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Severed corticospinal axons recover electrophysiologic control of muscle activity after x-ray therapy in lesioned adult spinal cord

(paralysis/recovery of posture/reinnervation/restitution of function)

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ABSTRACT **Mechanical injury to the adult mammalian spinal cord results in permanent loss of structural integrity at the lesion site and of the brain-controlled function distal to the lesion. Some of these consequences were permanently averted by altering the cellular constituents at the lesion site with x-irradiation delivered within a critical time window after injury. We have reported in a separate article that x-irradiation of sectioned adult rat spinal cord resulted in restitution of structural continuity and regrowth of severed corticospinal axons across and deep into the distal stump. Here, we report that after x-ray therapy of the lesion site severed corticospinal axons of transected adult rat spinal cord recover electrophysiologic control of activity of hindlimb muscles innervated by motoneurons distal to the lesion. The degree of recovery of control of muscle activity was directly related to the degree of restitution of structural integrity. This restitution of electrophysiologic function implies that the regenerating corticospinal axons reestablish connectivity with neurons within the target field in the distal stump. Our data suggest that recovery of structural continuity is a sufficient condition for the axotomized corticospinal neurons to regain some of their disrupted function in cord regions distal to the lesion site.**

Mechanical injury to the adult mammalian spinal cord results in irreversible paralysis of the muscles innervated by motoneurons distal to the lesion site, and in permanent disruption of the cord continuity at the lesion site (1–3). The permanent muscle paralysis is due to the severance/laceration of descending brain–spinal cord fibers that control motoneurons' activities (1). The physical disruption and the lack of structural recovery are due to the long-lasting degenerative processes (3, 4) that seem to be triggered around the site of lesion a few weeks after the injury (5).

We demonstrated previously (5, 6) that prevention of degeneration and structural recovery can be obtained in lesioned adult mammalian central nervous system (CNS) by modifying the cellular environment at the lesion site with x-irradiation provided it was delivered within a critical time window after injury. The restitution of structural continuity by the x-ray therapy of the lesion site, in injured olfactory bulb (6) and spinal cord (5), was associated also with structural recovery in axotomized neurons and severed fiber tracts. Irradiation in the severed olfactory bulb was accompanied by a rescue of some of the axotomized mitral cells from death (6) and in the sectioned spinal cord by the regrowth of some of the severed corticospinal (CS) axons across the lesion site and deep into the distal spinal cord stump (5).

Here, our objective was to determine whether the recovery in structure which is elicited by x-ray therapy is accompanied also by recovery of some of the disrupted function of the severed CS tract. We examined, under irradiation conditions that enable structural recovery, whether the regenerating CS axons reestablish synaptic connectivity with neurons within the distal stump. We determined whether the severed CS axons recover their electrophysiologic control on muscle activity distal to the lesion. For this purpose, the experimental lesion consisted of a complete transection of the left side (hemisection) extending over into the right side of adult rat spinal cord at segmental level T12–T13. This lesion resulted in complete severance of the left and right CS axonal tracts (7, 8). In addition, in several of the experimental lesions a bilateral complete transection of the cord was performed; thereby all the brain–spinal cord fiber tracts were severed completely. Electrophysiologic recovery was examined exclusively in the left CS tract; the pertinent studies were performed in the right cortical hemisphere because the neuronal cell bodies of this tract are situated in the right motor cortex (7, 8). The hindlimb area (9–11) of the right primary motor cortex was electrically stimulated and the evoked electromyogram (EMG) responses were recorded in several left hindlimb muscles innervated by lumbar and sacral motoneurons. As internal controls, evoked EMG responses were recorded also in a left forelimb muscle (proximal to the lesion site) and in a right hindlimb muscle (not controlled by the left CS tract). Finally, the potential of eliciting recovery of function of the hindlimbs by the x-ray therapy was evaluated by a comparative visual examination of the treated versus untreated rats, both of which sustained a complete spinal cord transection.

METHODS

Spinal Cord Injury. *Hemisection.* Adult Sprague–Dawley female rats (Charles River Breeding Laboratories), 3–6 months old, were anesthetized with 7% chloral hydrate injected i.p. (0.6 ml per 100 g of body weight), and with 0.2% Stadol (butorphanol) injected s.c. (0.01 ml per 100 g of body weight). Using a dissection microscope the spinal cord was exposed by laminectomy at vertebral level T12; the entire left hemicord was transected at segmental level T12–T13, and the incision always extended half-way into the right side of the cord (5). Finally, a loop was made with a surgical suture #8-0 around the cord tissue which remained intact, and the loop-enclosed tissue was cut with microscissors (5).

