-like EMG activity in subjects with complete and incomplete spinal cord injury. J Neurol Rehabil 9:183–90.

Duysens J, Pearson KG. 1980. Inhibition of flexor burst generation by loading ankle extensor muscle in walking cats. Brain Res 187:321–32.

Duysens J, Trippel M, Horstmann GA, Dietz V. 1990. Gating and reversal of reflexes in ankle muscles during human walking. Exp Brain Res 82:351–8.

Edgerton VR, Grillner S, Sjostrom A, Zangger P. 1976. Central generation of locomotion in vertebrates. In: Herman S, Grillner S, Stein P, Stuart DG, editors. Neural control of locomotion. New York: Plenum. p 439–64.

Eidelberg E, Walden JG, Nguyen LH. 1981. Locomotor control in macaque monkeys. Brain 104:647–63.

Erni T, Colombo G. 1998. Locomotor training in paraplegic patients: a new approach to assess changes in leg muscle EMG patterns [published erratum appears in Electroencephalogr Clin Neurophysiol 1998 Aug;109(4):385]. Electroencephalogr Clin Neurophysiol 109:135–9.

Fedirchuk B, Nielsen J, Petersen N, Hultborn H. 1998. Pharmacologically evoked fictive motor patterns in the acutely spinalized marmoset minkey (*Callithrix jacchus*). Exp Brain Res 122:351–61.

Fung J, Barbeau H. 1989. A dynamic EMG profile index to quantify muscular activation disorder in spastic paretic gait. Electroencephalogr Clin Neurophysiol 73:233–44.

Fung J, Stewart JE, Barbeau H. 1990. The combined effects of clonidine and cyproheptadine with interactive training on the modulation of locomotion in spinal cord injured subjects. J Neurol Sci 100:85–93.

Gordon KE, Ferris DP, Beres JA, Roberton M, Harkema SJ. 2000. The importance of using an appropriate body weight support system in locomotor training. Soc Neurosci 26:160.

Gossard JP, Hultborn H. 1991. The organization of the spinal rhythm generation in locomotion. In: Wernig A, editor. Plasticity of motoneural connections. Amsterdam, the Netherlands: Elsevier Science. p 385–404.

Grillner S. 1981. Control of locomotion in bipeds, tetrapods, and fish. In: Handbook of physiology: the nervous system II. Bestheda, MD: American Physiological Society. p 1179–236.

Grillner S. 1985. Neurobiological bases of rhythmic motor acts in vertebrates. Science 228:143–9.

Grillner S, Rossignol S. 1978. On the initiation of the swing phase of locomotion in chronic spinal cats. Brain Res 146:269–77.

Grillner S, Zangger P. 1975. How detailed is the central pattern generation for locomotion? Brain Res 88:367–71.

Grillner S, Zangger P. 1979. On the central generation of locomotion in the low spinal cat. Exp Brain Res 34:241–61.

Harkema SJ, Dobkin BH, Edgerton VR. 2000. Pattern generators in locomotion: implications for recovery of walking after spinal cord injury. Top Spinal Cord Injury Rehabil 6:82–96.
Harkema SJ, Hurley SL, Patel UK, Requejo P, Dobkin BH, Edgerton VR. 1997. Human lumbosacral spinal cord interprets loading during stepping. J Neurophysiol 77:797–811.
Jankowska E, Jukes MG, Lund S, Lundberg A. 1967a. The effect of DOPA on the spinal cord: 5. Reciprocal organization of pathways transmitting excitatory action to alpha motoneurones of flexors and extensors. Acta Physiol Scand 70:369–88.
Jankowska E, Jukes MG, Lund S, Lundberg A. 1967b. The effect of DOPA on the spinal cord: 6. Half-centre organization of interneurones transmitting effects from the flexor reflex afferents. Acta Physiol Scand 70:389–402.
Lovely RG, Gregor R, Roy RR, Edgerton VR. 1986. Effects of training on the recovery of full-weight-bearing stepping in the adult spinal cat. Exp Neurol 92:421–35.
Maegele M, Müller S, Wernig A, Edgerton VR, Harkema SJ. 2001. Differential recruitment of spinal motor pools during voluntary attempts at lower limb movements versus load bearing stepping following human spinal cord injury. J Neurotrauma. Forthcoming.
Maynard FM, Bracken MB, Creasey G, Ditunno JF, Donovan WH, Ducker TB, and others. 1997. International standards for neurological and functional classification of spinal cord injury. Spinal Cord 35:266–74.
Norman KE, Pepin A, Ladouceur M, Barbeau H. 1995. A treadmill apparatus and harness support for evaluation and rehabilitation of gait. Arch Phys Med Rehabil 76:772–8.
Patel UK, Dobkin BH, Edgerton VR, Harkema SJ. 1998. The response of neural locomotor circuits to changes in gait velocity. Soc Neurosci 24:2104.
Roby-Brami A, Bussel B. 1987. Long-latency spinal reflex in man after flexor reflex afferent stimulation. Brain 110:707–25.
Stewart JE, Barbeau H, Gauthter L. 1991. Modulation of locomotor patterns and spasticity with clonidine in spinal cord injured patients. Can J Neurol Sci 18:321–32.
Vilensky JA, Moore GP, Eidelberg E, Walden J. 1992. Recovery of locomotion in monkeys with spinal cord lesions. J Motor Behav 24:288–96.
Visintin M, Barbeau H. 1994. The effects of parallel bars, body weight support and speed on the modulation of the locomotor pattern of spastic paretic gait. A preliminary communication. Paraplegia 32:540–53.
Wernig A, Müller S. 1991. Improvement of walking in spinal cord injured persons after treadmill training. Amsterdam, the Netherlands: Elsevier Science. p 475–85.
Wernig A, Müller S, Nanassy A, Cagol E. 1992. Laufband locomotion with body weight support improved walking in persons with severe spinal cord injuries. Paraplegia 30:229–38.
Wernig A, Müller S, Nanassy A, Cagol E. 1995. Laufband therapy based on “rules of spinal locomotion” is effective in spinal cord injured persons. Eur J Neurosci 7:823–9.
Wernig A, Nanassy A, Mueller WM. 1999. Laufband (treadmill) therapy in incomplete paraplegia and tetraplegia. J Neurotrauma 16:719–26.
Wernig A, Nanassy A, Müller S. 1998. Maintenance of locomotor abilities following Laufband (treadmill) therapy in para- and tetraplegic persons: follow-up studies. Spinal Cord 36:744–9.
Yang JF, Fung J, Edamura M, Blunt R, Stein RB, Barbeau H. 1991. H-reflex modulation during walking in spastic paretic subjects. Can J Neurol Sci 18:443–52.