
RESTORING FUNCTION AFTER SPINAL CORD INJURY

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BACKGROUND– By affecting young people during the most productive period of their lives, spinal cord injury (SCI) is a devastating problem for modern society. A decade ago, treating SCI seemed frustrating and hopeless because of the tremendous morbidity and mortality, life-shattering impact, and limited therapeutic options associated with the condition. Today, however, an understanding of the underlying pathophysiological mechanisms, the development of neuroprotective interventions, and progress toward regenerative interventions are increasing hope for functional restoration.

REVIEW SUMMARY– This study addresses the present understanding of SCI, including the etiology, pathophysiology, treatment, and scientific advances. The discussion of treatment options includes a critical review of high-dose methylprednisolone and GM-1 ganglioside therapy. The concept that limited rebuilding can provide a disproportionate improvement in quality of life is emphasized throughout.

CONCLUSIONS– New surgical procedures, pharmacologic treatments, and functional neuromuscular stimulation methods have evolved over the last decades that can improve functional outcomes after spinal cord injury, but limiting secondary injury remains the primary goal. Tissue replacement strategies, including the use of embryonic stem cells, become an important tool and can restore function in animal models. Controlled clinical trials are now required to confirm these observations. The ultimate goal is to harness the body's own potential to replace lost central nervous system cells by activation of endogenous progenitor cell repair mechanisms.

KEY WORDS *excitotoxicity, regeneration, rehabilitation, spinal cord injury, stem cell*

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The annual incidence of traumatic spinal cord injury (SCI) in the United States is approximately 40 cases per million. The estimated prevalence is between 183,000 and 230,000 cases (1–3), of which more than 80% are male (4). Moreover, 55% of SCIs occur between ages 16 and 30 years, the average age at injury being 32.1 years. The incidence, prevalence, and causes of SCI vary greatly in other countries;

rates of occupational SCI tend to be higher outside the United States.

The most frequent neurologic category of traumatic SCI is incomplete tetraplegia (30.2%), followed by complete paraplegia (26.1%), complete tetraplegia (23.3%), and incomplete paraplegia (19.7%) (5).

Since 1994, motor vehicle crashes have accounted for 40.7% of injuries in this country, followed by acts of violence (primarily gunshot wounds) (21.8%), falls (21.3%), and recreational activities (7.9%) (5).

More than 88% of people who leave the hospital after treatment for SCI go to private, noninstitutional residences. However, average yearly health care expenses and estimated lifetime costs directly attributable to SCI vary greatly according to age and severity of injury. Lifetime costs range from \$300,000 for a person who suffers an incomplete motor lesion at any level at age 50 years to \$1.7

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million for someone who develops high tetraplegia at age 25 years (6).

Over the last decade, the life expectancy of individuals with SCI has continued to improve, and it now approaches normal for young individuals suffering lower level injuries. Mortality rates are higher during the first year after injury, particularly for individuals with high cervical lesions and associated multiorgan injuries. In the past, the leading cause of death was renal failure, but advances in urological management have dramatically lowered rates of genitourinary complications. Today, pneumonia, pulmonary emboli, and septicemia are the leading causes of death in individuals with SCI (4).

The epidemiology of SCI is largely restricted to traumatic causes, because state and federal registries are available for traumatic etiologies but not for nontraumatic causes. Estimates of the incidence and prevalence of nontraumatic causes are conservatively 4 to 5 times those corresponding to traumatic etiologies.

MECHANISMS OF SCI

Primary Injury

The mechanism of acute traumatic SCI usually consists of compression, distraction, laceration, and shear forces. Bone fragments, disc material, and ligamentous structures affect blood vessels, axons, neurons, oligodendrocytes at the injury site, and long tracts connecting multiple neural levels. After the initial trauma, the spinal cord undergoes chronological pathologic changes (Figure 1). Within minutes, hemorrhage, loss of microcirculation, and vasospasm occur inside the cord, resulting in a concentric expanding lesion (5). The cord

rapidly swells within the fixed space of the spinal canal, and once the pressure inside overcomes venous blood pressure, the original injury is exacerbated by a central venous-type infarction. After experimental compression trauma in rodents, spinal cord blood flow decreases (6). The systemic hypotension caused by neurogenic shock may enhance the injury.

