Late recovery following spinal cord injury

Case report and review of the literature

JOHN W. MCDONALD, M.D., PH.D., DANIEL BECKER, M.D., CRISTINA L. SADOWSKY, M.D., JOHN A. JANE, SR., M.D., PH.D., F.R.C.S.(C)., THOMAS E. CONTURO, PH.D., AND LINDA M. SCHULTZ, PH.D.

The Restorative Treatment and Research Program and Center for the Study of Nervous System Injury, Departments of Neurology and Neurological Surgery, and Radiology, Washington University School of Medicine, St. Louis Missouri; and Department of Neurosurgery, University of Virginia, Charlottesville, Virginia

The authors of this prospective, single-case study evaluated the potential for functional recovery from chronic spinal cord injury (SCI). The patient was motor complete with minimal and transient sensory perception in the left hemibody. His condition was classified as C-2 American Spinal Injury Association (ASIA) Grade A and he had experienced no substantial recovery in the first 5 years after traumatic SCI. Clinical experience and evidence from the scientific literature suggest that further recovery would not take place. When the study began in 1999, the patient was tetraplegic and unable to breathe without assisted ventilation; his condition classification persisted as C-2 ASIA Grade A. Magnetic resonance imaging revealed severe injury at the C-2 level that had left a central fluid-filled cyst surrounded by a narrow donutlike rim of white matter. Five years after the injury a program known as "activity-based recovery" was instituted. The hypothesis was that patterned neural activity might stimulate the central nervous system to become more functional, as it does during development. Over a 3-year period (5–8 years after injury), the patient's condition improved from ASIA Grade A to ASIA Grade C, an improvement of two ASIA grades. Motor scores improved from 0/100 to 20/100, and sensory scores rose from 5–7/112 to 58–77/112. Using electromyography, the authors documented voluntary control over important muscle groups, including the right hemidiaphragm (C3–5), extensor carpi radialis (C-6), and vastus medialis (L2–4). Reversal of osteoporosis and an increase in muscle mass was associated with this recovery. Moreover, spasticity decreased, the incidence of medical complications fell dramatically, and the incidence of infections and use of antibiotic medications was reduced by over 90%. These improvements occurred despite the fact that less than 25 mm^2 of tissue (approximately 25%) of the outer cord (presumably white matter) had survived at the injury level.

The primary novelty of this report is the demonstration that substantial recovery of function (two ASIA grades) is possible in a patient with severe C-2 ASIA Grade A injury, long after the initial SCI. Less severely injured (lower injury level, clinically incomplete lesions) individuals might achieve even more meaningful recovery. The role of patterned neural activity in regeneration and recovery of function after SCI therefore appears a fruitful area for future investigation.

KEY WORDS • activity-based • functional recovery • spinal cord injury • regeneration • functional electrical stimulation

THE ASIA developed international standards for examining and reporting the severity of SCI.[25,51] Table 1 presents ASIA's five grades of spinal cord function, A to E, where E is normal. Individuals with the least remaining function are described by the ASIA Grade A. Such patients have little hope for recovery.[53] Less than 1% of those with no muscle activity in the lower extremities 1 month after injury learn to walk again, and only 10% recover enough function to be reclassified as ASIA B or better.[47,77] Approximately 90% of patients remain classified as ASIA Grade A.[47]

Abbreviations used in this paper: ASIA = American Spinal Injury Association; CNS = central nervous system; EMG = electromyography; FES = functional electrical stimulation; MR = magnetic resonance; SCI = spinal cord injury.

Patients with SCI are often told that improvement or recovery occurs largely in the first 6 months after injury and is complete by 2 years. Indeed, the literature does not provide a single example of an individual with an ASIA Grade A SCI who recovered by more than one grade 2 years after injury.[61] Some delayed recoveries occur, but the timeframe is typically between 1 and 6 months after injury for large improvements.[78,79] Such recoveries are most common when an accompanying head injury impedes initial progress.[50] Small improvements can occur after periods longer than 2 years but typically occur in individuals with incomplete injuries.

A decade ago, the adult CNS was thought to be incapable of regeneration. Rehabilitation focused primarily on the immediate postinjury phase, when patients were still in the hospital, and aimed to maximize existing func-

TABLE 1
Description of ASIA International Standards for classifying SCI

Grade	Description
A	complete: no sensory or motor function preserved in S4–5
B	incomplete: sensory but no motor function preserved below the neurological level & extending through S4–5
C	incomplete: motor function preserved below the neurological level; majority of key muscle have a grade <3
D	incomplete: motor function preserved below the neurological level; majority of key muscles have a grade >3
E	normal motor & sensory function

tion and minimize complications. Although these goals are still important, the concept of spontaneous regeneration has emerged.[20,29,38,52,59,67,68,72]

A reasonable approach to promoting regeneration is to mimic conditions in the developing CNS, in which cell birth, migration, differentiation, selection of new circuits, and myelination occur routinely. A large body of evidence suggests that optimized patterned neural activity is important for these developmental processes.[33] Therefore, such activity might also be necessary for regeneration. Indeed, reports in the stroke literature indirectly support the role of neural activity in functional recovery.[66,75] Unfortunately, neural activity is markedly reduced in the segments below the level of an SCI. This is partly due to the lack of descending inputs and the limited transmission of sensory inputs. People with severe SCI, particularly tetraplegia, often develop severe muscle wasting, spasticity, cardiovascular deconditioning, and medical complications.[35] Such sequelae would cancel out any benefits from CNS regeneration.

We have been investigating the effects of patterned neural activity on physical conditioning and the potential for functional recovery. Not knowing what type of activity might be important, we examined the effects of reciprocal gaitlike movements of the legs that occur during bicycling. One advantage of this strategy is that reciprocal sensory feedback from the limbs might activate the central pattern generator that is responsible for gaitlike programs in the lumbar spinal cord. This program can operate without input from the brain. To promote simultaneous physical conditioning, we combined bicycling with FES of the hamstring, quadriceps, and gluteal muscles. Individuals with paralysis can use their own muscles to ride a recumbent bicycle even if those muscles are not under voluntary control.

We present a single prospective case using an "N of 1" design and a worst-case scenario. The patient was not predicted to recover any lost function because his ASIA classification had remained at Grade A for the first 5 years after injury.[2,34]

Case Report

History. This 42-year-old, right-handed man sustained a displaced C-2 Type II odontoid fracture due to an equestrian accident on May 27, 1995.

The mechanism of injury was direct axial loading. The patient's horse stopped suddenly; the patient's hands were caught in the reins and his 6 ft 4 in, 230-lb body was projected over the horse's head. He landed directly on the helmet in a near-perpendicular position. He was rendered apneic but was immediately maintained at the scene with artificial respiration. He was transferred to the University of Virginia Hospital.

Examination. Examination was consistent with a complete motor and sensory quadriplegia. Cervical traction was instituted. He received methylprednisolone (30 mg/kg bolus, followed in 1 hour by 5.4 mg/kg)[10] after the injury. Cervical spine x-ray films demonstrated a Type II odontoid fracture with fracture of the occipital condyle and displacement of the occiput anterior to C-1, suggesting occipitoatlantal dislocation.

Operation and Immediate Postoperative Course. Nine days later occiput–C2 fusion was performed (Fig. 1) using a titanium ring and sublaminar soft wire at C-1 and C-2. Bone for grafting was obtained from the iliac crest. Because the MR imaging appearance was consistent with preserved neural tissue, great care was taken to maintain alignment during the procedure and in particular when turning the patient from supine to prone.

As is usual in high cervical injuries, the patient underwent tracheostomy and gastric tube placement. All the early ASIA examinations for SCI demonstrated similar results. For example, the examination on June 24, 1995, almost 1 month after the injury, indicated a classification of ASIA Grade A, with complete motor and sensory function at level C-2, partial preservation of sensory function at C-3, and spotty sensation in the left hemibody, this level including absence of sacral function such as voluntary anal contraction. The patient received a single test dose of GM-1 ganglioside 39 days after injury, but mastocytosis precluded further doses.[30] The patient's initial hospital course, including inpatient rehabilitation, was uncomplicated except by sacral skin breakdown (Grade IV that healed by secondary intention). When the patient was discharged from the University of Virginia hospital on June 28, 1995, he was dependent on a ventilator and his SCI was classified as C-2 ASIA Grade A.

Long-Term Treatment Course

Informed Consent and Approval

The Human Studies Committee at Washington University in St. Louis approved our methods for collecting data and presenting the case. We obtained informed consent for participation in research activities in accordance with this committee's standards from the individual described herein. Inclusion of the quality of life questions and answers was approved by the patient.

The "N of 1" Study Design

The "N of 1" analytical method is an accepted rational design that has attracted interest from the National Institutes of Health.[2,34]

The ASIA Examinations

The ASIA examinations spanning the period prior to recovery (1999) through recovery (end 1999–2002) were performed in accordance with ASIA's International Standards by a single investigator (J.W.M.) trained in the measurements and in the specialty of SCI medicine.[25,51] The results of early examinations were obtained from ASIA