Complete transection. The two sides of the cord were cut as described for hemisection. Next, a loop was made with a surgical suture #8-0 that was threaded underneath the dorsal artery and around the entire cord tissue which remained intact, and the loop-enclosed tissue was cut. Upon completion of the injury, to prevent compression of the cord by the side muscles,

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Abbreviations: CS, corticospinal; CNS, central nervous system; EMG, electromyogram.

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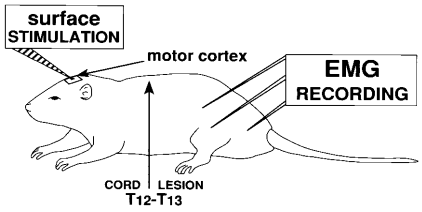

FIG. 1. Experimental paradigm: recording of CS-evoked EMG responses. The exposed surface of the right primary motor cortex of anaesthetized rat was electrically stimulated and the evoked responses were recorded in the left forelimb and hindlimb muscles and in right hindlimb muscles.

a strip of synthetic film (Durafilm; Codman & Shurtleff, Randolph, MA) was placed along each of the sides between the vertebra and the muscle and sutured at a few points to the side muscle. The overlying back muscles were sutured, the skin was closed with surgical wound clips, and the animal was given a s.c. injection of long-acting penicillin (300,000 units). When needed, bladders were expressed manually until automatic function was resumed; otherwise, no special postsurgical care was needed. At the end of the experiment, the rats were sacrificed and their cords around the lesion site were histologically examined (5).

Radiation. X-irradiation was delivered by a Clinac 600C linear accelerator (Varian) using a 6-MV beam at a dose rate of 200 cGy/min. Treatment was delivered through a posterior approach while the rat was anaesthetized, at a source-to-skin distance of 100 cm with a tissue buildup superflab of 1 cm. The dimensions of the radiation field were 25 mm × 20 mm (length × width) centered at the site of lesion. Radiation therapy was delivered as a single dose of 20 gray (Gy) at 17–18 days postinjury, and selection for treatment was randomized. At this dose level and the recovery period given until analysis was performed (2–5 months postinjury), no side effects were noticed except for hair loss limited to the radiation exposed field only.

Electrophysiology. EMG recordings were performed on pentobarbital anaesthetized rats clamped by ear bars to a stereotactic apparatus (Fig. 1). The dorsal surface of the right brain hemisphere of anaesthetized rats (i.p. injection of 5% sodium pentobarbital, 0.1 ml per 100 g of body weight) was exposed by a craniotomy; the dura was removed and immediately thereafter, for the course of the experiment, the exposed brain surface was covered with a mixture of mineral oil and petroleum jelly. Rectal temperature was maintained at 36.5–37°C by a servo-controlled heating pad. Supplementary i.p. injections of 0.05 ml 5% pentobarbital were given as necessary, and the mucous was periodically aspirated from the trachea throughout the experiment. The exposed surface of the right primary motor cortex was electrically stimulated (bipolar or monopolar) with silver-ball electrodes (diameter, 0.5 mm). For the specific stimulation of the hindlimb CS neurons (9–11) the electrodes were placed at the following P,L (P, posterior to bregma; L, lateral to the midline) coordinates: A, for bipolar stimulation, the rostral electrode at P = 0 to −1 mm, L = 1.5 to 2 mm and the caudal electrode at P = −4 to −5 mm, L = 1 to 2 mm; and B, for monopolar stimulation the single electrode at P = 0 to −1 mm, L = 1.5 to 2 mm and the reference, a brass rod electrode in the rectum. For the electrical stimulation, 5 pulse trains of biphasic current (500 Hz, 0.2 msec/phase) were generated at a frequency of 1 train/sec. EMG recording was performed with bipolar Teflon-coated and multistranded stainless steel wires (50 μm bare diameter) that were inserted into the individual exposed fore- and hindlimb muscles (12). The EMG signal was amplified and filtered (30 Hz to 3 kHz bandpass), and monitored and photographed from a Tetronix storage oscilloscope.