In general, spinal cord lesions at early postnatal ages are often followed by a better functional recovery than those in adults; the differences in primary mechanical forces and restrictions may account for this difference (7,8).

Secondary injury

First described in the early 19th century as a progressive posttraumatic destruction of spinal cord tissue, most of our present knowledge about secondary injury is based on cerebral trauma and ischemia (9,10). The progressive ischemia after the acute injury extends to the surrounding white matter, leading to additional axonal and neuronal necrosis (11–13). Microcirculatory impairment, ruptured blood vessels, and damaged cells and axons increase extracellular concentrations of excitatory amino acids, initiating excitotoxicity. This triggers the secondary loss of neighboring intact nerve fibers, neurons, and oligodendrocytes. Demyelination itself releases oligodendrocyte growth inhibitory molecules, myelin-associated glycoprotein, and the neurite outgrowth inhibitor NOGO-A (5).

The neurotransmitter glutamate is released by the damaged neurons, axons, and astrocytes after the injury. Its extracellular accumulation is the combined result of direct

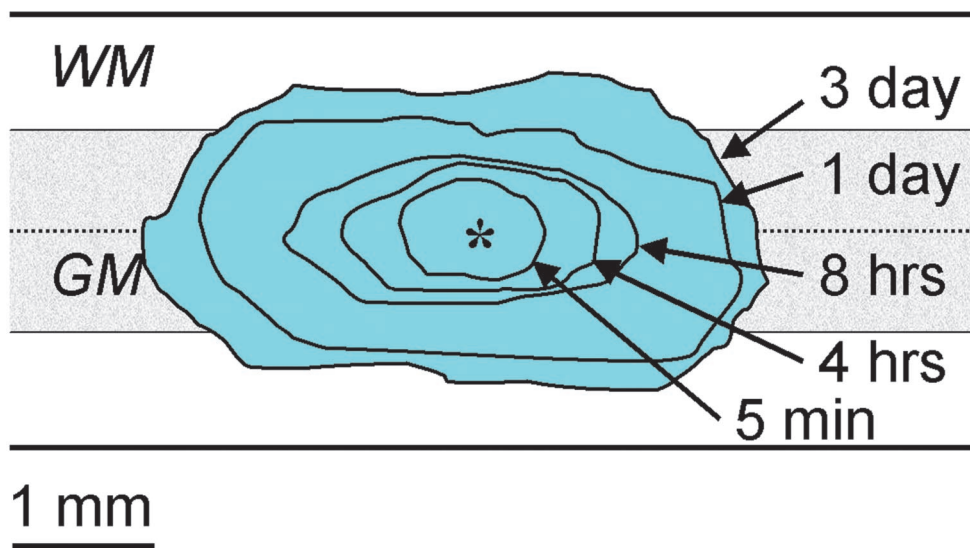


Figure 1. Sketches of longitudinal sections through the central canal of the spinal cord of a rat that sustained a moderate contusion injury. The drawings show the size of the lesion at 5 minutes, 4 hours, 8 hours, 1 day, and 3 days after the injury. WM indicates white matter; GM, gray matter. *Site of impact. Adapted from Liu et al, 1997.

release from disrupted membranes and axons and failure or even reversal of normal energy-dependent glutamate uptake. Such abnormally high levels of glutamate overexcite neighboring neurons, causing them to admit waves of calcium ions. The sudden influx of calcium triggers a series of destructive events, including the production of highly reactive free radicals that attack membranes and other cellular components, killing previously healthy neurons.