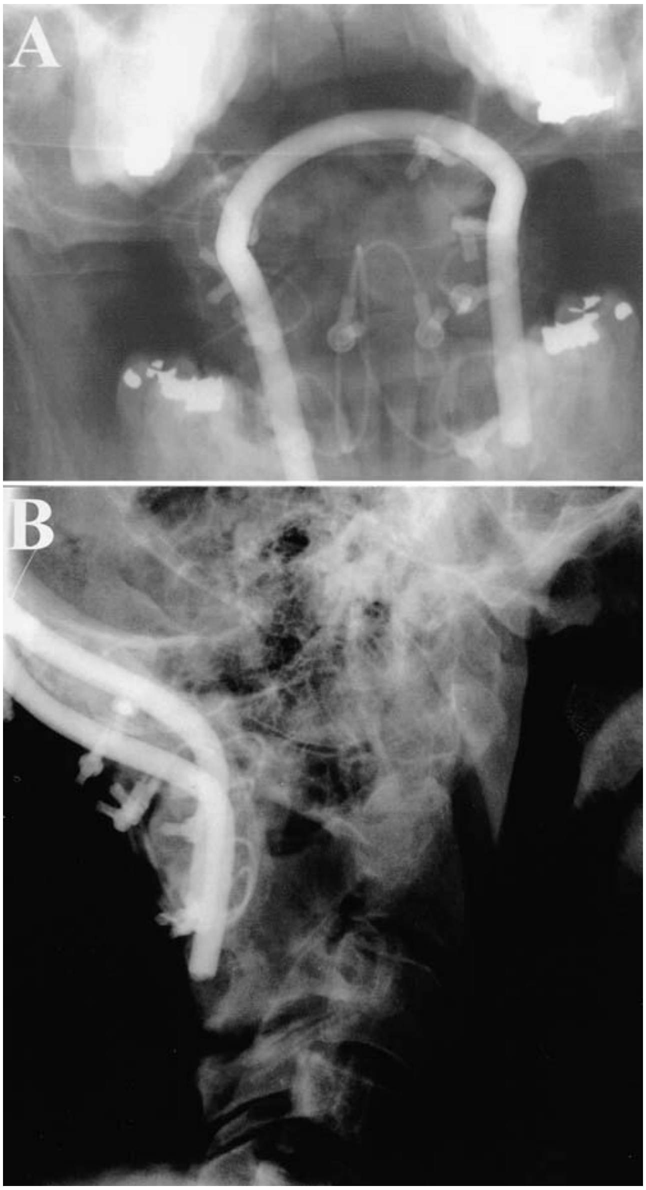


FIG. 1. X-ray films revealing an open mouth view (A) and a lateral view (B) of the cervical spine following internal stabilization. The type of injury incurred by this patient leads to bone dissociation of the head and spine. Reconstruction required fusion of the occiput to C-2 with titanium rods, wire, and bone graft.

sheets in the original hospitals' charts (1995–1999). The individuals who performed these examinations were also experts in SCI care and well versed in the clinical ASIA standard examination. Initial examinations by the serial examiner (J.W.M.) confirmed these earlier records (1999). All components of the examination were performed in accordance with ASIA standards while the individual was lying in bed.[51] The ASIA International Standard test for patients with complete tetraplegia has good intra- and interrater reliability.[16]

Electromyography Evaluation

The Advantage/Clarke-Davis (diaphragm) and Dantec/Keypoint (upper- and lower-extremity muscles and external sphincter muscle) instruments and a Medtronic disposable monopolar needle DMN 50 were used for EMG. Amplifier input impedance was set at 5 kOhm, with a high-pass filter of 2 Hz, a low-pass filter of 10 kHz, a sweep of 10 to 200 msec/D, and a sensitivity of 0.1 to 0.2 mV/D. The diaphragm was evaluated while the patient was seated, and the following muscles were assessed while the patient was lying down: right deltoid, biceps, extensor carpi radialis, and vastus medialis.

Bone Density

Bone densitometry was performed at Washington University School of Medicine's Bone and Mineral Diseases laboratories. Dual-energy x-ray absorptiometry measurements were compared using national standards for white males (based on age, weight, and height).[19,55,63]

Magnetic Resonance Imaging

All imaging was performed with a Signa 1.5-tesla superconducting system (General Electric, Milwaukee, WI) with phased array coils. A volume-acquired inversion-prepared fast–spoiled gradient echo acquisition was performed following an axial pilot at the level of the C-2 vertebral body. Sixty-four partitions (1-mm-thick equivalents) were acquired in a three-dimensional volume centered on the cervical spine, with the following parameters: (TE, 4.2 msec; TR, 17.8 msec; flip angle, 20°; 256 phase encodings in the z direction, 1 average, field of view 25 cm, matrix 256×256). The imaging time was 7 minutes.

From the volume data set a series of 10 contiguous 3-mm axial slices were reformatted on the Signa by using the center of the C2–C3 intervertebral disc as a caudal landmark, with the slices perpendicular to the spinal cord. Following this these data sets were uniformity corrected and histogram matched to a single control image by using a method previously described.

The images were displayed using a window-based image analysis software (Dispunc; © D. L. Plummer, University College London) and regions of interest were manually traced around each of the 10 axial slices. The operator visually defined the edge of the cord and the region was placed 2 pixels within this so as to avoid contamination from partial volume, which would artificially lower the measured signal intensity. A final signal intensity value for each subject was obtained by taking the mean of the 10 regions.

Cross-sectional area measurements were performed by one observer blind to the clinical details by using a previously described method. Intraobserver reproducibility was assessed for several steps in the process by using 15 scan–rescan data sets obtained in the patient. 1) The variation in mean signal intensity produced by the manual tracing technique on the same image. 2) The variation in mean signal intensity for scan–rescan within the same patient without histogram matching. 3) The variation in the mean signal intensity for scan–rescan within the same patient with histogram matching.

Quantification of Infectious Complications

The personal 24-hour nursing records for the patient were exceptionally detailed and this allowed us to track accurately the number and types of infections requiring antibiotic treatments each year. In addition, the total duration of each treatment was always recorded (Table 2). The prescription records provided by the local medical doctor verified these values. In most cases, cultures were also obtained to further verify the infection.

Quality of Life Evaluations

A single examiner (J.W.M.) performed the evaluations by telephone (July 15–30, 2002). These subjective measurements supplemented the quantitative data on functional recovery and emphasized the impact of limited motor and sensory recovery on quality of life.

Activity-Based Recovery Program

The activity-based recovery program consisted primarily of training on a FES bicycle. The customized recumbent bike system, designed for use with paralyzed individuals, integrated computer-assisted FES-induced cycling. The goal was 1 hour of activity (up to 3000 revolutions) per day three times per week. The FES bicycle modulates the intensity of stimulation to obtain a consistent rotation speed. Surface electrodes stimulate three muscle groups in each leg (Fig. 2): one electrode is placed at the superior edge of the gluteal muscle, another over the hamstring group midway between the knee and hip, and two over the quadriceps (one over the superior portion and the other over the inferior third of the quadriceps). During the exercise, the legs are balanced in three ways. The seated buttocks and boots anchor the legs at the upper and lower positions. Belts that attach to the upper leg with Velcro balance the mid-leg. A weighted fly-wheel ensures a smooth rotation by carrying momentum. The goal was to achieve the greatest number of revolutions (3000/hour). The FES bicycle therapy was supplemented with surface electrical stimulation to activate the following muscle groups: paraspinals, abdominals, wrist extensors, wrist flexors, deltoids, biceps, and triceps. The therapies were rotated daily, usually in a 3-day sequence. Each muscle group was activated for one-half hour by using intermittent 1 second on, 1 second off AC cycles. Once muscle recovery began, aquatherapy was incorporated into the program, with a goal of one 1-hour session per week. The aquatherapy focused on muscle groups in which voluntary control was recovered while participating in the activity-based recovery program.

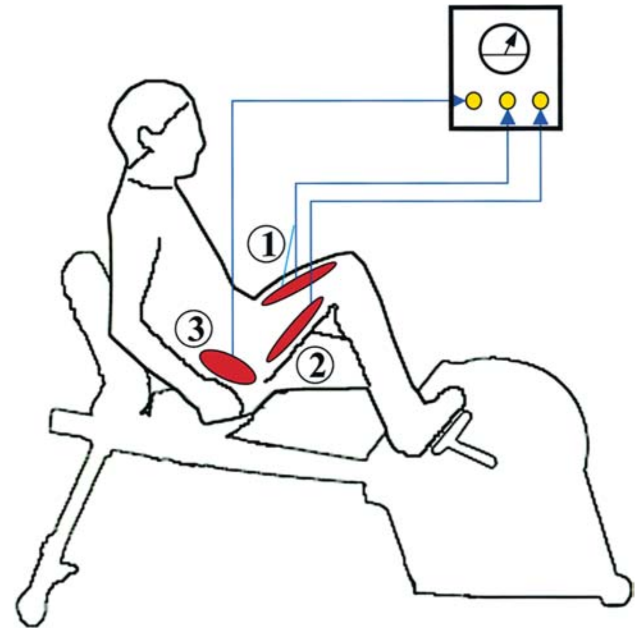


FIG. 2. Schematic drawing of the FES bicycle. The FES bicycle uses computer-controlled electrodes to stimulate the leg muscles in specific patterns. A paralyzed individual can therefore rotate the bicycle wheels even though he is unable to control his leg muscles voluntarily. In this study, three muscle groups *(red)* were stimulated bilaterally: the gluteal, quadriceps, and hamstring muscles. Electrodes *(blue)* went to pads attached to the skin over each muscle: two pads for each quadriceps (1) and one for each hamstring (2) and gluteal muscle (3).

Results

The Injury

Figure 3 depicts T_2-weighted MR images obtained in the patient's cervical spinal cord 5 years after the C-2 SCI. The injury epicenter contains a central cyst on level with the lower part of the C-2 vertebral body. As is typical in high cervical injuries, severe myelomalacia (shrinkage) has almost halved the diameter of the upper cord. Despite the severe damage, cross sections through the lesion indicate a variable donutlike rim of remaining white matter tissue. The presence of a variable donutlike rim of tissue at the injury site is typical of most SCIs.[14,43–45] Furthermore, the majority of clinically important motor and sensory tracts are normally present in the outer rim of white matter; however, the MR images do not indicate whether the donutlike tissue is functional cord or simply scar tissue. An interesting feature of the patient's images is that the cystic area is confined to the C-2 level rather than extending one level above and below, as is more typical with traumatic SCI. The likely explanation is that the cervical canal is wider at C-2, which protects the cord more than the canal at other levels.

Quantitative measures of remaining spinal cord cross-sectional areas in the upper cervical region revealed that approximately 25 mm^2 of tissue remained at the lower C-2 lesion epicenter, representing a donutlike tissue rim (Fig. 3F). The lesion epicenter was identified by reduced average signal intensities with corresponding minimal area values. As suggested in the MR images, the area of the most severe injury was primarily confined to one level (Fig. 3F); however, substantial atrophy of the cord was also present rostral and caudal to the injury level. This atrophy extends further rostral than caudal in keeping with the greater rostral axonal dieback observed in high cervical lesions in rodents.