RESULTS

CS Evoked EMGs in Normal Rats. First, the experimental conditions and cortical areal coordinates were identified and defined under which CS-evoked EMG responses can be elicited in the hindlimb muscles. In normal intact rat (n = 4), bipolar stimulation of the cortical hindlimb area with currents

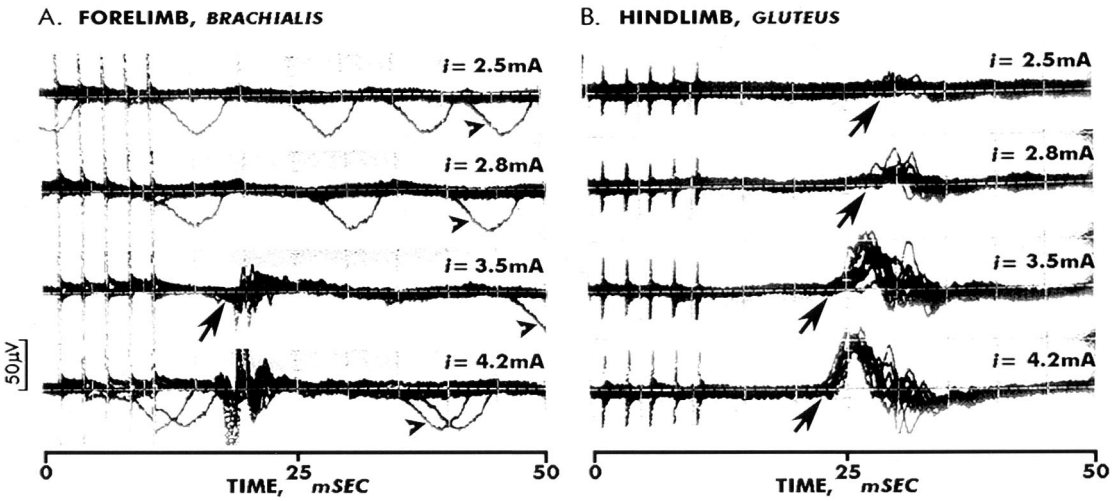

FIG. 2. Threshold and latencies of the CS-evoked EMG responses in the left forelimb and hindlimb muscles of a normal intact rat consequent to bipolar stimulation of the hindlimb area of the right motor cortex. Two composites of photographed traces of EMG responses that were recorded simultaneously in brachialis (A) and gluteus (B) and which are aligned from top-to-bottom according to the four stimulating current intensities (i). Each trace consists of ≈10 successive superimposed responses. The five deflections at the beginning of the trace are artifacts generated by the 5-pulse stimulus; their size grows with higher currents (B). Because the forelimb (A) is closer to the brain and heart, the artifact is larger than in the hindlimb's traces and the electrocardiogram appears in its traces as random downward deflections (arrowheads). The evoked responses in the fore- and hindlimb muscles have typical threshold latency values. Stimulating with 2.5 mA evoked a small response (arrow) in gluteus (B) at a latency of 28 msec; in contrast, there was no response in brachialis (A). The threshold response in brachialis (A) occurs at 3.5 mA with 17 msec latency (arrow). Increasing current intensity shortened the latency (arrows) (which reached in gluteus a value of 22 msec at 3.5 mA), recruited additional motor units, and increased the amplitude of the response (which peaked in gluteus to ≈50 μV). The response in brachialis was truncated for illustration purposes, its peak amplitude was over 200 μV.

