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Graded Histological and Locomotor Outcomes after Spinal Cord Contusion Using the NYU Weight-Drop Device versus Transection

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Injury reproducibility is an important characteristic of experimental models of spinal cord injuries (SCI) because it limits the variability in locomotor and anatomical outcome measures. Recently, a more sensitive locomotor rating scale, the Basso, Beattie, and Bresnahan scale (BBB), was developed but had not been tested on rats with severe SCI complete transection. Rats had a 10-g rod dropped from heights of 6.25, 12.5, 25, and 50 mm onto the exposed cord at T10 using the NYU device. A subset of rats with 25 and 50 mm SCI had subsequent spinal cord transection (SCI + TX) and were compared to rats with transection only (TX) in order to ascertain the dependence of recovery on descending systems. After 7–9 weeks of locomotor testing, the percentage of white matter measured from myelin-stained cross sections through the lesion center was significantly different between all the groups with the exception of 12.5 vs 25 mm and 25 vs 50 mm groups. Locomotor recovery was greatest for the 6.25-mm group and least for the 50-mm group and was correlated positively to the amount of tissue sparing at the lesion center ($p < 0.0001$). BBB scale sensitivity was sufficient to discriminate significant locomotor differences between the most severe SCI (50 mm) and complete TX ($p < 0.01$). Transection following SCI resulted in a drop in locomotor scores and rats were unable to step or support weight with their hindlimbs ($p < 0.01$), suggesting that locomotor recovery depends on spared descending systems. The SCI + TX group had a significantly greater frequency of HL movements during open field testing than the TX group ($p < 0.005$). There was also a trend for the SCI + TX group to have higher locomotor scores than the TX group ($p > 0.05$). Thus, spared descending systems appear to modify segmental systems which produce greater behavioral improvements than isolated cord systems. © 1996 Academic Press, Inc.

INTRODUCTION

Experimental models of acute spinal cord injury (SCI) are integral to the development of therapeutic regimens for clinical practice (2, 7–9, 12–14, 19, 20, 35, 40). An effective experimental model must produce consistent SCI with little variability (7, 9–11, 16, 17, 29, 38, 41). Moreover, this consistency should result in reproducible anatomical and behavioral outcomes.

A newly designed weight-drop device from New York University (NYU) standardizes contusion injuries of the spinal cord (19, 29). A 10-g rod released from incremental preset heights of 6.25, 12.5, 25, or 50 mm above the cord produces graded lesion severity. To reduce interanimal variability and thereby ensure lesion consistency, rats can be excluded whose impact velocities fall outside a predetermined range of the predicted values for each injury grade. However, relevant tests of lesion consistency such as detailed histological and behavioral outcomes have not been performed (19, 29). Although lesion severity has been characterized acutely using anatomical outcomes, there is only limited data on chronic SCI with the NYU device. A paucity of information also exists regarding behavioral outcomes for each of the four lesion severities. Given the limited data characterizing the injuries produced by the NYU device, it remains to be determined if it is possible to discriminate between the four trauma doses on the basis of anatomical and behavioral outcome measures.

We have recently reported the use of a new open field (overground) locomotor scale to assess recovery after contusion injuries in rat spinal cord. The Basso, Beattie, and Bresnahan (BBB) scale was developed by assessing recovery patterns in a large number of rats which sustained mild or moderate injuries of the cord using a controlled, electromagnetic device designed and built at Ohio State University (OSU) or the NYU weight-drop device. The most severe injury sustained in these studies resulted in complete flaccid paralysis for the first few days following contusion, which substantially improved until consistent stepping was typical (1). Thus, most locomotor behavior was assessed using the middle and upper regions of the scale while the lower scale regions were tested on a much more limited basis. In order to fully verify the BBB scale we need to evaluate rats that spend most of the recovery period in the lower regions of the scale such as after severe spinal cord contusion or complete cord transection.

In the course of developing outcome measures for a

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multicenter animal spinal cord injury study (MASCIS), we used the BBB scale to track the recovery of rats injured with the NYU device. The present study describes mild to severe locomotor deficits resulting from the four trauma doses using the NYU device. In addition, some rats received complete spinal cord transection and others with moderate or severe spinal cord contusions were given subsequent complete cord transection to determine whether residual fibers at the lesion center had contributed to the minimal locomotor recovery observed. Finally, histological outcome measures reported previously (6, 10, 17), which are being used as an additional outcome measure for the MASCIS study, were correlated with injury dose and with BBB locomotor outcome scores.

The results of this study show that the BBB scale can distinguish differences in neurological outcomes of rats given injuries at different trauma doses with the NYU device, that the behavioral outcome is highly correlated with histological damage, and that the minimal recovery noted by using the BBB scale in rats with severe injuries is due to a small number of spared fibers traversing the chronic contusion lesion. In addition, rats given complete spinal cord transections after having sustained chronic contusion lesions showed more locomotor-like movements as judged by the BBB scale than did animals with chronic complete spinal cord transections. This suggests that descending fibers, even in small numbers, may affect the process of reorganization of spinal circuits caudal to a lesion.

METHODS

Subjects

Twenty-five male and female adult Long–Evans rats (265–415 g) were randomly assigned to one of five groups, four SCI groups and one transection group (TX). Rats were housed two per cage, exposed to a 12-h light/dark cycle, and had free access to food and water. Five rats were withdrawn or died during this study. Two rats died because of surgical complications and three were sacrificed because of unresolved bladder complications.

Testing Procedures

Rats were trained preoperatively to locomote in an open field which was a molded-plastic circular enclosure with a smooth, nonslip floor (90-cm diameter; 7-cm wall height). Open field training and testing procedures have been described previously (1). Briefly, rats were gentled and adapted to the open field. Once a rat walked continuously in the open field, two examiners conducted a 4-min, preoperative testing session using the BBB locomotor rating scale (Table 1).

Postoperative (po) open field testing occurred at least once a week from Day 1 po to 6 weeks po for all animals. Testing was extended until 9 weeks po for some rats. The final open field test was videotaped for some rats. From this tape, two examiners quantitatively assessed the number of hindlimb (HL) movements performed during a 1-min period; this time period was a composite of episodes over the 4-min testing session when each HL was in full view of the camera. A 1-min time limit ensured that the right and left HLs of each animal were assessed for the same length of time since both HLs were not always in full view of the camera. The footage was reassessed in slow motion if the scores of the examiners disagreed.