Excitotoxic shock can harm myelinating oligodendrocytes as well as neurons (14,15). Because one oligodendrocyte myelinates 10 to 40 different axons, loss of even a single oligodendrocyte can contribute to the demyelination of several axons that remain intact after the primary injury. Oligodendrocytes are highly vulnerable to excitotoxic signals mediated by glutamate receptors of the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) and kainate classes (16). Cellular Ca^{2+} overload is a key trigger of this process (17).

Oligodendrocytes may also kill themselves after SCI through apoptosis (programmed cell death). Days or weeks after the initial trauma, apoptotic death of oligodendrocytes, located as far as 4 segments away from the trauma site, magnifies the original injury (18). In a rat model of contusion injury, cell death peaks 1 week after the injury and continues throughout the first month (19). Treatment with drugs that alter protein synthesis limit white-matter injury and improve

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behavioral recovery in a rodent spinal cord contusion injury model (20).

Many factors can promote this delayed death of oligodendrocytes, including tumor necrosis factor- α , the apoptosis antigen ligand FAS/p75 cytokine pathway, and lipid byproducts. Cytokine-mediated activation of FAS and p75 death-receptor pathways might be essential molecular events contributing to oligodendrocyte apoptosis (21). 4-Hydroxynonenal, a lipid peroxidation byproduct that accumulates after SCI, is directly cytotoxic to oligodendrocyte precursors (22). Mechanisms that kill oligodendrocyte precursors or inhibit their proliferation or migration could limit remyelination and recovery of function. Targeting the delayed, protracted wave of oligodendrocyte death, which might proceed for months in humans, is opening doors to novel protective therapies.

Many secondary mechanisms of injury to oligodendrocytes are common to traumatic and nontraumatic SCI. Thus, chronic demyelination after CNS injury shares common features with chronic degenerative disorders such as multiple sclerosis (23). Treatment with antagonists of AMPA-type glutamate receptors reduces injury severity and oligodendrocyte loss in experimental allergic encephalitis, a murine model of multiple sclerosis (24–27). Nontraumatic SCI has multiple etiologies that result in the same symptoms as traumatic SCI (Figure 2). However, these disease-specific causes are beyond the focus of this review.

Investigations of the immune system's role in secondary injury are challenging the traditional view that autoimmunity after CNS trauma is purely destructive (28,29). In animal models, proinflammatory cytokines help prevent injury, macrophages are needed for CNS repair, and SCI activates T cells that recognize CNS myelin basic protein (30–32). Thus, growing evidence suggests that the T cell-dependent immunity is a physiologic response to CNS trauma that, in part, limits secondary injury. Indeed, T cell-based active vaccination against myelin-associated antigens has proved neuroprotective in animal models and is being studied as a potential human therapy (33).

ACUTE TREATMENT

The management of acute SCI should seek primarily to protect the individual from additional injury. It is mainly directed at the prevention of secondary injury and control of the systemic physiologic derangements resulting from the original injury. Most traumatic SCI occurs as a result of rapid cord compression because of a fracture-dislocation or burst fracture (34). One necessary step is to decompress the swollen cord by removing damaging bone, disk, and ligament fragments. Early surgery is typically limited to individuals with continued neurologic decline and evidence from magnetic resonance imaging of acute compression (35). However, there is no standard of care regarding the role and timing of early surgical intervention because of insufficient data to support overall treatment standards. However, the clinical American Spinal Injury Association (ASIA) injury grade (Table 1) should not be used in the equation of who should receive early surgery, as has been the case in the past. Because of spinal shock, many individuals will present as ASIA A or a complete injury but will improve to a higher grade with resolution of spinal shock.

Some animal data strongly suggest that early decompression (<24 hours) can improve neurologic recovery and lower the rate of complications (36,37). There is a lot of clinical uncertainty about surgical intervention and its time window in the setting of human SCI. Most studies cannot identify a difference in clinical outcomes between operated and nonoperated patients (37–40). However, most studies are small and define early intervention as less than 72 hours, a period long after most secondary injury is complete (41,42).