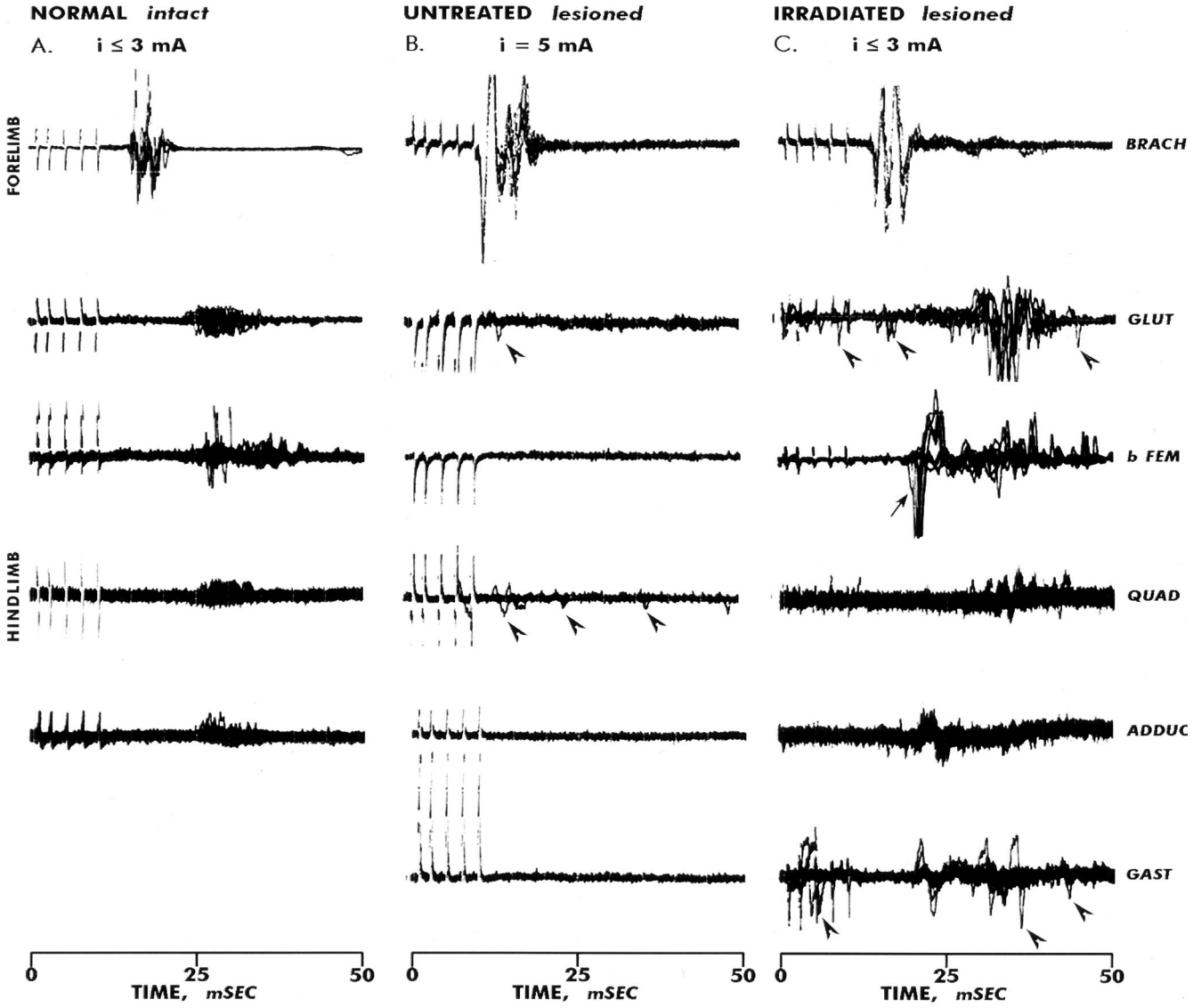

FIG. 3. CS-evoked EMG responses recorded in left limb muscles after bipolar stimulation of the hindlimb area of the right motor cortex of (*A*) normal intact rat, (*B*) untreated lesioned rat 65 days postinjury, and (*C*) irradiated lesioned rat 105 days postinjury. A composite of photographed traces of EMG responses are aligned from top-to-bottom according to the individual muscles recorded in: starting with the forelimb muscle (brachialis) and following with the hindlimb muscles (gluteus, biceps femoris, quadriceps, adductor, and gastrocnemius). Each trace consists of ≈10 successive superimposed responses that were evoked while the current intensity was increased, and the maximum intensities (*i*) applied are indicated for each of the rats; the five stimulus artifacts can be seen in most of the traces. In the three rats (*A–C*), evoked responses were recorded in the forelimb muscle at latencies in the range of 11–17 msec. No evoked responses were recorded in the hindlimb muscles of the lesioned unirradiated rat (*B*) (its cord is shown in Fig. 5 *a–d*). Evoked responses were recorded in all hindlimb muscles of the normal rat (*A*) and of the irradiated lesioned rat (*C*) (its cord is seen in Fig. 5 *Xa–Xd*), at latencies in the range of 22–27 and 21–28 msec, respectively. In the treated rat (*C*), in bicep femoris an additional evoked response was recorded at a latency of 17 msec (arrow); this appeared as a different component with a higher threshold current. Some of the hindlimb muscles of the lesioned rats (*B* and *C*) show spontaneous activity which is independent of the stimulus (recorded when no stimulation was given); this can be seen as random potentials (e.g., arrowheads) appearing without a fixed latency.