Surgical Procedures

Spinal cord contusion or TX surgeries were performed under pentobarbital (50–70 mg/kg) anesthesia and prophylactic administration of gentomycin sulfate (1 mg/kg). The thoracic area was shaved and prodine and alcohol were applied to the skin. Duratears lubricated the eyes. During surgery, body temperature was maintained at 37°C using either a Harvard homeothermic feedback controlled heating pad or heated gel packs. An incision extended from mid to low thoracic regions. Laminectomy of the caudal portion of T9 and all of T10 exposed the spinal cord. For the TX group ($n = 4$), the spinal cord was severed with microscissors and gentle aspiration. The ends of the cord distracted and the cavity was then carefully explored with a glass probe to cut any residual fibers. After determining that the TX was complete, the cavity was packed with gel foam. For contusion injuries, spinal clamps were attached to T8 and T11/12 spinous processes, a transducer was placed over the transverse process of T9, and the impact rod was centered above T10. The rod was slowly lowered until it contacted the dura, which was determined by completion of a circuit that activated a tone. The cord was then contused with the NYU weight-drop device. Different injury groups were produced by dropping the 10-g rod a distance of 6.25 ($n = 6$), 12.5 ($n = 5$), 25 ($n = 7$), or 50 mm ($n = 9$). Hence, there were four SCI groups named according to the drop distance. The surgical site was sutured in layers and an antibacterial spray was applied. Immediately after surgery, all rats were given lactated Ringers (5–10 cc) subcutaneously and were maintained in an incubator until thermoregulation was reestablished. Postoperative nursing care included bladder expression two to three times per day, administration of lactated Ringers for dehydration, administration of Nutri-cal food supplement (Evsco Pharmaceuticals) for weight loss, visual inspection for skin irritation or decubitus ulcers, and cleansing the hindquarters with soap and water followed by rapid drying of the fur with a blow dryer.

The NYU device detects rod velocity (displacement over time) and impact-induced vertebral movement using digital optical potentiometers. The data were

TABLE 1

Basso, Beattie, and Bresnahan Locomotor Rating Scale

0	No observable hindlimb (HL) movement
1	Slight movement of one or two joints, usually the hip and/or knee
2	Extensive movement of one joint or extensive movement of one joint *and* slight movement of one other joint
3	Extensive movement of two joints
4	Slight movement of all three joints of the HL
5	Slight movement of two joints *and* extensive movement of the third
6	Extensive movement of two joints *and* slight movement of the third
7	Extensive movement of all three joints of the HL
8	Sweeping with no weight support or plantar placement of the paw with no weight support
9	Plantar placement of the paw with weight support in stance only (i.e., when stationary) or occasional, frequent, or consistent weight-supported dorsal stepping and no plantar stepping
10	Occasional weight-supported plantar steps; no FL–HL coordination
11	Frequent to consistent weight-supported plantar steps *and* no FL–HL coordination
12	Frequent to consistent weight-supported plantar steps *and* occasional FL–HL coordination
13	Frequent to consistent weight-supported plantar steps *and* frequent FL–HL coordination
14	Consistent weight-supported plantar steps, consistent FL–HL coordination, *and* predominant paw position during locomotion is rotated (internally or externally) when it makes *initial contact* with the surface as well as just before it is *lifted off* at the end of stance; or frequent plantar stepping, consistent FL–HL coordination, and occasional dorsal stepping
15	Consistent plantar stepping and consistent FL–HL coordination *and* no toe clearance or occasional toe clearance during forward limb advancement; predominant paw position is parallel to the body at initial contact
16	Consistent plantar stepping and consistent FL–HL coordination during gait *and* toe clearance occurs frequently during forward limb advancement; predominant paw position is parallel at initial contact and rotated at lift off
17	Consistent plantar stepping and consistent FL–HL coordination during gait *and* toe clearance occurs frequently during forward limb advancement; predominant paw position is parallel at initial contact *and* lift off
18	Consistent plantar stepping and consistent FL–HL coordination during gait *and* toe clearance occurs consistently during forward limb advancement; predominant paw position is parallel at initial contact and rotated at lift off
19	Consistent plantar stepping and consistent FL–HL coordination during gait, toe clearance occurs consistently during forward limb advancement, predominant paw position is parallel at initial contact *and* lift off, and tail is down part or all of the time
20	Consistent plantar stepping and consistent coordinated gait, consistent toe clearance, predominant paw position is parallel at initial contact and lift off, *and* trunk instability; tail consistently up
21	Consistent plantar stepping and coordinated gait, consistent toe clearance, predominant paw position is parallel throughout stance, and consistent trunk stability; tail consistently up

Note. Slight: Partial joint movement through less than half the range of joint motion. Extensive: Movement through more than half of the range of joint motion. Sweeping: Rhythmic movement of HL in which all three joints are extended and then fully flex and extend again; animal is usually sidelying and plantar surface of paw may or may not contact the ground; no weight support across the HL is evident. No weight support: No contraction of the extensor muscles of the HL during plantar placement of the paw; or no elevation of the hindquarter. Weight support: Contraction of the extensor muscles of the HL during plantar placement of the paw; or, elevation of the hindquarter. Plantar stepping: The paw is in *plantar* contact with weight support and then the HL is advanced forward and *plantar* contact with weight support is reestablished. Dorsal stepping: Weight is supported through the dorsal surface of the paw at some point in the step cycle. FL–HL coordination: For every FL step a HL step is taken and the HLs alternate. Occasional: Less than or equal to half; ≤50%. Frequent: More than half but not always; 51–94%. Consistent: Nearly always or always; 95–100%. Trunk instability: Lateral weight shifts which cause waddling from side to side or a partial collapse of the trunk.

relayed to an Everex 386sx computer. Using these parameters, a computer program calculated impact velocity and compression rate. Impact velocity is derived from the rod trajectory 2 ms prior to impact. Compression rate is the ratio of cord compression depth over time where compression is determined from rod and vertebral movements. [For a detailed description of the NYU device see references (19, 29)].

In order to evaluate the contribution of descending systems to locomotor recovery, a subset of rats that had attained maximal behavioral recovery from 25-mm ($n = 2$) or 50-mm ($n = 4$) SCI underwent spinal cord transection (SCI + TX) at the original contusion site. The surgical procedures and postoperative care were similar to those described above. Confirmation of cord TX at the time of surgery included visual observation of separation and distraction of the ends of the spinal cord as well as passage of a small glass probe along the ventral and lateral canal in order to disrupt any small fibers which had not been severed.