Table 1.
ASIA Impairment Scale

Grade	Description
A	Complete. No sensory or motor function preserved in the sacral segments S4–S5.
B	Incomplete. Sensory but not motor function preserved below the neurologic level and extending through the sacral segments S4–S5.
C	Incomplete. Motor function preserved below the neurologic level; most key muscle have a grade <3.
D	Incomplete. Motor function preserved below the neurologic level; most key muscles have a grade >3.
E	Normal motor and sensory function.

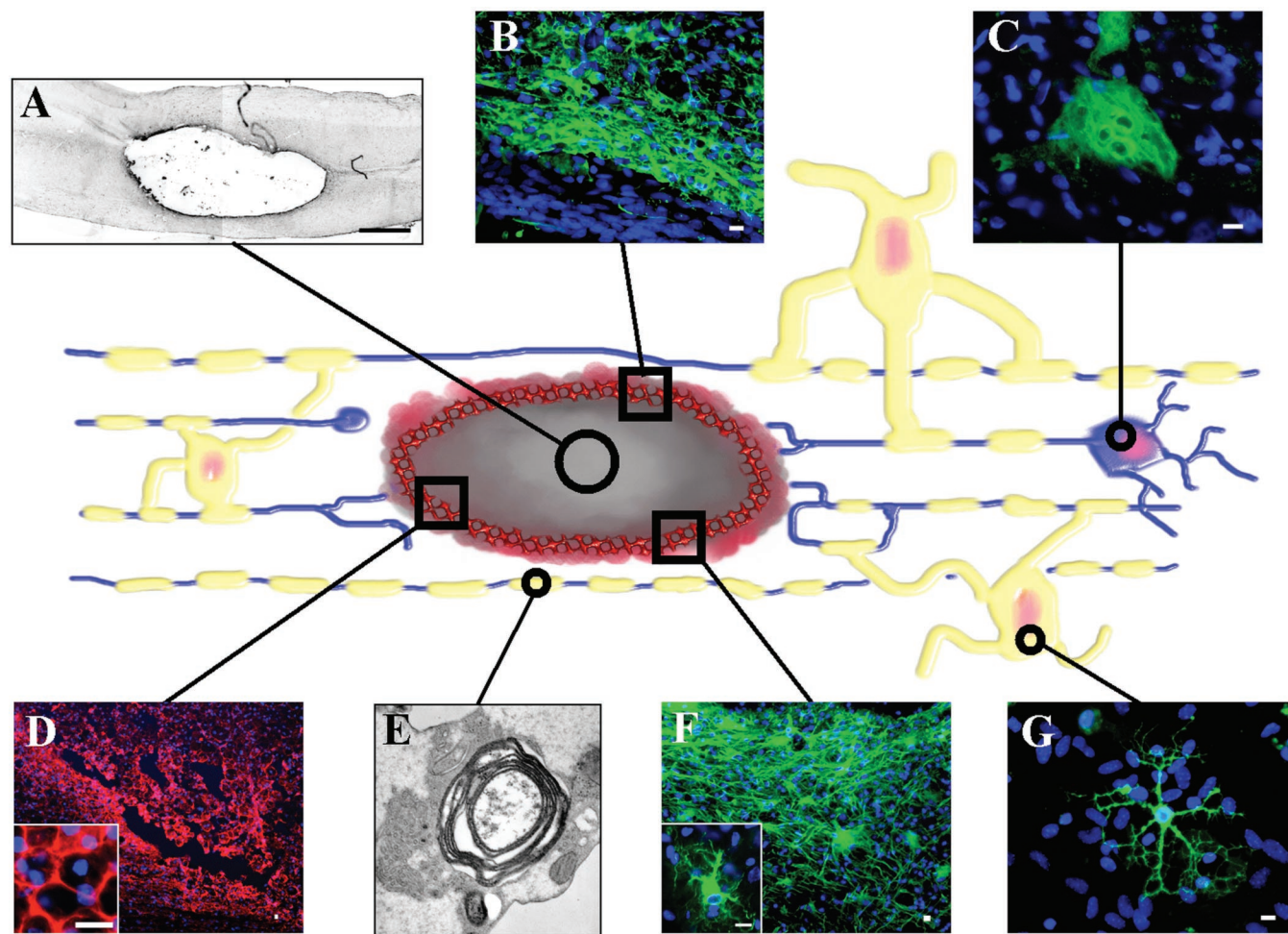


Figure 2. After traumatic SCI, blood vessels and axons are disrupted and microcirculation is impaired. Because of the dying tissue, a fluid-filled syrinx can form within days. Prolonged oligodendrocyte death occurs, resulting in demyelinated and dysmyelinated axons with conduction blocks. The formation of a glial scar surrounding the lesion makes repair mechanisms difficult. A, Cyst formed in a rat spinal cord 3 weeks after contusion injury. As a sign of ongoing tissue removal and inflammation response, the fluid-filled cyst contains high numbers of macrophages (D). The glial scar is mainly characterized by high numbers of astrocytes expressing GFAP (B). Surrounding the scar are many proliferating neural progenitor cells, predominantly expressing the intermediate filament protein Nestin (F). Motor neurons (C) in the gray matter adjacent to the injury site and white matter oligodendrocytes (G) continue to die. Limited neuronal repair mechanism (sprouting) and remyelination attempts occur. Faulty myelination is likely to occur in this highly aggressive environment (E). (Scale bars, A=1 mm; B through G=10 μ m.)

To answer these questions, randomized, controlled prospective human trials are needed.

Nevertheless, new surgical procedures and better hardware for internal spine stabilization have evolved in the past

decade (43). Moreover, early surgery might be justified even if immediate recovery is not expected, because internal stabilization of the spine permits earlier mobilization, an essential approach to limiting secondary complications such as skin