in the range of 1.8–3 mA evoked EMG responses in forelimb (brachialis) and hindlimb (gluteus, biceps femoris, quadriceps, adductor, and gastrocnemius) muscles (Figs. 2 and 3*A*). The latency times for the threshold responses in brachialis and in the hindlimb muscles (measured from the onset of the stimulus) were 17–19 and 27–30 msec (Fig. 2), respectively. Increasing the stimulating current from threshold level to 5 mA evoked responses in additional motor units while the latencies of the responses were shortened to 11–12 msec in brachialis (Fig. 3*B*) and to 18–22 msec in hindlimb muscles (Fig. 2*B*). The time interval between the latencies of the responses evoked by the same stimulus in forelimb and hindlimb muscles was in the range of 5–10 msec (e.g., Fig. 2). Based on these time interval values and the approximated distance of 70 mm between cord segments C6 and L4, the estimated values of the conduction velocity of the axons mediating the responses in the hindlimb muscles were deduced to be in the range of 7–14 m/sec. These values fit well with the measured antidromic conduction velocities in the rat CS tract, reported to be in the range of 5–19 m/sec (mean 11.4 ± 2.9 m/sec) (13). The properties of the evoked EMG responses were the same when using monopolar stimulation in the range of 0.75–1.25 mA. The differences between the latencies of the forelimb and hindlimb responses were 5–9 msec and the estimated conduction velocities were in the range of 7.8–14 m/sec.

Further, the experimental conditions under which EMG responses were elicited in discrete muscles were extremely sensitive to small changes in the placement of the stimulating

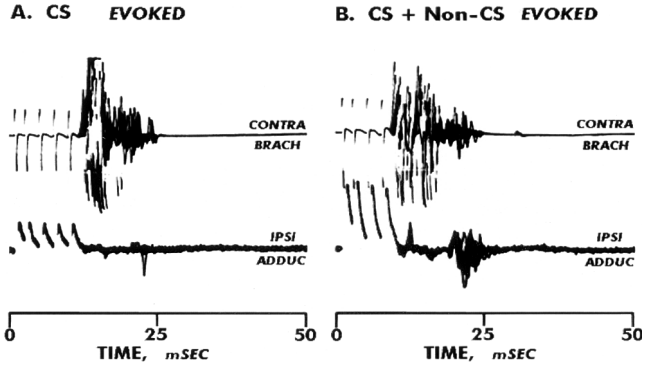

FIG. 4. Specific stimulation of the CS pathway and/or of a non-CS pathway. Evoked EMG responses recorded in a left forelimb muscle and in a right hindlimb muscle of a normal intact rat after monopolar stimulation of the right primary motor cortex. (*A*) Response evoked by 1.5 mA; under these conditions only the left muscle (brachialis) responds at a latency of 12 msec. (*B*) Responses evoked by a 2-mA stimulus (four pulses only). Under these conditions, the current spread to pathways other than the CS and responses were evoked also in the right muscle (adductor); these non-CS-evoked responses have latency times of 9 msec in brachialis, and 11 and 17 msec in the right adductor. It is assumed that the second response in adductor was evoked by a stimulus propagating via a combined pathway of the lateral cortico-reticulospinal tracts (14).

electrode in the anterior–posterior direction. For example, by moving the rostral electrode from 0 to −1 mm (with respect to bregma) at bipolar stimulating current of 1.8–2.5 mA, the evoked response in the forelimb muscle was lost (Fig. 2*A*) while it persisted in the hindlimb muscle (Fig. 2*B*). The stimulation evoked also discrete body/muscle movements that were exclusively unilateral, and no responses were recorded in the right hindlimb muscle (adductor) with either bipolar stimulation at 5 mA or with monopolar stimulation at current levels up to 1.4–1.5 mA (Fig. 4*A*).

In addition, areal and electrical stimulation conditions were identified under which non-CS-evoked EMG responses can be elicited. For example, increasing the current in monopolar stimulation to 2 mA evoked ipsilateral EMG responses—i.e., in the right hindlimb muscle (Fig. 4*B*). These responses had parameters different from those typical for the CS-evoked responses; they had shorter latency times of 6.5–8 and 8–10.5 msec in the forelimb and the hindlimb muscles, respectively, and a shorter interval in between the two latencies of 1–2.5 msec (Fig. 4*B*). The estimated values of conduction velocity of the axons mediating these responses (deduced as described above) are in the range of 28–70 m/sec, values typical for the reticulospinal tract that were reported to be in the range of 16–80 m/sec (mean = 37 m/sec) (15). Thus, we assume that these responses were evoked by the reticulospinal tract. These low-threshold contralateral and high-threshold ipsilateral evoked responses as obtained here by surface stimulation (Fig. 4) are similar to those obtained by intracortical microstimulation of the motor cortex in normal adult rat (16).