Histology

Rats were perfused transcardially with 10% buffered formalin under deep anesthesia. The spinal cords were embedded in paraffin in 5- or 10-mm blocks containing the contusion or TX site, respectively. The cords were sectioned at 20 mm coronally for the SCI groups and horizontally for the TX and SCI + TX groups. Every fifth section was retained for the SCI groups and every other section for the rats with TX. Sections were stained with luxol fast blue for myelin and cresyl violet for nissl substance. Camera lucida drawings demarcating intact white and gray matter were made of the

TABLE 2

Group	Impact velocity (m/s)	Compression (mm)	Compression rate (m/s)	Spared tissue (%)	Locomotor score (BBB)
6.25	0.332 ± 0.01	1.268 ± 0.091	0.312 ± 0.006	48.0 ± 15.8	19.0 ± 15.8
12.5	0.484 ± 0.005	1.568 ± 0.124	0.620 ± 0.021	23.0 ± 3.3	11.4 ± 1.1
25	0.687 ± 0.007	2.05 ± 0.153	0.640 ± 0.076	9.9 ± 4.8	10.6 ± 0.6
50	0.963 ± 0.011	2.599 ± 0.028	0.824 ± 0.155	1.2 ± 1.3	7.9 ± 1.8
TX	—	—	—	—	3.3 ± 2.1

Note. All values are means ± standard deviation.

section with the largest lesion extent for each SCI cord. The percentage of spared spinal cord tissue was derived from measurements of the total cross-sectional and spared tissue areas using a Zeiss Videoplan morphometrics computer (8). The horizontal sections for the TX and SCI + TX rats were analyzed microscopically for evidence of tissue sparing.

Statistical Analysis

For each rat, the locomotor scores for the hindlimbs were averaged together to yield one score per test session. With the exception of the first postoperative week, multiple scores for the same week were averaged and used for all statistical analyses. Daily scores were used for the first week po. Scores were interpolated in the event of missing data. Open field locomotor scores were compared using a two-way analysis of variance (ANOVA). The factors were groups ($n = 5$) and trials (nine sessions) with repeated measures on the second factor. Tukey's honestly significant difference test was used for post hoc analyses. The harmonic mean of the groups was used to correct for unequal group sizes. One-way ANOVAs were used for between-group comparisons of impact velocity, cord compression, compression rate, and amount of spared tissue. Pairwise post hoc comparisons were made with Bonferroni corrected t tests. Linear and curvilinear regression analysis was used to examine the relationship between contusion parameters, tissue sparing, and final locomotor performance. Differences in male vs female locomotor recovery scores were analyzed for eight females and seven males in the 25-mm, 50-mm and TX groups using t tests. Three time points were assessed: 1 day, 3 weeks, and 6 weeks postinjury. For the SCI + TX group, matched pairs t tests were used to compare open field scores pre-TX vs 1 day post-TX, and 1 day post-TX vs 2 weeks post-TX. To assess differences in recovery between the TX and SCI + TX groups, the frequency of HL movements in 1 min was compared using a t test. All statistical analyses were done using the Systat for Windows, version 5 (Systat, Inc.).

RESULTS

Contusion Parameters

The NYU weight-drop device produced incremental increases in impact velocity, cord compression, and compression rate with increasing drop height (Table 2). These contusion parameters showed very little interanimal variability in the 12.5-, 25-, and 50-mm groups. The mean drop height deviated from the expected values by 0.07, 0.06, and −0.04 mm, indicating that the actual drop height was accurate for the 12.5-, 25-, and 50-mm groups, respectively. This consistency resulted in impact velocities similar to those expected. In fact, the mean percentage error from expected impact velocity was below 2.82% for all three groups. The contusion parameters were more variable for the 6.25-mm group. The actual drop height ranged from 5.8 to 6.43 mm, creating a higher error in impact velocity than for drop heights of 12.5 and above. The mean percentage error in impact velocity was 5.2%, which is nearly a twofold increase over the other groups.

Significant group differences were found for impact velocity ($F3 = 8261.00$; $p < 0.0001$), cord compression ($F3 = 131.78$; $p < 0.0001$), and compression rate ($F3 = 751.70$; $p < 0.0001$). Between-group comparisons found significant differences between the 6.25-, 12.5-, 25-, and 50-mm groups for impact velocity ($p < 0.0001$), cord compression ($p < 0.0001$), and compression rates ($p < 0.0001$).

Histology

Weight-drop contusion of the spinal cord created a central core lesion, sparing a peripheral rim of tissue in most cases which decreased significantly in size as drop height increased ($F15 = 23.58$; $p < 0.0001$) (Fig. 1; Table 2). The central lesion area included spared fibers (open block arrow, Fig. 1B), cyst formations (stars, Fig. 1B), gliosis (double arrows, Fig. 1B), zones of partial demyelination and microcysts (curved arrow, Fig. 1B), and scarring (larger arrow, Fig. 1C). The largest amount of peripheral sparing was found in the 6.25-mm group. Large cystic cavities were observed in regions previously occupied by the gray matter (star, Fig. 1A). Usually a small region of gray matter was spared in the superficial dorsal horns. The cavity was primarily open with minimal gliosis or scarring and few macrophages. Thick, densely stained white matter in the ventral, lateral, and dorsal funiculi appeared spotted due to microcysts which were sites of diffuse axonal injury (15, 18).