Activity-Based Recovery Program

When we first evaluated the patient, we were studying the activity-based recovery program's effects on physical as well as functional recovery. Early results suggested that the physical benefits alone were sufficient reason to incorporate activity-based therapy into daily life. Those benefits included enhancement of muscle mass and bone density, increased cardiovascular endurance, and decreased spasticity (data not shown).

After the initial evaluation at Washington University in St. Louis, the patient was trained to use a FES bicycle

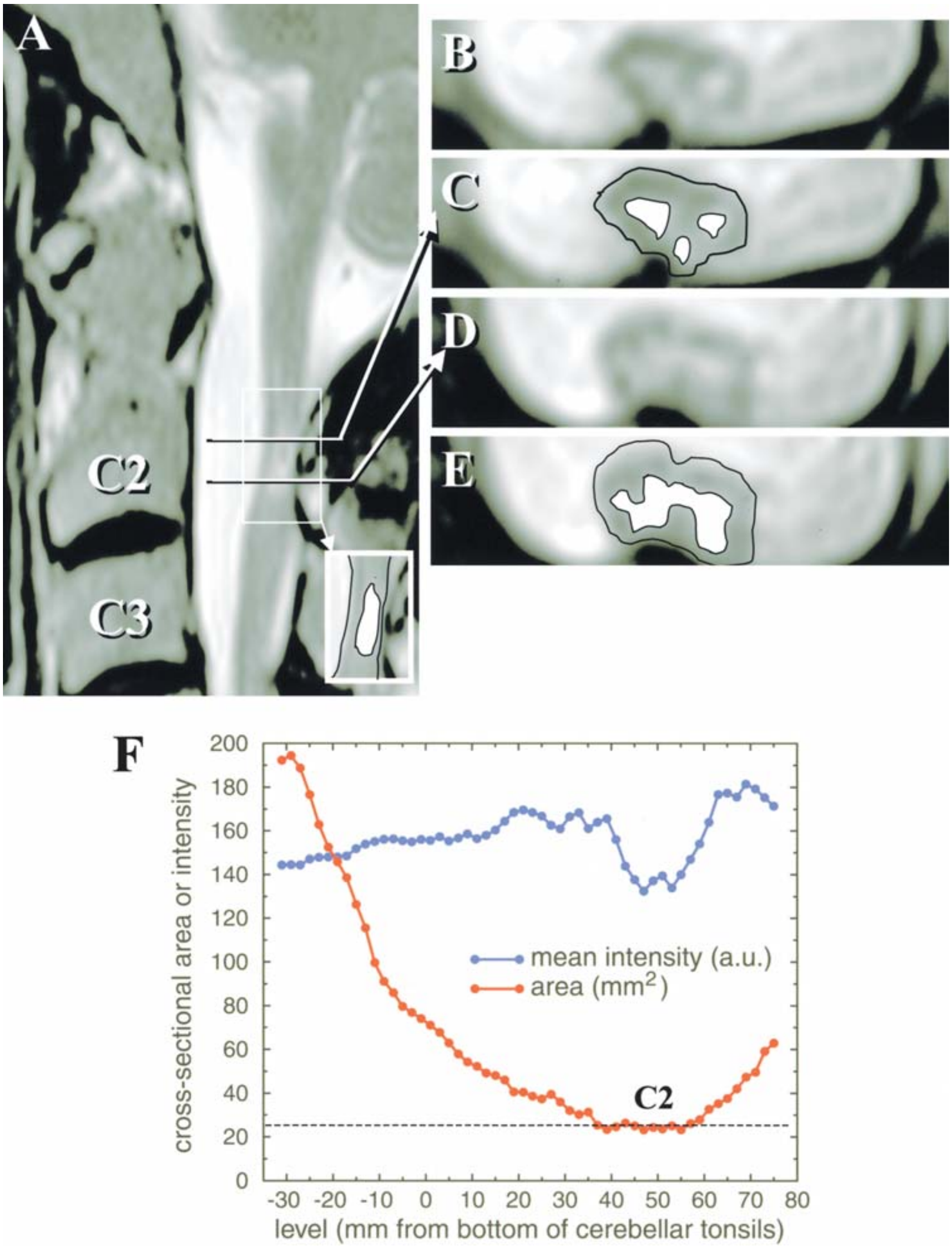


FIG. 3. Serial T_2-weighted MR images of the cervical spinal cord demonstrating a posttraumatic cyst at C-2 and severe myelomalacia in a patient who suffered a traumatic SCI 5 years earlier. A sagittal MR image is shown on the left (A) and the corresponding coronal sections are shown the right (B–E). For ease of identification, the perimeter of the cord is circled in *black* and the internal cyst is *white* in panels C and E, which are duplicate images of panels B and D. Graph showing quantitative analysis of spinal cord area by using MR imaging signal. Areas (in mm^2) of the MR image signal in cross sections through the spinal cord are shown as a function of distance from the cerebellar tonsils (0 reference point). The lesion epicenter is indicated by the lowest point on the U-shaped area curve. Based on a normal C-2 cervical cross-sectional area of approximately 1 cm^2, then approximately 25% of the MR imaging signal remains at the injury epicenter, representing a donutlike rim of tissue.

(Fig. 2). A similar bicycle was installed in his home so he could exercise frequently in his city of residence. The goal was to complete a 1-hour session three times per week.

At first, the patient's leg muscles fatigued rapidly with surface stimulation, but within approximately 20 sessions he was able to ride the bicycle continuously for 1 hour. Once motor recovery began, the program was supplemented with weekly aquatherapy to work muscle groups that had regained voluntary function but were too weak to oppose gravity. Surface, nonload-bearing electrical stimulation was also performed on the following muscle groups on an alternating 3-day schedule: the paraspinal group, the abdominal group, and the upper-extremity groups. Standard range-of-motion physical therapy was also performed daily, but this regimen was not changed from the time the individual was first discharged from rehabilitation. Breathing exercises also became part of the daily routine beginning in 1998. Increased muscle size and a generalized improvement in health were clearly evident by the year 2000; however, functional recovery was slower.

Major Medical Complications

As usually happens with a high cervical SCI, the patient developed many severe medical complications, particularly between 1996 and 1999 (Fig. 4). Despite his severe injury and immobility, however, he fared extremely well. These complications included skin breakdown, heterotopic ossification, autonomic dysreflexia, pathological bone fractures, deep venous thrombosis, and acute respiratory distress consequent to mucous plugging.

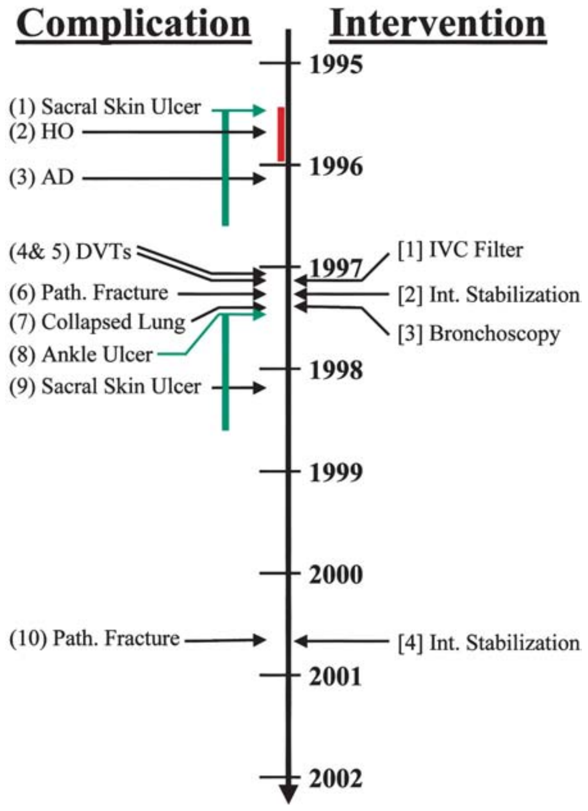
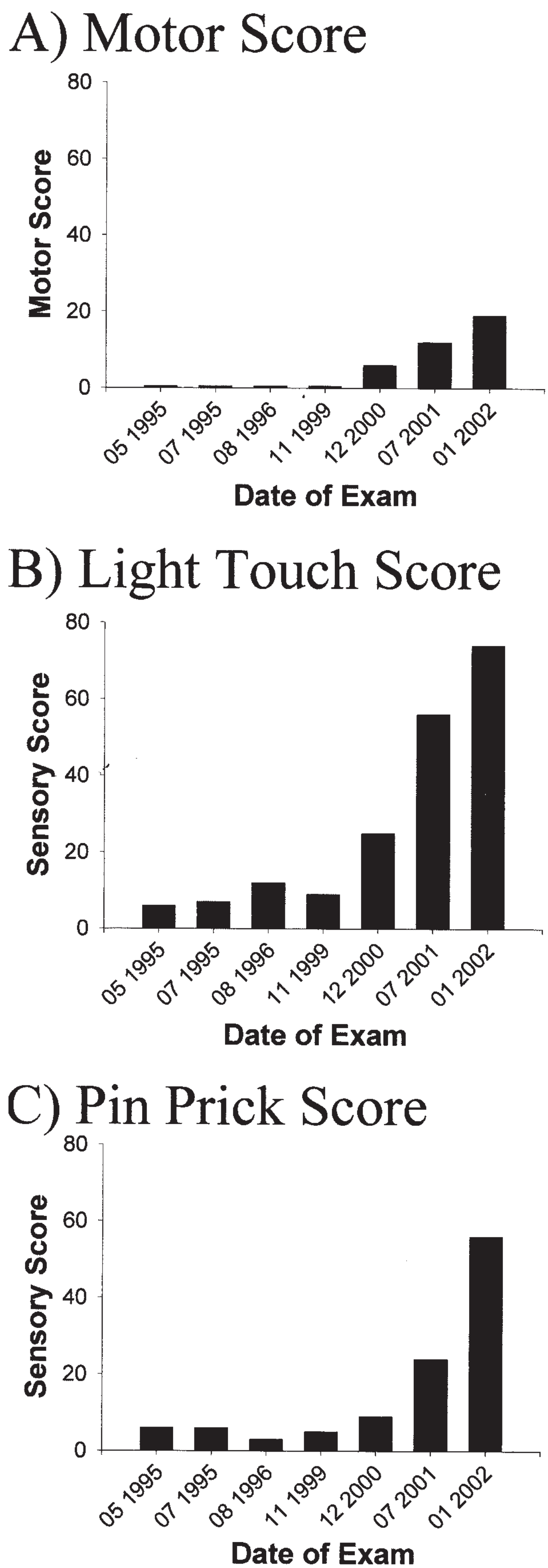