Response in Control Lesioned and Untreated Rats. Severance of the CS tract (Fig. 5 *a–c*) above the lumbar segments resulted in a complete loss of the CS control of the hindlimb muscle activity (Fig. 3*B*). No CS-evoked EMG responses—as defined for the normal intact rat—were recorded in hindlimb muscles of the rats with lesioned spinal cords (hemisection, n = 7; completely transected, n = 2), consequent to either bipolar stimulation (n = 7) at currents up to 5 mA (Fig. 3*B*) or monopolar stimulation (n = 2) at currents up to 1.5 mA. However, concurrently CS-evoked responses were recorded from the forelimb muscle (Fig. 3*B*) that is innervated by cervical motoneurons situated rostral to the cut. These lesioned and unirradiated rats were examined at 2, 20, 34, 40, 42, 65, 151, or 156 days after injury. In some of the rats with hemisectioned spinal cord non-CS-evoked responses—as defined for the normal intact rat (Fig. 4*B*)—were recorded in some of their hindlimb muscles. These responses were evoked presumably by the ipsilateral (right) reticulospinal axons (17–19), which were spared during the hemisection. No such responses were recorded in the rats with the completely transected cords.

Recovery of CS-Evoked EMGs in Irradiated Rats. In comparison with the lesioned untreated rats, we found that the severed CS tract in the rats with irradiated lesioned spinal cords (Fig. 5 *Xa–Xd*) regained some of its electrophysiologic control of the hindlimb muscles (Fig. 3*C*). CS-evoked EMG responses—as defined for the normal intact rat—were elicited (Fig. 3*C*), after stimulation of the cortical hindlimb area of the irradiated lesioned rats (hemisectioned, n = 6; completely transected, n = 3), in at least one of the hindlimb muscles in eight of the nine tested animals (Table 1). The EMG responses in the irradiated rats had properties similar to the CS-evoked responses in normal intact rats, in that they were evoked at the same or lower threshold (bipolar, 1.3–2.5 mA) and had similar latencies. In the treated rats, the measured time interval between the latencies of the evoked responses in the forelimb

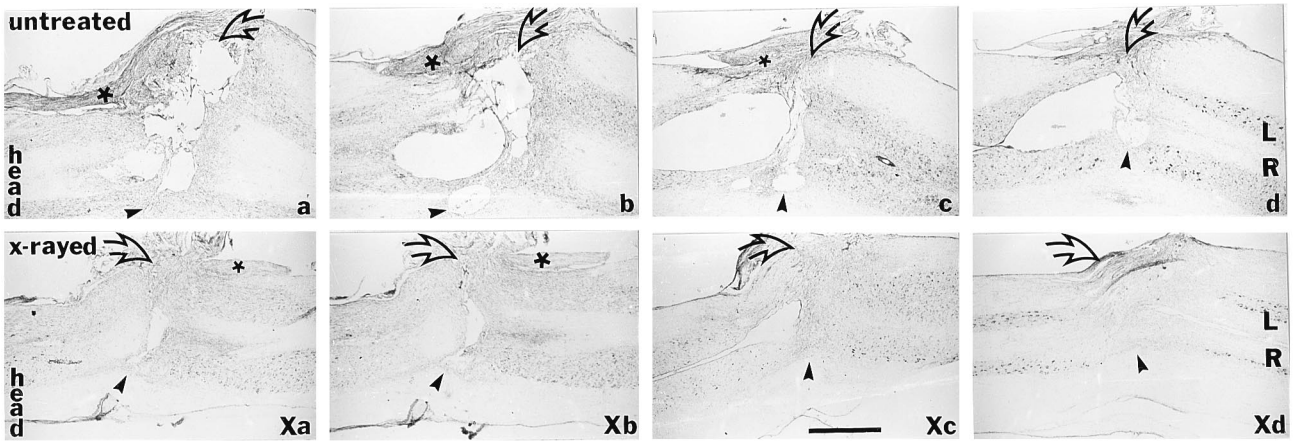

FIG. 5. The morphological features of the lesion site in two lesioned cords, unirradiated (*a–e*) and irradiated (*Xa–Xe*), obtained from the rats whose EMG recordings are shown in Fig. 3*B* and Fig. 3*C*, respectively. Serial reconstruction of the two cords are shown; each panel is a composite of thionin-stained horizontal sections taken from different regions along the dorsal–ventral direction. Indicated are the left (L) and the right (R) hemicords, the extent of incision traversing from left (clear arrow) past the midline and into the right hemicord (arrowhead), and the dorsal nerves (asterisks). Note in the untreated cord the cavitation and tissue degeneration throughout the entire volume surrounding the incision site. In the irradiated cord the incision disappeared and an almost complete structural continuity was established. (Bar = 1 mm.)