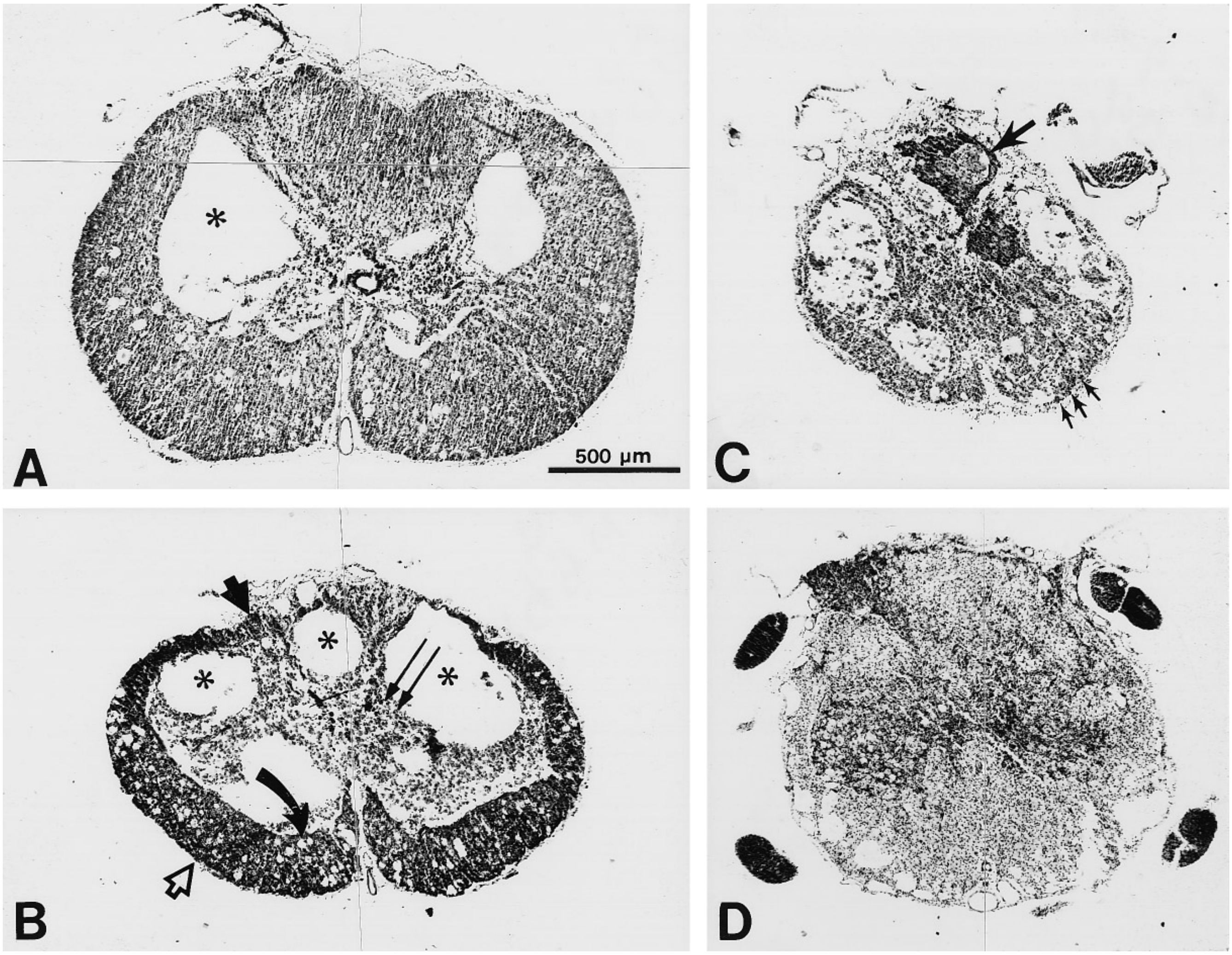

FIG. 1. Representative coronal sections at the lesion center for a 6.25 mm (A), 12.5 mm (B), 25 mm (C), and 50 mm (D) weight-drop contusion using the NYU device. Increasing the drop height resulted in greater damage to the spinal cord (A–C) until no spared tissue was evident (D) on sections stained for luxol fast blue and cresyl violet. Arrows indicate some regions of spared tissue and asterisks indicate cystic cavities.

Moderate sparing occurred in the 12.5-mm group with thick regions in the ventral funiculi tapering down laterally to a very thin rim in the dorsal funiculus (Fig. 1B, solid block arrow). The expanded lesion cavity completely disrupted all portions of the gray matter. In most cases, more of the cavity was filled with gliosis and macrophages than in the 6.25-mm group (double arrows, Fig. 1B) but large cysts remained (stars, Fig. 1B). Some of the lesions had two distinguishable zones in the white matter: a dense, heavily myelinated rim at the peripheral edge of the cord (open block arrow, Fig. 1B) and an internal region with less luxol fast blue staining. The internal region consisted of zones of partial demyelination and fewer myelinated axons. Small round microcysts and numerous irregular-shaped spaces occurred throughout the spared white matter.

For the 25-mm group, small areas of spared axons occurred at the periphery of the cord primarily in the ventral funiculi (small arrows, Fig. 1C). These areas were clearly distinguished at higher magnification and represent survival of small fascicles of myelinated axons in regions otherwise devoid of normal white matter. The central lesion was markedly larger and the majority of the area was composed of scar tissue (large arrow, Fig. 1C), gliosis, and macrophages. None of the spared tissue was densely stained by luxol fast blue as in the 6.25- and 12.5-mm groups. The spared tissue was lightly stained and appeared similar to that of the partial demyelination zone observed in the 12.5-mm group (small arrows, Fig. 1C).

The most severe SCI occurred in the 50-mm group. Almost no spared fibers were found at the contusion site based on the observation of little or no luxol fast blue staining (e.g., Fig. 1D). Any surviving myelinated axons were in tiny, isolated patches located on the

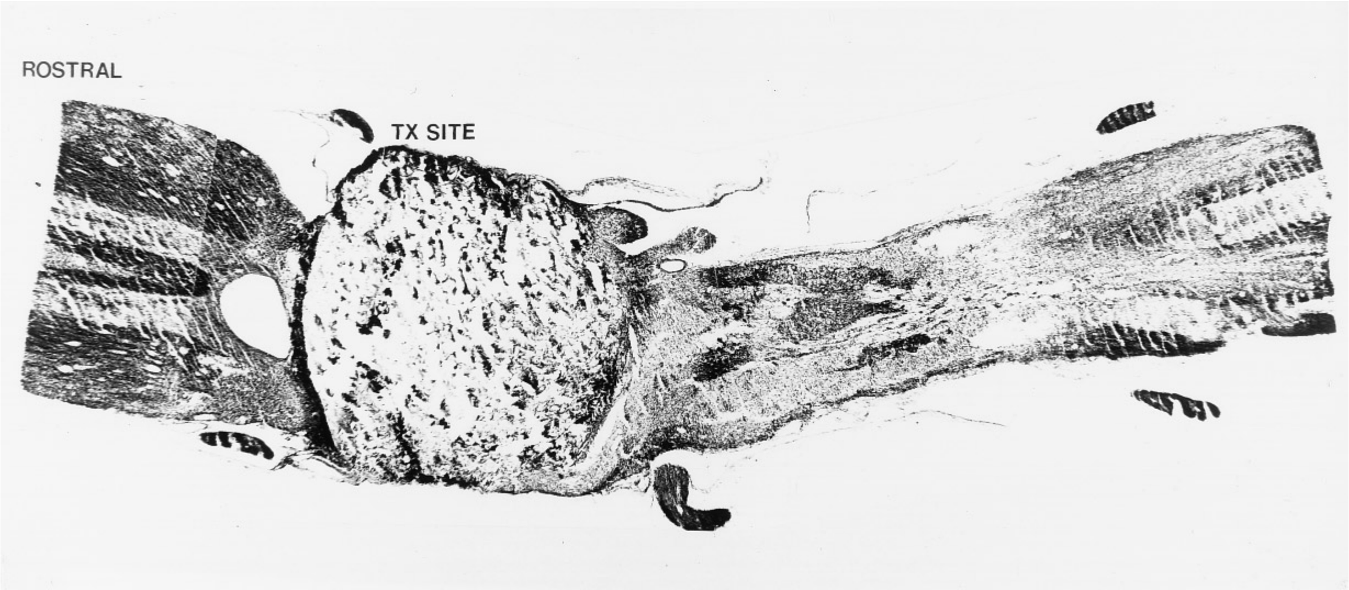

FIG. 2. A representative horizontal section, stained for myelin and nissl substance, taken through the spinal cord of a rat with a 25-mm SCI and subsequent complete transection (TX). Note the absence of myelin-stained fibers crossing the TX site and the dense glial border separating the TX site from the nearly intact rostral cord. The contusion produced substantial injury in the caudal regions of the cord. Gelfoam can be seen at the TX site.

peripheral edge of the ventral funiculus. Dense scarring and gliosis were apparent throughout the lesion site and many large macrophages formed aggregates within the scar, leaving almost no cystic cavity. In most cases, the macrophage conglomerates primarily occupied ventral regions of the cord.