FIG. 4. Schematic illustration of the timeline of injury and complications. The patient suffered a C-2 ASIA Grade A SCI on May 27, 1995. As often happens in tetraplegia, he accumulated many severe medical complications, which are listed in this timeline. The vertical *red bar* indicates inpatient medical care and rehabilitation through the end of 1996. In addition to the complications shown here, urinary tract and pulmonary infections were frequent in the years before 1999. Note that the complication rate accelerated between 1995 and 1999, a situation common in tetraplegia. The paucity of similar complications after 1999 is highly unusual. 1) Coccyx skin ulcer. A large, Grade IV sacral skin ulceration developed early during the hospitalization period. Aggressive treatment produced healing by secondary intention 1 year later (the vertical *green bar* indicates healing time). 2) HO. Heterotopic ossification (lesser trochanter of right femur) developed in July 1995, as indicated by acute swelling of the right thigh. A Doppler study was negative for deep venous thrombosis, and x-ray films and CT scanning failed to reveal a fracture. Treatment with Didronel was initiated to prevent further bone resorption. Heterotopic ossification is a common complication in the acute postinjury period. 3) AD. Severe autonomic dysreflexia required inpatient treatment. 4 & 5) DVTs. Left deep venous thrombosis occluded the large draining vein of the leg and required hospitalization for anticoagulation with heparin and then Coumadin. The DVT recurred 1 month later, requiring adjustment of the anticoagulation regimen and placement of an inferior vena cava (IVC) Greenfield filter. Life-long treatment with Coumadin and weekly blood anticoagulation testing was then required. 6) Pathological fracture. Pathological fracture of the left femur resulted from a low fall during transfer. Surgical intervention was required to stabilize the fractured bone. 7) Collapsed lung. Acute shortness of breath required emergency hospitalization and bronchoscopy to remove a mucous plug. 8) Ankle ulcer. A left lateral malleolus skin ulceration (Grade IV) was complicated by slow healing and osteomyelitis, threatening amputation. Aggressive treatment and healing by secondary intention took more than 1 year. 9) Sacral skin ulcer. Pilonidal cyst removal and suture closure was complicated by dehiscence and development of a sacral wound that required aggressive treatment and healing by secondary intention (vertical *green bar* indicates healing time). 10) Pathological fracture. The left femur fractured while the patient was attempting weight-supported standing. Treatment required hospitalization and surgical internal fixation. Additional treatment of severe osteoporosis included vitamin D, calcium supplements, and pharmacological treatment to limit bone resorption.

Recovery of Function

The patient experienced no functional improvement during the first 5 years after injury, thereby retaining the C-2 ASIA Grade A classification, and the likelihood of any substantial improvement in the following years seemed negligible.[53] Multiple ASIA examinations during the first 5 years after the patient's injury documented a lack of substantial motor or sensory function because motor scores were consistently 0/100 and sensory scores ranged from 5–7/112. The first ASIA examination at Washington University in 1999 was consistent with these observations (Fig. 5). The patient did begin to recover sensation to deep palpation in the upper torso and upper arms in early 1999, but this did not translate into substantial changes in the ASIA grade because detection of light touch and pinprick sensation are the only measures.

After the first 6 months of the activity-based recovery program (January 2000), little recovery of function was evident: the arms and legs still displayed no motor function and a light touch or pinprick could be sensed only above the affected dermatomes in the neck (C1–C2/3). The patient first noted the ability to control a twitching movement of his left index finger in early November 2000. The first documented recovery on ASIA examination was at the end of 2000 (Fig. 5). Although modest improvements in sensory and motor scores were observed, sacral sparing of light touch sensation was first evident, changing the patient's ASIA classification to ASIA Grade B. Twenty-two months into the program (July 2001), however, light touch sensation improved to 52% of normal. It recovered to 66% of normal in 2002. Pinprick assessment, which requires discrimination and is therefore more difficult, did not improve until the last year of the 3-year program, which is ongoing to date. Sensation was appreciable throughout most dermatomes of the body (Fig. 6), including the sacral



region (S-3, S4–5). In addition to recovery of pinprick and light touch, recovery of additional sensory modalities occurred and included vibration, proprioception, and ability to differentiate heat and cold.

The most notable change was an improvement in motor function of up to 20% (20/100). Voluntary control of the external anal sphincter is possible (S4–5). The conversion of the patient's condition to ASIA Grade C thus occurred in July 2001. Motor recovery was first evident in the left fingers, then the right hand, and then the legs. Movement is now possible for most muscles of the upper arms but for fewer muscles in the legs. Most muscles in the legs are not yet able to oppose gravity.

The following comparison puts this motor recovery into perspective. The National Acute Spinal Cord Injury Study II and III trials documented an average 4.8-point improvement in the motor scores of patients receiving methylprednisolone compared with those receiving placebo if methylprednisolone was given within 8 hours of injury.[10] In our patient's case, there was a 20-point improvement in motor score over Years 5 to 8 postinjury (Fig. 5), which translates into movement in most joints, including the elbows, wrist, fingers, hips, and knees (Fig. 6); thus, the patient's condition is now categorized as ASIA Grade C rather than Grade A. This degree of movement gives the patient better control of the environment and of his powered wheelchair. The direct consequences of the recovered movement are limited but the consequences of the sensory recovery are substantial. In addition, the other benefits associated with enhanced muscle function have tremendously improved the patient's quality of life.

Reduction of Infections and Physical Improvements

Strikingly, the patient's infection complication rate began to decline dramatically in 1999, in parallel with reductions in major complications and recovery of neurological function. The incidence of infections requiring antibiotics and total days of antibiotic treatment per year also dramatically improved following 1999. Evaluation of total days of antibiotics required revealed over a 90% reduction in Years 2000 to 2002 compared with Years 1996 to 1998 (Table 2).

In addition to these improvements, the patient also achieved substantial physical benefits. His severe osteoporosis (bone density t-scores > -4.0), which contributed to pathological fractures of two of the largest bones in his body (femur and humerus), was completely reversed and

FIG. 5. Graphs showing marked recovery from SCI. Data are presented as parameter values (x-axis) and total motor and sensory function (light touch, pinprick; y-axis) based on the international ASIA standard scale for rating severity of SCI.[25,51] Motor function was assessed in five myotomes in the arms and five myotomes in the legs, and the scale of 0 to 5 provided a maximum score of 100 (10 muscles on each side). Sensation was measured in 28 dermatomes on each side. The scale of 0 to 2 (0 = absent, 1 = impaired, 2 = normal) provided a maximum score of 112. The ASIA classification runs from Grade A to E, with E being normal. This individual displayed no motor function during the first 5 years after injury. Sensory function over the first 5 years was restricted to upper neck dermatomes. The activity-based recovery program was instituted mid-1999. After 6 months, no recovery was observed; however, progressive and considerable motor and sensory recovery was evident over the next 2.5 years.

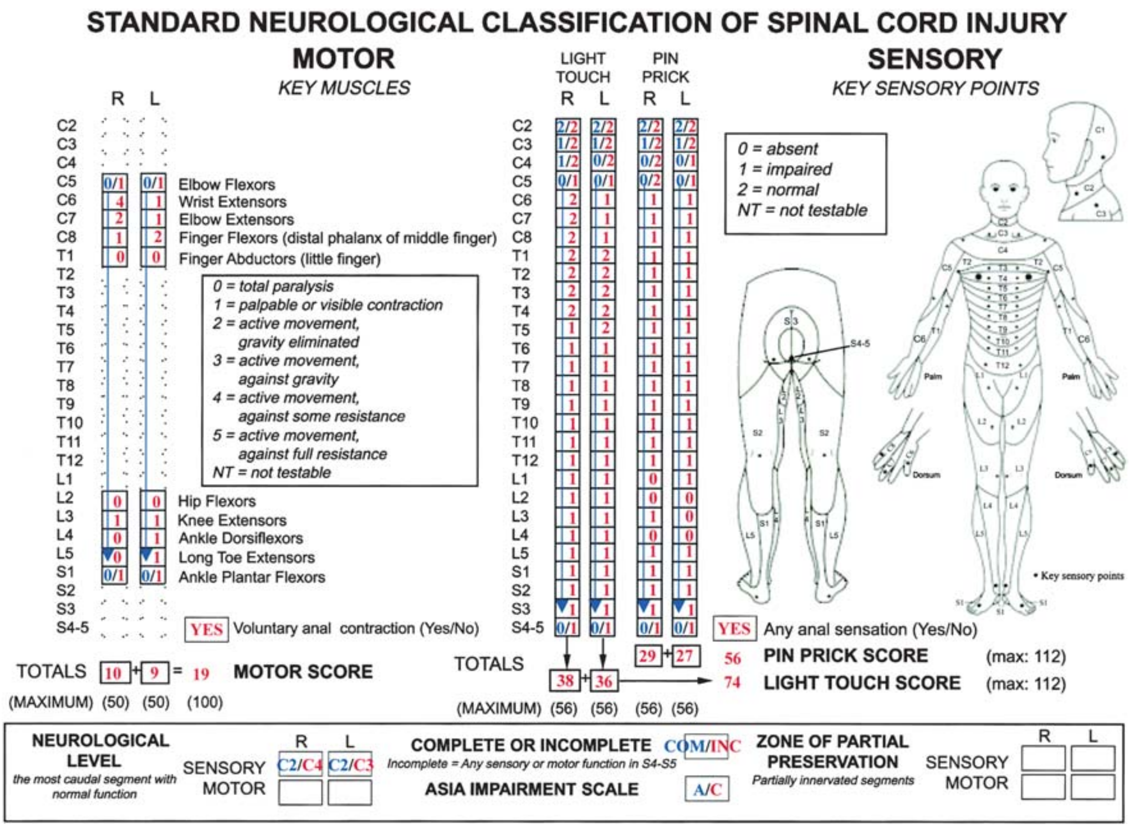


FIG. 6. Schematic drawing showing a comparison of ASIA grades between 1995 and 2002. Values in *blue* indicate scores from 1999; those in *red* indicate 2002 scores. Note that all the 1995 motor scores and the sensory scores obtained below T-4 were zero. The 1995 scores were taken from the July 1995 ASIA sheet.