Table 1. Functional recovery of the severed left CS tract in irradiated hemisectioned and completely transected cords

Rat no.	Days Post injury	CS evoked EMG response in muscles						
		Left side					Right side	
		Glut.	Bic. fem.	Quad.	Add.	Gast.	Glut.	Add.
8a	105	+	−	−	−	−	ND	−
9a	101	+	−	+	+	−	ND	−
13a	105	+	+	+	+	+	ND	−
3a*	41	+	ND	+	+	ND	ND	+
4a*	46	+	−	−	+	+/−	ND	−
11a*	70	−	+	−	−	ND	ND	−
3b	130	+	−	+	−	−	ND	+
11b	143	−	+	+	+	−	+	−
12b	147	−	−	−	−	−	−	−

Summarized are the CS-evoked responses recorded in five left and two right hindlimb muscles in a total of nine irradiated rats. a, Hemisectioned; b, Completely transected; ND, not determined; Glut., gluteus; Bic. fem., biceps femoris; Quad., quadriceps; Add., adductor; Gast., gastrocnemius. *Monopolar stimulation.

and hindlimb muscle were in the range of 6–12 msec when the stimulation was either bipolar or monopolar at currents up to 5 mA and 1.25 mA, respectively. The estimated conduction velocities of the axons mediating these responses were in the range of 5.4–11.7 m/sec. It appears that some of the regenerated CS axons had slower conduction velocities than those of the normal intact CS tract as described above—i.e., 5.4 versus 7 m/sec. The decrease in conduction velocity suggests that some of the regenerated axons were not remyelinated (20).

In five of the nine irradiated lesioned rats, CS-evoked responses were recorded in three or more of the hindlimb muscles (Table 1). Most importantly, the degree of recovery of CS-evoked EMG responses appears to be related to the degree of structural recovery of the lesioned cord. The best recovery of control of muscle activity was observed (Fig. 3*C*) in the rat in which an almost complete structural continuity of the transected cord was obtained (Fig. 5 *Xa–Xd*). In this rat the regenerating CS axons had reached sacral cord segments establishing direct or indirect synaptic connection with motoneurons innervating the gastrocnemius. Finally, as established anatomically (5), upon regeneration the severed CS tract seems to loose its unilaterality. In several cases, primarily in the completely transected cords, some of the severed left CS axons also regrew into the right hemicord, establishing synaptic connectivity there and control of right hindlimb muscles (Table 1).

Functional Recovery in the Hindlimbs by X-Ray Therapy. The recovery in function of severed axons induced by the irradiation could be detected also visually. Irradiated ($n = 11$) and unirradiated ($n = 6$) rats that sustained a complete transection of their spinal cords were qualitative observed 4–5 months postinjury for the function and control of their hindlimbs when placed on a smooth metallic platform. Complete transection of the cord results in complete loss of function and control of the hindlimbs; the posterior body, distal to the cut, is paralyzed and lies flat on the surface (Fig. 6 *A–C*). In comparison, irradiation of the lesion site appears to elicit some functional recovery in the hindlimbs and in the body muscles distal to the lesion; some of the irradiated rats ($n = 6$) regained plantar foot contact and the ability to support weight and body posture (Fig. 6 *Ax–Cx*). This recovery of function correlates with the degree of restitution of structural continuity as determined histologically. It should be noted that none of the rats were exercised, and that in both groups there was a recovery within a few days postinjury of the reflex responses elicited, for example, by pinching of the skin distal to lesion.