The group differences in the percentage of spared tissue (white and gray combined) were statistically significant for the 6.25-mm group when compared to all other groups ($p < 0.006$). The 12.5-mm group had a significantly greater percentage of spared tissue than the 50-mm group ($p < 0.035$). No significant differences in percentage of spared tissue were found between the 12.5- and 25-mm groups or the 25- and 50-mm groups.

Complete transection of the spinal cord was microscopically confirmed for rats in the SCI + TX and TX groups. Obvious discontinuity of the spinal cord and/or the lack of myelin-stained fibers crossing the injury site was evidence of complete TX. Figure 2 shows a horizontal section through the center of a contusion site which was subsequently transected (TX site). In only one case was there a possibility of continuity across the transection site. A small fascicle of axons at the ventral border of the cord appeared to traverse the lesion site. These fibers may have been constitutive elements of spinal cord white matter but were more likely part of a ventral root given the observation of distraction of the ends of the spinal cord immediately following TX in all cases.

Behavioral Recovery

Contusion injuries of increasing severity produced concomitant degradations in behavioral performance as measured by BBB scores (Fig. 3; Table 1). The 6.25-mm group had the greatest locomotor recovery; animals in this group progressed from extensive joint movements or taking an occasional step to normal locomotion occasionally hampered by trunk instability.

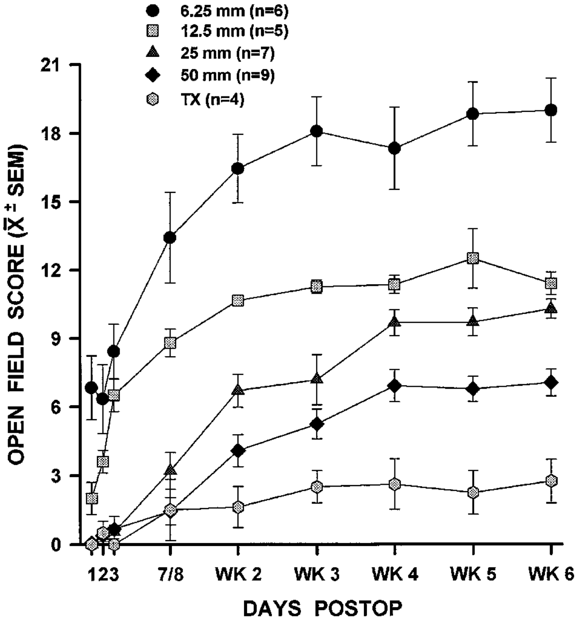

FIG. 3. The time course of locomotor recovery as measured by BBB open field scores for groups with TX, 6.25, 12.5, 25, and 50 mm SCI. Following SCI, the 6.25-mm group demonstrated the greatest recovery and the 50-mm group the least, while the 12.5- and 25-mm groups attained intermediate levels. The TX group showed no substantial improvement throughout the 6-week recovery period. (Scores are means and SEM.)

Most rats in this group demonstrated behavioral improvement between 3 days po and 5 weeks po. The large variability in this group is due to one rat which showed greater locomotor deficits throughout the recovery period than other rats at this injury level.

The 12.5-mm group demonstrated an intermediate level of recovery. As early as 1 day po, most rats produced slight HL joint movements which rapidly improved over the next 2 days. By 3 weeks po, these rats were usually stepping consistently but were unable to coordinate the forelimbs and hindlimbs consistently. There was no behavioral improvement between 3 and 6 weeks po. Interestingly, the locomotor performance of these rats at 6 weeks po was no better than the behaviors demonstrated by some of the 6.25-mm animals on 1 day po.

The rats in the 25-mm group had little or no HL movements until 7 days po and then demonstrated a gradual, progressive recovery over the next 4–5 weeks po. All but one rat regained the ability to take weight-supported steps; most were stepping consistently but lacked FL–HL coordination.

Immediately after 50-mm SCI, rats demonstrated flaccid paralysis which persisted for 3–7 days po. Most of the behavioral recovery occurred between 2 and 4 weeks po when most rats were able to move the joints of the HL extensively. No further recovery was observed over the remaining 2 weeks po. Thus, even after 6 weeks of training the 50-mm rats never progressed beyond the behavioral performance level attained by the 12.5-mm group by 7 days po.

Surprisingly, in some respects the recovery pattern of the 25-mm group was not distinct from either the 12.5- or 50-mm groups. Early after SCI, the 25-mm group demonstrated flaccid paralysis like the 50-mm group but recovered to the level of the 12.5-mm group. However, unlike the 12.5- and 50-mm groups, rats with 25-mm SCI demonstrated behavioral improvement over a prolonged recovery period lasting up to 5 weeks po in some animals.

The TX group demonstrated very little behavioral recovery. During locomotion, the forelimbs propelled the animal while the HLs dragged behind. The HLs exhibited flaccid paralysis which began immediately po, lasting at least a week for most rats. Between 2 and 6 weeks po, most rats recovered only slight HL joint movements.

There was no significant difference in behavioral recovery between males and females with 25-mm SCI, 50-mm SCI, or complete TX at 1 day, 3 weeks, and 6 weeks postinjury ($p > 0.05$). Data were pooled across sexes for all remaining comparisons.

A two-way ANOVA showed that there were significant differences in locomotor recovery between groups (F4 = 49.96; $p < 0.0001$) and across sessions (F8 = 141.13; $p < 0.0001$). The group by session interaction was also significant (F32 = 6.40; $p < 0.0001$). Using post hoc comparisons, significant group differences were found as early as 1 day po when the 6.25-mm group had significantly higher locomotor scores than all other groups ($p < 0.01$) (Table 3). By 2 weeks po, the 6.25- and 12.5-mm groups were different from all other groups ($p < 0.01$) and the 25-mm group demonstrated significantly greater recovery than the TX group ($p < 0.01$). At 6 weeks po, all between-group differences were significant except for the 25-mm group which did not differ from the 12.5- or 50-mm groups (Table 3).

Regression Analysis

The biomechanical descriptors of the contusion injury, drop height, impact velocity, cord compression, and compression rate correlated significantly with one another as expected (Table 4). Linear regression was the best fit of these data; curvilinear methods did not account for more variance. For instance, the r^2 values for drop height and compression rate were 0.963 and 0.99 for linear and curvilinear regressions, respectively.