is now within the normal range (t-score −0.5 in 2002 compared with −4.1 pre-1999). Ashworth measurements of spasticity have improved from 3 to 1–2 (Table 3), and the patient has also increased his endurance.[1]

Electromyography Results

The EMG analysis of volitional movements was completed in the winter of 2001 (Table 4), and the results were compared with those from phrenic nerve testing performed on June 21, 1995, shortly after the injury. At that time, there was evidence of intact anterior horn cells. Latencies were less than 10 msec, and right and left amplitudes were 0.9 mV and 0.5 mV, respectively. Diaphragmatic movement, albeit small, was noted on fluoroscopic examination. In contrast, amplitudes were greater in 2001 (2–7 mV), but there was further evidence of denervation (Table 4). Voluntary elicited EMG responses were evident in other muscle groups tested, including the right deltoid, right biceps, right extensor carpi radialis, and right vastus medialis. Most of these groups showed evidence of denervation, as indicated by positive sharp waves, fibrillation, and complex repetitive discharges. Overall, the numbers of recruited motor units were predictably small.

Quality of Life Assessment

Table 5 lists the responses the patient made in 2002 to questions about quality of life. Overall, recovery impacted many domains of daily living; however, some of the changes were perceived as life-altering. We did not use the semiquantitative quality-of-life measures that are available because of their limited ability to detect the impact of such a recovery.

Discussion

The major novelty of this report is the finding that sub-

TABLE 2

*Yearly incidence of infection and requirement for antibiotic treatment**

Year	Total No. Events	Type of Infection				Total Days of Tx
		Urinary	Pulmonary	Bowel	Skin	
1996	23	10	9	3	1	169
1997	13	4	4	0	4	190
1998	13	5	6	0	2	168
1999	8	1	4	0	3	99
2000	5	3	2	0	0	36
2001	3	3	0	0	0	18
2002	1	1	0	0	0	10

* Events were recorded from detailed personal nursing records and indicate total number of infectious events requiring antibiotic treatment, types of infections, and total days of antibiotic treatment required. Abbreviation: Tx = treatment.

TABLE 3

Ashworth scale for measuring spasticity

Ashworth Score	Degree of Muscle Tone
1	no increase in tone
2	slight increase in tone resulting in a "catch" when affected limb is moved in flexion & extension
3	more marked increase in tone; passive movement difficult
4	considerable increase in tone; passive movement difficult
5	affected part rigid in flexion & extension

stantial recovery of motor and sensory function can occur long after SCI, even with a stable ASIA Grade A injury. Most notable is that the patient experienced minimal recovery in the first 5 years after injury, during which he remained at ASIA Grade A (C-2 level). He began to recover substantial motor and sensory function during Years 5 to 8, improving two ASIA grades to reach Grade C. Of considerable additional interest is the demonstration of the impact of the activity recovery program on physical factors and complications of SCI. Most striking are the reductions in life-threatening medical complications and the 90% reduction in the incidence of annual infections and requirements for antibiotic treatment. Finally, there is the demonstrated life-altering impact, across many functional domains, associated with recovery even when motor and sensory improvements themselves did not markedly alter daily functional abilities.

Substantial Recovery of Function 5 to 8 Years After SCI

This case provides the first evidence that substantial recovery of motor and sensory function is possible 5 to 8 years after severe traumatic SCI in an individual who remained at C-2 ASIA Grade A for the previous 5 years. There are several levels of evidence for functional recovery, including longitudinal ASIA scale measurements, EMG measurements showing voluntary control of muscle movements, and a decreased incidence of medical complications. The reliability of the ASIA measurements was confirmed in examinations performed by several physicians trained in SCI medicine and well-versed in the measurement scale. Furthermore, the ASIA scale is particularly reliable across time when the condition of a patient is initially classified as ASIA Grade A with no zone of partial preservation of function, as happened in this severe case.

Using a standardized scale for assessing functional recovery after SCI—the ASIA International Standards for SCI assessment—the patient demonstrated recovery through two grades, from A to C. During the same period, the neurological level changed from C-2 to C-3. Before 1999, the zone of partial preservation was extremely limited: it included C-3 with no spared motor or consistent sensory function below that level. Current sensory function is spared to the sacral region (S4–5), and voluntary control of the external anal sphincter is possible (S4–5). The patient's motor scores now range from 0 to 4 on the standardized 0-5 muscle-grading scheme. Although the patient can control his left fingers well enough to utilize environmental control systems, including those of a wheelchair, he continues to use his current mobility system, which is operated by sip and puff controls. Sensation has recovered to 50% of normal pinprick (56/112) and to 66% of normal light touch (74/112) based on the ASIA grading scale. This degree of recovery allows the patient to differentiate between hot and cold, to know when his position needs to be changed to avoid skin ischemia, to detect painful stimuli, and to appreciate the pleasantness of human touch. His ability to breathe without his ventilator has also improved dramatically: he can now manage for more than an hour, which was not possible 4 years ago. Nonetheless, he remains ventilator-dependent, confined to a wheelchair, and has seen no substantial improvement in bowel, bladder, or sexual function.

How Meaningful is This Recovery?

The responses shown in Table 5 illustrate the profound impact of this recovery on the patient's life and the lives of his family.

Reduction of Major Complications and Numbers of Infections

A striking and very interesting observation in this case is the reduction in major complications and numbers of infections, with a clear dividing time point of 1999; nine of 10 major complications occurred pre-1999. Furthermore, 74% of the total number of infectious events occurred pre-1999 compared with only 13% after 1999. Similarly, 76% of total days (527 total days 1996–1998) of antibiotic treatment occurred pre-1999 compared with only 9% (64 total days 2000–2002) after 1999. The economic benefits associated with these changes are overwhelming based on reduction of sick days, improved gainful employment days, and reduced medication and medical costs; however, the

TABLE 4

*Electromyography characteristics of muscles during volitional activation**

						Motor Unit Characteristic		
Muscle Group	Voluntary Response	Latency (msec)	Motor Units Used	Insertional Activity	Spontaneous Activity	Amplitude (mV)	Duration (msec)	Config
lt diaphragm	no	NA	1–2	no	no	2	5	NL
rt diaphragm	yes	NA	3–4	no	no	2–7	5–20	NL
rt deltoid	yes	180	1	yes	PSW, fibs	0.7	5	polyphasic
rt biceps	no	NA	NA	yes	PSW, fibs	NA	NA	NA
rt extensor carpi radialis	yes	<200	2	yes	PSW, fibs, CRD	1.5–2	5	polyphasic
rt vastus medialis	yes	200–500	1–2	yes	PSW, fibs	1.5–2	4	NL

* Abbreviations: Config = configuration; CRD = complex repetitive discharge; fibs = fibrillations; NA = not assessed; NL = normal; PSW = positive sharp waves.

TABLE 5

*Life impact questions and answers**

Question 1: What does your recovery mean to you in terms of "changes in your life?"

The recovery has given me the security of knowing that I run minimal risk of infection, minimal risk of hospitalization. At the moment, recovery is important in terms of any incremental improvement on the way to the ultimate goal. I have been able to stay out of the hospital for more than 3.5 years. Before I had blood clots, pneumonia, a collapsed lung, very serious decubitus ulcers, and an infected ankle, which threatened amputation of my leg. I was always very tentative about my life because I never knew what would go wrong next. Over the last couple of years, I have become very confident with my health. I have been able to stay off antibiotics. My weight is under control. I can stay up in the chair for as much as a 15 or 16 hours without a problem. Given the fact that I am a ventilator dependent C2, I would say that I am probably in the best possible condition. I am able to work and travel in a way that is very satisfying. The next incremental goal will be to get off the ventilator. I feel I am making progress in that direction. I would like more useful functional recovery. I am able to move my arms, fingers, and legs, and yet, I am still sitting in this wheelchair. I hope I will be able to get incremental recovery along those lines so I can be in a different wheelchair and I could have more freedom, be less dependent on others than I am now.

Question 2: How has the recovery changed your "life's goals"?

My life's goals are more attainable now because I can tell the producer of a film that I can travel to location to direct, which is my profession. To give speeches, which is also part of my profession. I can be counted on. In the past, infections or other illness would prevent me from fulfilling my obligations. It is a great relief to know I can make a commitment and keep it because of my health.

Question 3: How has your recovery impacted your daily life?

The impact on my daily life has been increased mobility and respiratory benefits. A ventilator failure back in 1995, 96, 97, would have been a terrifying experience because I really couldn't breathe. Now, I can breathe quite well. When I breathe, I use the correct technique; I am able to move my diaphragm, an ability that was achieved by exercise and training. That is the most comforting aspect of my recovery, that safety factor.

Question 4: How has your recovery impacted the life of your family?

My recovery so far has helped my family worry less about me. Our life is much more normal. Even though I am in the same kind of chair as before, they see me quite differently. They know I am healthier, stronger; and that on any day I might have a surprising new recovery. For example, the other day I came back from a session in the pool. My ability to push-off from the wall against resistance was about twice as strong as it was weeks earlier. A gain like this or a longer, successful breathing set is very uplifting for my family and myself. They feel, especially my youngest who was only 3 when I was injured, that I'm on a good road, making progress, going in the right direction, and that helps all of us.

Question 5: How has your recovery affected the economics of your life?

The economics of my life has been very strongly impacted because I have stayed out of the hospital. The hospital costs are staggering, but we saved a lot of money these past several years. Even though I require around the clock nursing, just in case of equipment failure and because of my travel and work schedule, I am available to take on more work projects. I just wrote another book. I have participated in a documentary about the last 3 years of my life I am in negotiations now to start directing another film. These are all things that I would not have been able to do if I had been stuck in limbo the way I was before I really began an aggressive program of activity-based training.