DISCUSSION

The present study demonstrates that the anatomical recovery of the severed CS tract (5), made possible by the x-ray treatment, is accompanied by some electrophysiological recovery of its disrupted circuitry. That is, the regenerating CS axons establish connections, in remote cord regions distal to the lesion site, with neurons that control muscle activity. Our data are consistent with data obtained in a different CNS region (21); in that study, utilizing peripheral nerve grafts it was demonstrated that severed optic nerve fibers that regenerate along the graft and succeed in penetrating into the superior colliculus (CNS environment) also reestablish synaptic functional connectivity with target neurons there. Raisman (22), in a comparative study about synapse formation after injury in the adult peripheral and central neural tissues, demonstrated that the mechanisms of synapse formation and synapse matching are preserved in adult CNS. He also noted that the major difference in response to injury between the peripheral and the central neural tissues is that: "in the peripheral nervous site the originally cut axons can regenerate back to their former targets. [while in the CNS] . . . it seems most likely that the defect resides in an inability of the cut axons to regenerate across the site of injury in a manner necessary for them to reach the denervated target tissue." (22). In our study, the "defect" in lesioned spinal cord was corrected by a timed specific elimination of a group of reactive cells and

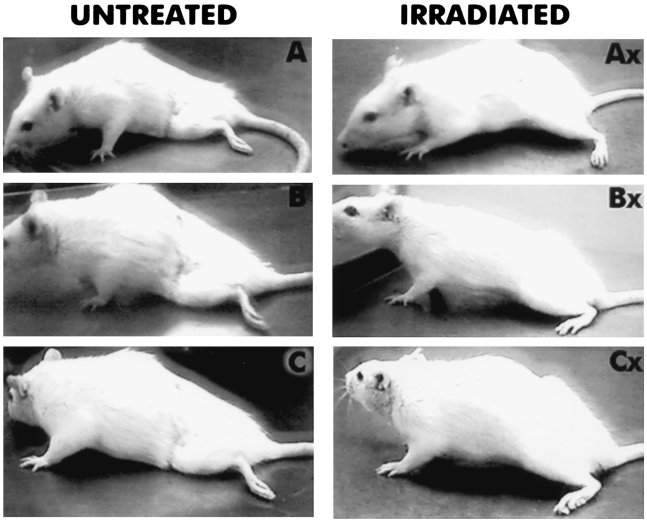

FIG. 6. Recovery of function of the hindlimbs. Photographs of two rats with completely transected spinal cords 4–5 months after injury. (*A–C*) Control, untreated rat. (*Ax–Cx*) Irradiated rat. The two rats are shown at identical views, focusing on their back distal to the lesion. Note in the irradiated rat the recovery in hindlimb posture and weight support—i.e., the position of the leg and the distance of the body, distal to the cut, from the surface on which the rat is standing.

the cut axons regenerated across the site of injury reaching denervated tissue forming synapses there, though not necessarily with their former target cells. Thus, it appears that the ability of the cut axons to cross the lesion site is related to the prevention of the degeneration and of the cavitation.

Irradiation seems to be a powerful tool for analyzing the sequelae of CNS injury (5, 6). It appears that it also may be developed into a therapeutic modality for facilitating functional recovery from injury. We can conclude from data presented here that prevention of tissue degeneration and the establishment of structural continuity is a sufficient requirement for the severed CS axonal tracts to reestablish synaptic connectivity and regain electrophysiologic control of neurons within the target field in the distal cord stump. We can infer from the recovery of function, such as recovery of body posture distal to the lesion site, that other disrupted circuitries had been reconnected. Thus, we propose that the first and essential step of a therapeutic protocol for the prevention of muscle paralysis—the reestablishment of synaptic connectivity—can be achieved by posttraumatic irradiation of the lesioned cord. As for reaching the final therapeutic goal of acquiring recovery of locomotion, this requires, in addition to the restitution of the disrupted individual circuitries, the restitution of the synaptic coordination between the individual circuitries that have been disrupted by the injury (see ref. 23). Manipulation and modulation of multiple circuitries (e.g., in the visual system), changing the cortical ocular dominance pattern can be achieved by training (e.g., eye patching) and/or by pharmacological treatment (24, 25). Thus, in addition to radiation therapy, a protocol for achieving behavioral motor recovery in adult mammals may require exercising, retraining, and/or pharmacological manipulations that affect synaptic remodeling and innervation patterns (see refs. 24–26).

This paper is dedicated to Miriam Salpeter and Mary Ellen Michel-Cheung, who examined our data with open mind and intellectual enthusiasm and infused encouragement during our effort to bring this research to light. The electrophysiological data, except for those reported in Fig. 2, were collected at The Rockefeller and Hahnemann Universities in the laboratories of Susan Schwartz-Giblin. We thank William Paul Hurlbut and Patricia Wade for their comments and help in the writing and editing of this article, and Philip Siekevitz for his unfailing help in publishing our studies.

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