The relationships between the biomechanical parameters and outcome measures, i.e., open field locomotion and tissue sparing, were highly significant (Table 4). Although linear regression described the data reasonably well, second order polynomial regressions ac-

TABLE 3

Behavioral Recovery between-Group Comparisons

	Day 1				
	TX	50	25	12.5	6.25
TX	—	ns	ns	ns	*
50		—	ns	ns	*
25			—	ns	*
12.5				—	*
6.25					—
	2 weeks PO				
	TX	50	25	12.5	6.25
TX	—	ns	*	*	*
50		—	ns	*	*
25			—	*	*
12.5				—	*
6.25					—
	6 weeks PO				
	TX	50	25	12.5	6.25
TX	—	*	*	*	*
50		—	ns	*	*
25			—	ns	*
12.5				—	*
6.25					—

Note. ns, not significant.
*$p < 0.01$.

TABLE 4

Linear and Curvilinear Polynomial Regression Analysis

	Impact velocity		Drop height		Compression		BBB score		% spared tissue	
	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd
Compression rate	0.990	0.990	0.963	0.990	0.934	0.935	0.697	0.766	0.745	0.824
Impact velocity	—	—	0.978	0.999	0.932	0.940	0.697	0.722	0.731	0.816
Drop height			—	—	0.886	0.945	0.623	0.735	0.631	0.792
Compression					—	—	0.644	0.666	0.669	0.704
BBB score							—	—	0.876	0.878

Note. All data are r^2 values for first and second order polynomial regressions. All values are significant at $p < 0.0001$. BBB score, open field score.

counted for more of the variance. In all cases, curvilinear patterns provided the best fit with the data. In fact, the r^2 values for the second order polynomial regressions were quite high and ranged from 0.722 to 0.824. Of the biomechanical parameters, compression rate had the highest correlation with open field locomotion and amount of tissue sparing (0.766 and 0.824, respectively, Table 4).

The outcome measures were significantly correlated with one another (Table 4) and were best described using linear regression ($r^2 = 0.876$). This positive linear relationship (Fig. 4) showed that with increased tissue sparing, higher locomotor scores occurred. Not only were rats able to recover nearly normal locomotion after a loss of up to 50% of spinal cord tissue at the lesion center but with as little as 2% tissue sparing, rats exhibited HL plantar placing and in one case took occasional steps.

CONTUSION + TRANSECTION

After 7 weeks of behavioral recovery (Fig. 5), a group of seven rats with 25-mm ($n = 2$) or 50-mm ($n = 4$) SCI underwent complete cord transection to ascertain the role of the remaining fibers at the lesion center. The locomotor scores decreased significantly the first day post-TX ($p < 0.01$); only slight movement of the three joints of the HL were observed (Fig. 5). A decline in locomotor performance continued until 5 days post-TX when slight movement of only one or two joints was typical. A slight increase in locomotor scores occurred by 2 weeks po but this was not significantly different from the 1-day post-TX performance levels ($p > 0.05$). In general, locomotor scores for the SCI + TX group were higher than that of the TX group at 1 and 2 weeks post-TX (Fig. 5) although the difference was not significant. Analysis of the frequency of HL movements in the open field 7 or 14 days post-TX showed that the SCI + TX group made significantly more movements than the TX group ($p < 0.005$) (Fig. 6).

DISCUSSION

An important aspect of modeling SCI is that cord contusions be graded, consistent, and reproducible from rat to rat (10, 17, 38). In order to standardize injuries, current approaches alter the mechanical parameters of the contusion device like the amount of impactor displacement (10, 17) or the drop height of a weight (11, 19, 22, 29, 38, 41). By monitoring these parameters for fluctuations across animals and experiments, a measure of consistency and reproducibility is achieved for each graded injury.

The NYU weight-drop device monitors at least three mechanical parameters: drop height, impact velocity, and compression rate for four injury levels. In the present experiment, impact velocity appeared to be the

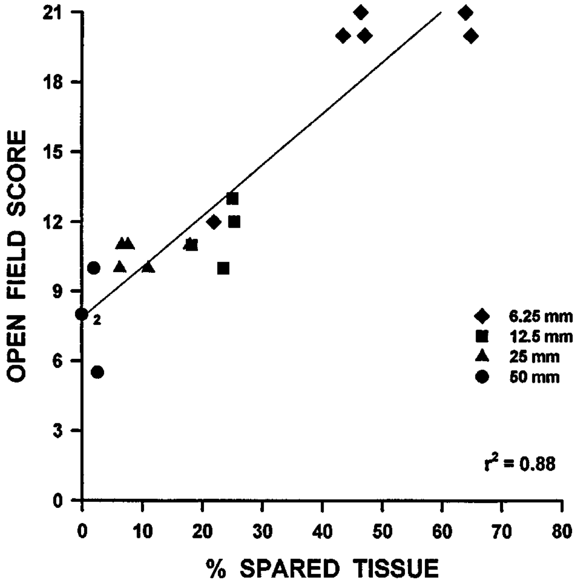

FIG. 4. Correlational analysis of locomotor recovery as measured by BBB scores and the percentage of spared tissue after 6.25, 12.5, 25, and 50 mm SCI. The positive linear relationship suggests that greater locomotor recovery occurred in rats with greater tissue sparing. Note that this relationship held for severe injuries and low BBB scores as well as for mild injuries and maximal BBB scores.

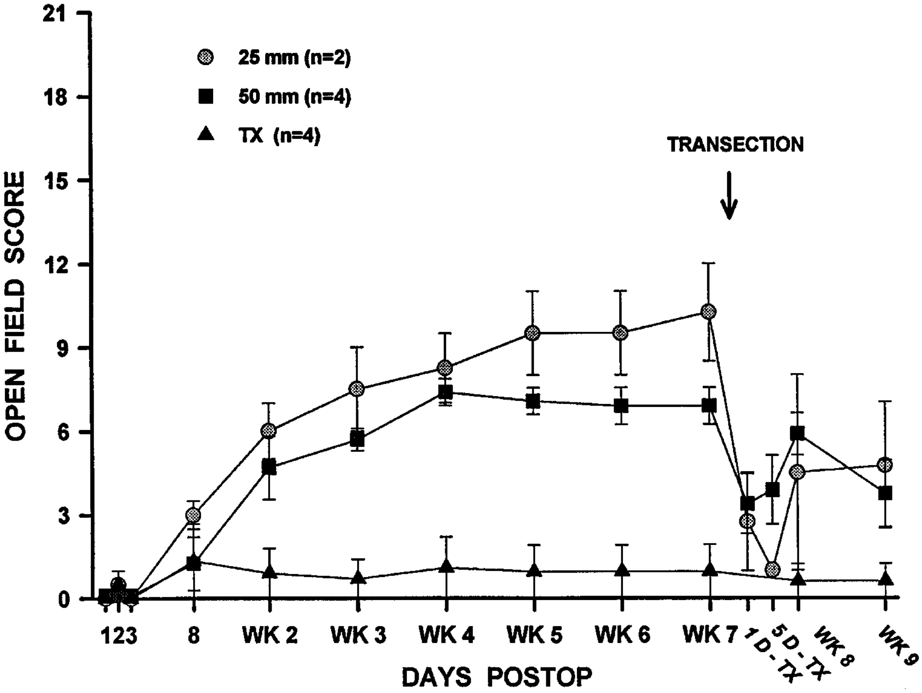

FIG. 5. Recovery of locomotion for 25- and 50-mm SCI + TX groups compared to a TX-alone group. Rats with SCI demonstrated marked improvement in locomotion well above that of the TX group over a 7-week period; then, as a result of complete cord TX, they had a dramatic drop in performance to the level of the TX-alone control group. Note the increase in locomotor scores for the SCI + TX groups but not the TX-alone group between 8 and 9 weeks.