Question 6: How has your improvement in sensation impacted your life?

Sensation has improved from nothing below the neck to about a 65% improvement. What is so important about sensation is contact with other people. It makes a huge difference if someone touches you on the hand and you can feel it. You make a much more meaningful connection.

Question 7: You have had two changes with motor function. One is regaining the ability to move, and the second is building muscle mass. Can you describe what building muscle mass alone, independent of movement, means? I look on building muscle mass as preparation for recovery, which is the long-term goal. But more importantly, muscle mass is essential to any movements you need to make, to keep your cardiovascular system working well, and it also relates to maintaining adequate bone density. Let's say you have very weak leg muscles. Standing on a tilt table would be dangerous for the bones in your legs because they don't have enough support. I went through that. I did not know that I had severe osteoporosis. Through exercise and an intense course of calcium, I have completely reversed osteoporosis. I have the bones back that I did when I was thirty. It is important that the medical system knows that osteoporosis can be reversed in spinal cord injury. But, also in terms of my self-image, to look down at my legs and not see noodles is very important. In fact, my leg and bicep dimensions are almost the same as before the injury, this is 7 years later, so that does a lot to make me feel better about myself.

Question 8: How has your recovery affected your ability or time off the ventilator?

It has made it so that being off the vent is not an issue.

Question 9: How has your recovery affected your bowel and bladder function?

Bladder function has always been good. I would say "no change", but my bladder is not shrinking and I am not having bladder spasms. The bowels have not improved. My motility is still very slow.

Question 10: How has your recovery changed the leisure aspects of your life?

Just last week I was able to go with the family out to Lake Tahoe to a friend's house, and even though I can't go water skiing or play tennis, I'm free to get close to the water or court and watch my kids and friends play. I can be as close as I can to the site without participating, but I have also learned how to get satisfaction out of watching my family and friends do leisure activities. So, I am there and a part of it even though I can't do it the way that I used to.

Question 11: How has your recovery affected your work productivity?

It has greatly increased my productivity by increasing my daily endurance, reducing the number of sick or hospitalized days, and providing confidence that I will fulfill commitments. The recovery has given me the freedom to assure employers that I am ready, willing and able to meet the challenges of the work.

Question 12: How has your recovery been most significant to you?

My recovery has been most significant to me in the implications for the future based on the fact that we can do this much just with exercise. I was particularly impressed by the fact that exercise gave me more muscle strength and motor function while I stayed on the same amount of medications to prevent spasticity; that was an extraordinary finding. I feel that the progress I've made so far is symbolic of the progress that is yet to come. In other words, if exercise has gotten me this far, the medical interventions that will be coming will get me to my ultimate goal of recovery.

Question 13: What does your recovery mean to you in terms of "hope"?

My recovery means everything to me because while some people are able to accept living with a disability, I am not one of them. I want to recover to as near normal as possible and I hold that dream. I don't want to let go of it and perhaps a psychological indication of what I believe is that in the 7 years since my injury I have never had a dream in which I am disabled. I want my life back.

* To determine how recovery from SCI affects quality of life, we asked the patient questions during a phone interview. The answers were recorded and analyzed. The survey was completed in the summer of 2002.

psychological benefits of feeling predictably well are perhaps even more meaningful.

In addition to these medical improvements, successful and complete reversal of severe osteoporosis was also achieved. It has been previously held that intensive exercise or FES can not be used to offset loss of bone density successfully in individuals with SCI and perhaps that is true for the manner in which FES has been previously used primarily for nonload-bearing movement.[42,53] Apparently sufficient load-bearing combined with the physical bone stress of contracting muscles by using the FES bike in conjunction with pharmacological treatments to offset bone resorption is able to reverse even severe bone density loss as in this case. It is also predictable that enhanced gluteal muscle mass will translate into superior seating pressure distribution with a corresponding reduction in skin breakdown.

Although it is expected that the overall experience in care of this patient would improve his medical status and perhaps reduce complications somewhat, the magnitude of the changes observed in this case are highly unlikely to be the result of such a learning curve.

Donutlike Sparing of Spinal Cord White Matter and Implications of Limited Repair for Disproportionate Recovery of Function

Perhaps a substantial number of individuals with ASIA Grade A SCI might have at least some functional connections across the lesion.[14,23,24,43] Indeed, it is rare for the cord to be completely severed by spinal trauma unless a gunshot or knife attack causes the wound. Because the majority of individuals with SCI are classified as ASIA Grade A, it will be important to identify the subclass that has retained some functional connections and therefore has recovery potential.

Studies perfomed in the 1950s indicate that limited preservation of white matter can sustain substantial spinal cord function. Preservation of less than 10% of the normal axon complement in the cat spinal cord can support walking, although this should not be viewed as the optimal requirement.[9] Moreover, detailed anatomical postmortem studies of chronic SCI in humans reveal that small residual connections across the lesion can preserve some function.[43,44] For example, one individual with ASIA Grade C SCI had retained only 1.17 mm^2 of white matter at the level of the lesion. Another patient with some preserved motor function below the level of a cervical injury had only 3175 corticospinal axons—less than 8% of the number (41,472) found in normal controls. The current case reinforces these data, showing that limited sparing of white matter may be associated with substantial preservation of motor and sensory function. In the patient's case, high-resolution MR imaging demonstrated that less than 25% of the cord had survived at the injury level (and the proportion was probably lower because MR imaging cannot distinguish between functional tissue and scar tissue). Yet substantial motor and sensory recovery was possible. These observations imply that small stepwise treatments can be expected to produce large gains in function. Development and application of novel methods for determining persistent connections across the lesion in individuals with ASIA Grade A injuries will be important. Such techniques could include diffusion tensor imaging, functional MR imaging, and motor/sensory evoked potentials.

The MR imaging analysis of the lesion indicated residual sparing of approximately 25 mm^2 of tissue in an outer donutlike rim of the cord at the C-2 level. The analysis would tend to err on the side of inflated area measurements, as the demarcation of tissue and cerebrospinal fluid in the central cyst was not always a clean border. Nonetheless, the lesion epicenter can be identified in Fig. 3 by a simultaneous drop in signal intensity and minimal residual area. Previous work in normal volunteers suggests the area of C2–4 spinal cord cross-sections ranges from 67 to 101 mm^2, with study means ranging from 78.1 to 84.7 mm^2. Previously published data obtained in normal human volunteers at the C2–3 and C3–4 disc space levels, some of which was based on MR imaging, is as follows: mean age 31 years (range 23–49 years), area 78.1 mm^2 (range 70.1–86.1 mm^2) for 15 volunteers; mean age 38 years (range 26–57 years), area 84.7 mm^2 (range 67–101 mm^2) for 30 volunteers.[12,48] Therefore, it is reasonable to assume that approximately 25% of the cord remains at the injury level in the patient.

Limited Treatments for SCI

Current treatments for SCI are both limited and controversial. Administration of methylprednisolone within 8 hours of traumatic injury was one of the first drug therapies to receive support.[10,11] Limitations in technical design and the marginal clinical effect of methylprednisolone seen in the original multicenter studies have raised concern about this approach.[17,39,58] Other medications, including Naloxone and Tirilazad, have also been examined; however, those studied did not achieve their primary endpoints.[10,11] Most recently, the ganglioside, GM-1, has shown promise when administered in the subacute injury period, although primary endpoints were again not achieved.[30] In general, most rehabilitation approaches are accepted in the field but specific aspects have not been tested for efficacy in the SCI population. Moreover, the duration of inpatient rehabilitation has dramatically decreased over the last 10 years, necessitating the development of cost-effective inhome therapies.

Activity-Based Recovery Program: Theory and Application

The activity-based recovery program is based on a substantial amount of data on the role of patterned neural activity in normal CNS development. The program assumes that similar processes are required for successful regeneration of the injured nervous system. It is known that reduction of neural activity disrupts nervous system development, including cell birth, migration, determination of cell fate, synapse elimination and circuitry selection, and myelination and that CNS injury dramatically reduces patterned neural activity, particularly below the level of the SCI.[33] This happens when some pathways between the brain and limbs become interrupted, reducing the transmission of patterned sensory afferent activity from the periphery (for example, that associated with movement). Therefore, we explored the possibility that promoting patterned activity could enhance regeneration and functional recovery, using both basic science and clinical studies.

We divided the possible benefits of patterned neural activity into two categories: physical and regeneration/recovery of function. Our early clinical experience suggested that the physical benefits provide sufficient reason for participating in an activity-based recovery program. The individual described in this paper has experienced a number of physical benefits, including increased muscle mass, reversal of osteoporosis, decreased spasticity, and improved overall health with an associated reduction of major medical complications, incidence of infections, and use of antibiotics. Although it was not considered possible to reverse osteoporosis with FES, it appears that FES can be effective; calcium supplements and pharmacological therapy to limit bone resorption were also required. Another physical benefit was maintenance of skin integrity, particularly over weight-bearing bone prominences such as the coccyx. Regaining muscle mass between the bone and skin distributed pressure over a much larger area, just as the flat sole of a shoe distributes pressure over the foot more effectively than a spiky high heel.

The second level of potential benefits—reduction of spasticity and regeneration—is of particular interest. Although the individual described here experienced less spasticity, only animal studies will determine whether regeneration might be responsible for this improvement. Nonetheless, substantial experimental data, particularly from studies of CNS development, indicate that patterned neural activity might be an important mechanism for developing and maintaining inhibitory circuitry.[3,8,18,28,36,37,56,62,64,65,69–71] Chemical inhibition of neural activity in culture and in animals reduces the number of inhibitory synapses, and partial removal of this blockade can result in nervous system overactivity, such as spasticity. A similar scenario appears to follow SCI, perhaps partly in response to reduced neural activity. Moreover, antispasmodic agents, such as Baclofen, can reduce overall neural activity and therefore might shift the balance from excitation to inhibition, as can happen during development. The selection and maintenance of new excitatory synapses might also require coincident neural input.