most relevant mechanical parameter because it best predicted anatomical and behavioral outcome. On the basis of deviations of impact velocity from expected values, the NYU device was found to be very consistent for the 12.5-, 25-, and 50-mm groups. The deviations were below 3%. Less consistency occurred with 6.25-mm injuries; more than 5% error in impact velocity was found in this group. Additionally, the 6.25-mm group had the highest variability in both tissue sparing (mean = 47.96; SD = 15.79) and final locomotor scores (mean = 19.0; SD = 3.46), indicating large interanimal differences. The variability in these parameters was between 2 and 15 times greater for the 6.25-mm group than for the other SCI groups. While it is possible that a 5% reduction in impact velocity resulted in greater tissue sparing and locomotor recovery, it seems unlikely that so small an error could account for outcome variability of such a large magnitude. Perhaps the reduction in impact velocity was coupled with biological differences across animals which were obvious only in cases of minor spinal cord injury. This contention is supported by the finding that the 6.25-mm rat, with the largest deviations in outcome measures when compared to the rest of the group, sustained an impact velocity central to the group.

The NYU device is designed to create four graded injuries. Previously, differences in behavioral and anatomical outcomes were evidence of gradations (10, 11, 16, 17, 23, 29, 36, 37, 41). An important finding of this

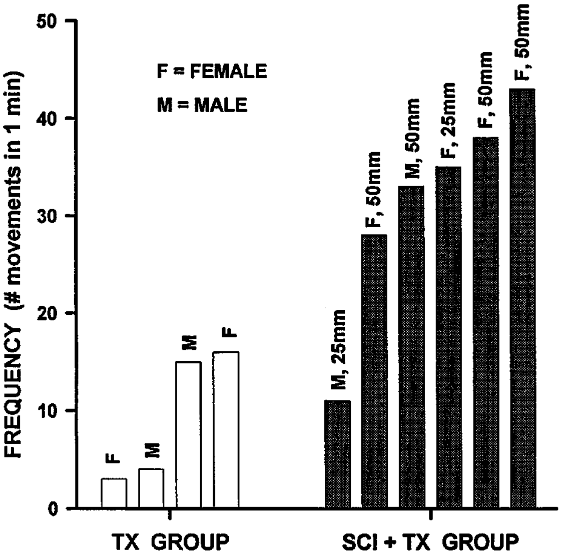

FIG. 6. The frequency of hindlimb movements for individual rats in the TX and SCI + TX groups as measured from videotapes in which each HL was visible for a total of 1 min during open field testing 7 or 14 days post-TX. With the exception of one rat, all SCI + TX rats demonstrated a greater frequency of HL movements than rats with TX alone. The numbers of right and left HL movements were summed. M, male; F, female; 25 mm and 50 mm indicate weight-drop height.

experiment was that only three groups were significantly different from one another in terms of locomotor outcome. The 6.25-mm group demonstrated maximal locomotor recovery which was significantly better than all other groups as early as 1 day po. These rats progressed from extensive HL joint movements or occasional stepping to near normal locomotion within 3 weeks. At the other extreme, the 50-mm group gained only minimal locomotor recovery. Most of these rats failed to show any HL movement until 2 weeks po and then, the window of recovery was limited to 2 weeks so that they never progressed beyond extensive HL joint movements. The 12.5- and 25-mm groups attained moderate locomotor recovery. The rats in both of these groups had little or no HL movement initially. Although these groups were not significantly different initially or late in recovery, they demonstrated different rates of recovery almost immediately. The 12.5-mm group rapidly progressed from little or no HL movements to stepping consistently in just 3 weeks. In contrast, the 25-mm group had a slower, more sustained rate of recovery with most rats still showing some improvement in locomotion as late as 5 weeks after contusion. The variations in rate of recovery across groups was unexpected given that previous studies have shown maximal behavioral recovery by 3 weeks po using either an electromagnetic or a weight-drop device (17, 23, 37).

Although only three of the contusion groups were statistically differentiable, each group had unique patterns of locomotor recovery which offer greater specificity when designing experiments. For instance, a comparison of 25- and 50-mm injuries would be appropriate for an investigation into the substrates of stepping. Likewise, an examination into the effects of therapeutic regimens on rapid and slow rates of recovery may be most apparent in the 12.5- and 25-mm groups. Finally, the 6.25-mm injury may be useful in experimental paradigms that tolerate greater variability, depend on FL–HL coordination, or require minimal residual deficits.

Gradation in anatomical outcome was apparent across all groups. Increasing drop heights resulted in greater damage to the spinal cord and lower percentages of spared tissue, relative to the total cross-sectional area. The failure of differences in sparing to reach statistical significance for the 12.5-, 25-, and 50-mm groups was probably related to small group sizes. The inverse relationship between drop height and spared tissue has been well described for a 10-g weight dropped from 2.5–17.5 cm above the cord by Wrathall and collaborators (23, 36, 37, 41). The amount of tissue sparing is apparently greater with the Wrathall device despite equivalent weight and height parameters with the present study. In fact, the sparing associated with a 5-cm injury, 23.4% (37), was similar to that of the 12.5-mm group produced with the NYU device, 23.0%; and sparing from a 17.5-cm weight drop, 3.1% (37), was approximately equal to a 50-mm SCI with the NYU device, 1.2%. The spinal cord was contused at T8 in the Wrathall studies rather than T10 but this difference would not account for greater sparing since contusions at lower (lumbar) but not higher (thoracic) cord levels result in greater sparing (16). Apparent design differences between the Wrathall and NYU devices appear to be responsible for the anatomical discrepancies. In the Wrathall device, the 10-g weight does not strike the cord directly but rather hits an impounder rod resting on the dura of the cord (38, 41). It is likely that dissipation of force occurs at the weight–impounder junction, thereby reducing impact velocity on the cord. Unfortunately, the Wrathall device does not monitor impact velocity and the NYU device does not monitor force, making direct comparisons of mechanical parameters impossible.

Previous studies with the NYU device report a graded increase in lesion volume as measured by the volume of spinal cord cells with no ionic gradient at 24 h postinjury (19, 29). However, the differences between ionic lesion volumes of 22.2 ± 2.7, 32.3 ± 1.0, and 34.2 ± 2.3 ml for 12.5-, 25-, and 50-mm SCI, respectively, were not significant (19). Constantini and Young (19) also investigated the qualitative histological changes at the lesion site 24 h after 25-mm SCI. They found patchy hemorrhage and necrosis at the lesion site. White-matter sparing was evident but no distribution pattern within the funiculi was described. The relationship of lesion size among 12.5-, 25-, and 50-mm SCI as predicted by ionic integrity of the cells at 24 h was remarkably similar to that reported in this study, 6–9 weeks postinjury. That is, both studies found a large magnitude of change in lesion size between the 12.5- and 25-mm groups and very little change between the 25- and 50-mm groups. It remains unclear how ionic measures relate to precise histological measures of tissue sparing as used in this study. Further investigation is needed to determine the precision with which ionic lesion volumes can predict the percentage of spared spinal cord tissue for each injury severity.

All mechanical parameters of the NYU device were significantly correlated with each other as well as with the anatomical and behavioral outcome measures. Impact velocity correlated most highly with all other measures. An important finding of this study was that curvilinear rather than linear regression provided the best fit for the relationship between mechanical parameters and outcome measures. This is the first study to examine this relationship in weight-drop contusions using curvilinear regression, although several previous studies present data that appear to be curvilinear: drop height and mean combined behavioral score [Fig. 1; (23)]; drop height and mean area of spared white matter [Fig. 5; (36)]; and drop height and locomotor recovery [Fig. 5; (22)].

A curvilinear relationship has also been described previously for anatomical and behavioral outcome measures after contusion (1) or clip compression (21) injury of the cord. A curvilinear pattern indicates that the magnitude of change for one variable is greater than that for the other variable at certain points. Hence, we have established that small incremental changes in the percentage of spared tissue at the lesion center are related to large increases in BBB scores at the low end of the scale when the animals are capable of only basic locomotor features. For instance, rats with less than 5% spared tissue are unable to support weight with the HLs while rats with 10% sparing not only support weight but consistently step with the HLs. Unfortunately, continued incremental increases in spared tissue are not related to large improvements in locomotor outcome as measured by BBB scores. For example, locomotor characteristics are indistinguishable for rats with 45 or 90% tissue sparing. The present study confirms these findings and more importantly that the positive correlation between tissue sparing and locomotion remained very strong even though the data represent a broader range of spinal cord damage and an expanded distribution of behavioral scores than in most previous studies (17, 22, 36, 37). A linear rather than curvilinear relationship was the best fit for the data because minimal intermediate data (30–45% tissue sparing and 14–19 BBB scores) were generated by the four trauma doses. The injury groups examined in our previous study (1) produced very discrete behavioral and anatomical data in the mid and higher ranges of the continuum, resulting in a curvilinear pattern; however, the present study primarily evaluated data in the low and high ends which yielded a linear relationship.

The amount of spared spinal cord tissue is closely related to behavioral recovery (1, 3–5, 10, 17, 22, 36, 37). We confirmed that greater tissue sparing is highly correlated with final locomotor performance using the BBB rating scale (1). An important finding in this study was the fact that very small increases in spared tissue at the lesion center had profound effects on basic locomotor recovery but the more skilled, detailed aspects of locomotion were not augmented by these small increases. This finding suggests that sparing as few as 5–10% of the fibers at the lesion center is sufficient to help drive the segmental circuits involved in the production of basic locomotion.

The BBB rating scale is a 21-point system based on operationally defined behavioral features which follow the recovery progression from complete paralysis to normal locomotion (1). The impact of scale design and usage by raters with minimal training has been previously examined in detail (2). Previously, the scale was shown to be valid and reliable for intermediate and high locomotor performances but lower ranges were not thoroughly examined (1, 2). In this study, most rats with severe spinal cord contusion or transection were unable to support weight with the HLs so that only isolated joint movement occurred, represented by scores 1–8. The fact that significant differences were found between the movements made by rats with TX and those with severe contusion indicates that the BBB scale is valid and has a high degree of sensitivity at lower scores.

Locomotor recovery after partial spinal cord damage is associated with alterations in descending brainstem (10, 27, 30, 39) and segmental spinal cord systems (4, 25, 26, 30, 31, 34). The role of these systems has been differentiated for various forms of locomotion (25, 26). Descending brainstem systems are necessary for overground locomotion such as that tested in this experiment (3, 10, 27, 28, 32, 33). We show that the spared fibers at the lesion support the recovery of locomotion to minimal and intermediate levels in rats with 50- and 25-mm SCI, respectively. A significant reduction in locomotor scores occurred immediately after complete TX for the SCI groups to the level of rats with TX only. Surprisingly, the extent and frequency of HL movements increased over the next 2 weeks for the SCI + TX rats and were higher than those of rats with TX alone on the final testing day. These findings suggest that even minimal descending input (1–5% axonal sparing at the epicenter) may greatly influence the segmental systems of the distal cord. If the few axons spared played no role, then the extent and frequency of HL movements after SCI + TX should not have been significantly higher than those of the TX-only group.

Previously, Behrmann *et al.* (10) showed a permanent reduction in modified-Tarlov locomotor scores subsequent to cord TX in SCI rats injured with the OSU device. The extent of movement in these rats 6 weeks post-TX ranged from flaccid paralysis to isolated hip or knee movement which was similar to that of the TX-alone control group. In the present study, the BBB scale used eight scoring categories (0–7) to evaluate the extent of HL joint movement, whereas the modified-Tarlov scale had only six categories ranging from 0 to 2. Therefore, the increase in scores found in this study may be due to an expansion of the scoring system rather than actual improvements in performance. However, scale differences do not explain the higher movement frequency since these were measured from videotape and were unrelated to the scale. Perhaps the higher performance of SCI + TX vs TX-alone rats is due to serial lesion effects (24, 30). Helgren and Goldberger (30, 31) showed significant locomotor improvement in cats with delayed, offset spinal cord hemisections which equaled a complete TX when compared to a single TX. Their data and ours suggest that the preservation of as few as 5% of descending brainstem systems to the lumbar cord will alter the function of the segmental systems that control HL movement. Whether motor improvement is due to mechanisms of plasticity, disinhibition, or denervation supersensitivity remains to be tested.

In summary, the NYU device produces graded, consistent contusion injuries of the spinal cord, enabling the prediction of anatomical and behavioral outcomes. Use of sensitive behavioral measures such as the BBB rating scale and videotape analyses provided a view of the recovery process after SCI and subsequent cord TX not previously described. Together, these methods should facilitate the modeling of spinal cord injury and the determination of therapeutic efficacy in preclinical trials.

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