Patterned neural activity might also help correct the dysmyelination and demyelination that contributes to functional deficits after SCI.[9,13,14,31,32] Remyelination of axons that were stripped after injury requires optimal electrical activity in the nerve being myelinated.[21] The strongest evidence comes from the peripheral nervous system, but there are similar data for the CNS.[6]

Recovery in the adult CNS might also involve the production of new neural cells, particularly oligodendrocytes needed for remyelination.[29,38,40,54] Although this mechanism of cell renewal is not well understood, recent work from several laboratories has shown that running can boost the production and survival of new brain cells.[46] The survival of injured or newborn neurons and glia also requires optimal levels of neural activity.[6]

Additional clinical data support the idea that activity might promote functional recovery after nervous system insults such as trauma and stroke.[15,26,41,57,75,76,83] Early work focused on concepts of operant conditioning to explain these observations. In 1993, Taub, et al.,[74] described a method called "constraint-induced" movement therapy to restore function in people with long-term paralysis after stroke and other CNS lesions. By constraining the good side and forcing patients with hemiplegia to use their paralyzed limbs, they were able to reverse "learned non-use," which was proposed by Taub, et al.,[73] to explain the excess motor disability that occurs after CNS injury. Despite the evidence supporting the beneficial effects of constraint-induced therapy, many patients and therapists expressed skepticism about the therapy because the approach was not very practical and required long-term intensive inpatient care.[60]

Perhaps the most dramatic demonstration of reversing "learned non-use" has come from the results of training people with SCI. In 1992, Wernig and Muller[80] reported that treadmill (laufband) locomotion with body weight support improved walking in people after severe SCIs. They trained eight people with "incomplete" SCI for 1.5 to 7 months (5 days/week, 30–60 minutes/day) beginning 5 to 20 months after injury. This training significantly improved locomotion capabilities, including the ability to walk unsupported 100 to 200 m on a flat surface. Their additional work demonstrates that these training benefits can be maintained without further training.[81,82] Dietz and colleagues[22] suggest that two forms of adaptations occur after injury that may contribute to improved locomotor function: development of spastic muscle tone and activation of spinal locomotor centers induced by treadmill training. Building on this work, additional groups have shown that a distal disconnected region of the spinal cord is capable of "learning" and that early gait training might promote improved gait, endurance, and energy consumption, enhanced ground speed walking, and, in a minority of individuals with incomplete SCI, improved overground walking.[4,5,7,27,49,80] The major benefits of gait training are reserved for those with incomplete injuries, particularly ASIA Grades C and D.[53] Therefore, motor training appears to have effects that exceed those produced by exercise or FES alone. The FES bicycle system described here may provide a unique balance to gait training in that it may prove to provide benefits in the more severely affected individuals with SCI. Thus, a growing body of work supports the activity-based recovery hypothesis and the lack of alternative treatments accelerates the need to test promising new approaches.

Long-Term Recovery After SCI

This report does not address the basis for the patient's recovery, mechanisms of regeneration, or whether regeneration accompanied functional recovery because such associations cannot emerge from studies in living humans. It does demonstrate, however, that substantially delayed recovery is possible. Therefore, further investigations into the role of neural activity in regeneration and functional recovery appear warranted, both in the laboratory and in clinical trials. Predictably, the most rapid progress will occur through basic science, which can tightly control variables and assess indices of regeneration; however, we hope the work described here will spark additional clinical investigations into the effects of long-term rehabilitative and medical interventions for individuals with SCI and other disorders involving immobility. Such interventions might enable individuals with spinal cord disabilities to achieve physical and functional benefits that previously were not thought possible. Because extensive patterned neural activity appears important for recovery, we suspect that patterned activities will show much promise.

In summary, the individual described in this paper has experienced substantial recovery of function and his condition is now classified as ASIA Grade C, two ASIA grades better than ASIA Grade A. Associated physical benefits include reduced spasticity and increased bone density and muscle mass. Although we cannot conclude that the activity-based recovery program produced the functional benefits, we believe it was responsible for the physical benefits. As this outcome was seen in a worst-case scenario, the program might provide even more dramatic benefits for individuals who are less severely injured (ASIA Grades B–C).

Acknowledgments

The authors thank the great number of individuals who have made these studies possible over these past 3 years. It is with great appreciation that we also acknowledge the excellence of all the levels of caregivers involved in the care of this individual since his injury. The recovery and health of this individual is a testament to their expertise. We thank David Gray, Ph.D., for his expertise and help with deriving the life impact questions. Finally, we thank Dennis Choi, M.D., Ph.D., and Ralph Dacey, M.D., for mentorship and support.

References

1. Ashworth B: Preliminary trial of carisoprodol in multiple sclerosis. **Practitioner 192:**540–542, 1964
2. Backman CL, Harris SR: Case studies, single-subject research, and N of 1 randomized trials: comparisons and contrasts. **Am J Phys Med Rehabil 78:**170–176, 1999
3. Baker RE, Ruijter JM: Chronic blockade of bioelectric activity in neonatal rat neocortex in vitro: physiological effects. **Int J Dev Neurosci 9:**321–329, 1991
4. Barbeau H, McCrea DA, O'Donovan MJ, et al: Tapping into spinal circuits to restore motor function. **Brain Res Brain Res Rev 30:**27–51, 1999
5. Barbeau H, Rossignol S: Recovery of locomotion after chronic spinalization in the adult cat. **Brain Res 412:**84–95, 1987
6. Barres BA, Raff MC: Proliferation of oligodendrocyte precursor cells depends on electrical activity in axons. **Nature 361:** 258–260, 1993
7. Behrman AL, Harkema SJ: Locomotor training after human spinal cord injury: a series of case studies. **Phys Ther 80:** 688–700, 2000
8. Benevento LA, Bakkum BW, Cohen RS: Gamma-aminobutyric acid and somatostatin immunoreactivity in the visual cortex of normal and dark-reared rats. **Brain Res 689:**172–182, 1995
9. Blight AR: Cellular morphology of chronic spinal cord injury in the cat: analysis of myelinated axons by line-sampling. **Neuroscience 10:**521–543, 1983
10. Bracken MB, Shepard MJ, Collins WF, et al: A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. Results of the Second National Acute Spinal Cord Injury Study. **N Engl J Med 322:**1405–1411, 1990
11. Bracken MB, Shepard MJ, Holford TR, et al: Methylprednisolone or tirilazad mesylate administration after acute spinal cord injury: 1-year follow up. Results of the third National Acute Spinal Cord Injury randomized controlled trial. **J Neurosurg 89:** 699–706, 1998
12. Brex PA, Leary SM, O'Riordan JI, et al: Measurement of spinal cord area in clinically isolated syndromes suggestive of multiple sclerosis. **J Neurol Neurosurg Psychiatry 70:**544–547, 2001
13. Bunge MB, Bunge RP, Ris H: Ultrastructural study of remyelination in an experimental lesion in adult cat spinal cord. J Biophys Biochem Cytol 10:**67–94, 1961**
14. Bunge RP, Puckett WR, Becerra JL, et al: Observations on the pathology of human spinal cord injury. A review and classification of 22 new cases with details from a case of chronic cord compression with extensive focal demyelination. **Adv Neurol 59:**75–89, 1993
15. Chollet F, DiPiero V, Wise RJ, et al: The functional anatomy of motor recovery after stroke in humans: a study with positron emission tomography. **Ann Neurol 29:**63–71, 1991
16. Cohen ME, Ditunno JF Jr, Donovan WH, et al: A test of the 1992 International Standards for Neurological and Functional Classification of Spinal Cord Injury. **Spinal Cord 36:**554–560, 1998
17. Coleman WP, Benzel D, Cahill DW, et al: A critical appraisal of the reporting of the National Acute Spinal Cord Injury Studies (II and III) of methylprednisolone in acute spinal cord injury. **J Spinal Disord 13:**185–199, 2000
18. Corner MA, Ramakers GJ: Spontaneous firing as an epigenetic factor in brain development—physiological consequences of chronic tetrodotoxin and picrotoxin exposure on cultured rat neocortex neurons. **Brain Res Dev Brain Res 65:**57–64, 1992
19. Cummings SR, Black DM, Nevitt MC, et al: Bone density at various sites for prediction of hip fractures. The Study of Osteoporotic Fractures Research Group. **Lancet 341:**72–75, 1993
20. Davies SJ, Silver J: Adult axon regeneration in adult CNS white matter. **Trends Neurosci 21:**515, 1998
21. Demerens C, Stankoff B, Logak M, et al: Induction of myelination in the central nervous system by electrical activity. **Proc Natl Acad Sci USA 93:**9887–9892, 1996
22. Dietz V: Spinal cord lesion: effects of and perspectives for treatment. **Neural Plast 8:**83–90, 2001
23. Dimitrijevic MR: Residual motor functions in spinal cord injury. **Adv Neurol 47:**138–155, 1988
24. Dimitrijevic MR, Faganel J, Lehmkuhl D, et al: Motor control in man after partial or complete spinal cord injury. **Adv Neurol 39:**915–926, 1983
25. Ditunno JF Jr: Scoring, scaling and classification., in Ditunno JF Jr, Donovan WH, Maynard FM Jr (eds): **Reference Manual for the International Standards for Neurological and Functional Classification of Spinal Cord Injury.** Atlanta: American Spinal Injury Association, 1994, pp 19–42
26. Elbert T, Flor H, Birbaumer N, et al: Extensive reorganization of the somatosensory cortex in adult humans after nervous system injury. **Neuroreport 5:**2593–2597, 1994
27. Field-Fote EC: Combined use of body weight support, functional electric stimulation, and treadmill training to improve walking ability in individuals with chronic incomplete spinal cord injury. **Arch Phys Med Rehabil 82:**818–824, 2001
28. Furshpan EJ: Seizure-like activity in cell culture. **Epilepsy Res 10:**24–32, 1991
29. Gage FH: Stem cells of the central nervous system. **Curr Opin Neurobiol 8:**671–676, 1998
30. Geisler FH, Coleman WP, Grieco G, et al: The Sygen multicenter acute spinal cord injury study. **Spine 26:**S87–S98, 2001
31. Gledhill RF, Harrison BM, McDonald WI: Demyelination and remyelination after acute spinal cord compression. **Exp Neurol 38:**472–487, 1973
32. Griffiths IR, McCulloch MC: Nerve fibres in spinal cord impact injuries. Part 1. Changes in the myelin sheath during the initial 5 weeks. **J Neurol Sci 58:**335–349, 1983
33. Grill WM, McDonald JW, Peckham PH, et al: At the interface: convergence of neural regeneration and neural prostheses for restoration of function. **J Rehabil Res Dev 38:**633–639, 2001
34. Guyatt G, Sackett D, Taylor DW, et al: Determining optimal therapy—randomized trials in individual patients. **N Engl J Med 314:**889–892, 1986
35. Hall KM, Knudsen ST, Wright J, et al: Follow-up study of individuals with high tetraplegia (C1–C4) 14 to 24 years postinjury. **Arch Phys Med Rehabil 80:**1507–1513, 1999
36. Hendry SH, Jones EG: Reduction in number of immunostained GABAergic neurones in deprived-eye dominance columns of monkey area 17. **Nature 320:**750–753, 1986
37. Hendry SH, Jones EG: Activity-dependent regulation of GABA expression in the visual cortex of adult monkeys. **Neuron 1:** 701–712, 1988
38. Horner PJ, Gage FH: Regenerating the damaged central nervous system. **Nature 407:**963–970, 2000
39. Hurlbert RJ: The role of steroids in acute spinal cord injury: an evidence-based analysis. **Spine 26:**S39–S46, 2001
40. Ishii K, Toda M, Nakai Y, et al: Increase of oligodendrocyte progenitor cells after spinal cord injury. **J Neurosci Res 65:** 500–507, 2001
41. Jenkins WM, Merzenich MM: Reorganization of neocortical representations after brain injury: a neurophysiological model of the bases of recovery from stroke. **Prog Brain Res 71:** 249–266, 1987
42. Jones LM, Legge M, Goulding A: Intensive exercise may preserve bone mass of the upper limbs in spinal cord injured males

but does not retard demineralisation of the lower body. **Spinal Cord 40:**230–235, 2002
43. Kakulas BA: A review of the neuropathology of human spinal cord injury with emphasis on special features. **J Spinal Cord Med 22:**119–124, 1999
44. Kakulas BA: The applied neuropathology of human spinal cord injury. **Spinal Cord 37:**79–88, 1999
45. Kakulas BA, Lorimer RL, Gubbay AD: White matter changes in human spinal cord injury, in Stalberg E, Sharma HS, Olsson Y (eds): **Spinal Cord Monitoring.** New York: Springer-Verlag, 1998, pp 395–407
46. Kempermann G, Gage FH: New nerve cells for the adult brain. **Sci Am 280:**48–53, 1999
47. Kirshblum SC, O'Connor KC: Predicting neurologic recovery in traumatic cervical spinal cord injury. **Arch Phys Med Rehabil 79:**1456–1466, 1998
48. Losseff NA, Wang L, Miller DH, et al: T1 hypointensity of the spinal cord in multiple sclerosis. **J Neurol 248:**517–521, 2001
49. Lovely RG, Gregor RJ, Roy RR, et al: Effects of training on the recovery of full-weight-bearing stepping in the adult spinal cat. **Exp Neurol 92:**421–435, 1986
50. Maynard FM, Reynolds GG, Fountain S, et al: Neurological prognosis after traumatic quadriplegia. Three-year experience of California Regional Spinal Cord Injury Care System. **J Neurosurg 50:**611–616, 1979
51. Maynard FM, Jr., Bracken MB, Creasey G, et al: International Standards for Neurological and Functional Classification of Spinal Cord Injury. American Spinal Injury Association. **Spinal Cord 35:**266–274, 1997
52. McDonald JW: Repairing the damaged spinal cord. **Sci Am 281:** 64–73, 1999
53. McDonald JW, Sadowsky C: Spinal-cord injury. **Lancet 359:** 417–425, 2002
54. McTigue DM, Wei P, Stokes BT: Proliferation of NG2-positive cells and altered oligodendrocyte numbers in the contused rat spinal cord. **J Neurosci 21:**3392–3400, 2001
55. Melton LJ III, Atkinson EJ, O'Fallon WM, et al: Long-term fracture prediction by bone mineral assessed at different skeletal sites. **J Bone Miner Res 8:**1227–1233, 1993
56. Micheva KD, Beaulieu C: Neonatal sensory deprivation induces selective changes in the quantitative distribution of GABA-immunoreactive neurons in the rat barrel field cortex. **J Comp Neurol 361:**574–584, 1995
57. Miltner WH, Bauder H, Sommer M, et al: Effects of constraint-induced movement therapy on patients with chronic motor deficits after stroke: a replication. **Stroke 30:**586–592, 1999
58. Nesathurai S: Steroids and spinal cord injury: revisiting the NASCIS 2 and NASCIS 3 trials. **J Trauma 45:**1088–1093, 1998
59. Nicholls J, Saunders N: Regeneration of immature mammalian spinal cord after injury. **Trends Neurosci 19:**229–234, 1996
60. Page SJ, Levine P, Sisto S, et al: Stroke patients' and therapists' opinions of constraint-induced movement therapy. **Clin Rehabil 16:**55–60, 2002
61. Piepmeier JM, Jenkins NR: Late neurological changes following traumatic spinal cord injury. **J Neurosurg 69:**399–402, 1988
62. Ramakers GJ, Corner MA, Habets AM: Development in the absence of spontaneous bioelectric activity results in increased stereotyped burst firing in cultures of dissociated cerebral cortex. **Exp Brain Res 79:**157–166, 1990
63. Ross PD, Davis JW, Epstein RS, et al: Pre-existing fractures and bone mass predict vertebral fracture incidence in women. **Ann Intern Med 114:**919–923, 1991
64. Ruijter JM, Baker RE, De Jong BM, et al: Chronic blockade of bioelectric activity in neonatal rat cortex grown in vitro: morphological effects. **Int J Dev Neurosci 9:**331–338, 1991
65. Rutherford LC, DeWan A, Lauer HM, et al: Brain-derived neurotrophic factor mediates the activity-dependent regulation of inhibition in neocortical cultures. **J Neurosci 17:**4527–4535, 1997
66. Schallert T, Hernandez TD, Barth TM: Recovery of function after brain damage: severe and chronic disruption by diazepam. **Brain Res 379:**104–111, 1986
67. Schwab ME: Repairing the injured spinal cord. **Science 295:** 1029–1031, 2002
68. Schwab ME, Bartholdi D: Degeneration and regeneration of axons in the lesioned spinal cord. **Physiol Rev 76:**319–370, 1996
69. Seil FJ, Drake-Baumann R: Reduced cortical inhibitory synaptogenesis in organotypic cerebellar cultures developing in the absence of neuronal activity. **J Comp Neurol 342:**366–377, 1994
70. Seil FJ, Drake-Baumann R, Leiman AL, et al: Morphological correlates of altered neuronal activity in organotypic cerebellar cultures chronically exposed to anti-GABA agents. **Brain Res Dev Brain Res 77:**123–132, 1994
71. Simons DJ, Land PW: Early experience of tactile stimulation influences organization of somatic sensory cortex. **Nature 326:** 694–697, 1987
72. Steeves JD, Keirstead HS, Ethell DW, et al: Permissive and restrictive periods for brainstem-spinal regeneration in the chick. **Prog Brain Res 103:**243–262, 1994
73. Taub E, Crago JE, Burgio LD, et al: An operant approach to rehabilitation medicine: overcoming learned nonuse by shaping. **J Exp Anal Behav 61:**281–293, 1994
74. Taub E, Miller NE, Novack TA, et al: Technique to improve chronic motor deficit after stroke. **Arch Phys Med Rehabil 74:** 347–354, 1993
75. Taub E, Uswatte G, Pidikiti R: Constraint-Induced Movement Therapy: a new family of techniques with broad application to physical rehabilitation—a clinical review. **J Rehabil Res Dev 36:**237–251, 1999
76. van der Lee JH, Wagenaar RC, Lankhorst GJ, et al: Forced use of the upper extremity in chronic stroke patients: results from a single-blind randomized clinical trial. **Stroke 30:**2369–2375, 1999
77. Waters RL, Adkins R, Yakura J, et al: Donal Munro Lecture: Functional and neurologic recovery following acute SCI. **J Spinal Cord Med 21:**195–199, 1998
78. Waters RL, Adkins RH, Yakura JS: Definition of complete spinal cord injury. **Paraplegia 29:**573–581, 1991
79. Waters RL, Adkins RH, Yakura JS, et al: Motor and sensory recovery following complete tetraplegia. **Arch Phys Med Rehabil 74:**242–247, 1993
80. Wernig A, Muller S: Laufband locomotion with body weight support improved walking in persons with severe spinal cord injuries. **Paraplegia 30:**229–238, 1992
81. Wernig A, Nanassy A, Muller S: Laufband (treadmill) therapy in incomplete paraplegia and tetraplegia. **J Neurotrauma 16:** 719–726, 1999
82. Wernig A, Nanassy A, Muller S: Maintenance of locomotor abilities following Laufband (treadmill) therapy in para- and tetraplegic persons: follow-up studies. **Spinal Cord 36:** 744–749, 1998
83. Wolf SL, Lecraw DE, Barton LA, et al: Forced use of hemiplegic upper extremities to reverse the effect of learned nonuse among chronic stroke and head-injured patients. **Exp Neurol 104:**125–132, 1989

Manuscript received August 15, 2002.

Accepted in final form August 19, 2002.

This work was funded by grants from the Sam Schmidt Foundation, Las Vegas, NV; ALS Hope Foundation, St. Louis, MO; Kent Waltdep National Paralysis Foundation, Dallas, TX; and the Barnes-Jewish Hospital Foundation, St. Louis MO. We are also particularly thankful for monies directed from William Peck, M.D., Executive Director for Medical Affairs and Dean of the School of Medicine, Washington University in St Louis.

Address reprint requests to: John W. McDonald, M.D., Ph.D., Spinal Cord Injury Program, Department of Neurology, Campus Box 8518, 4444 Forest Park Avenue, Suite E226, Washington University School of Medicine, St. Louis, Missouri 63108. email: mcdonald@neuro.wustl.edu.