breakdown, pulmonary and urological infections, autonomic dysfunction, and loss of muscle mass and bone density. Individuals with internal spine stabilization can participate in rehabilitation programs more fully than those with external stabilization devices (eg, halo). Thus, the entire process of recovery needs to be considered when deciding whether to perform surgery early or late.

Where do we stand with pharmacologic treatment of acute SCI in humans? To date, 8 prospective clinical trials have been completed in acute SCI, including study of methylprednisolone, naloxone, tirilazad, GM-1 ganglioside, thyrotropin-releasing hormone, and nimodipine. Excellent reviews on this subject are available, and additional discussion will focus on methylprednisolone and GM-1 gangliosides (44). The first neuroprotective agent for SCI was introduced in the 1990s after a multicenter randomized clinical study (National Acute Spinal Cord Injury Study [NASCIS-2]) found that a high dose of the steroid methylprednisolone sodium succinate (MPSS) resulted in a modest, although statistically significant, recovery effect when administered within 8 hours of trauma (45,46). The subsequent multicenter NASCIS-3 trial in 1997 examined the potential benefit of extending the NASCIS-2 regimen of 24-hour therapy to 48 hours of MPSS treatment and treatment with tirilazad mesylate, a synthetic steroid. Most benefit from the 48-hour treatment was reported in individuals whose MPSS therapy

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was initiated between 3 hours and 8 hours after injury and resulted in higher motor improvement scores (47,48).

However, there is considerable controversy about the use of MPSS in the acute SCI setting because of scientific limitations of the original studies. The design and outcome limitations and lack of public availability of the data have been extensively reviewed, and the interested reader is referred to excellent reviews in this area for additional information (49–52). Suffice to say, treatment with MPSS remains largely a clinical decision, incompletely supported by scientific data, requiring clinical expertise and cautious application. Although a consensus is not clear, most centers treat with MPSS using the following guideline based on onset to treatment relative to injury: MPSS bolus (30 mg/kg) delivered over the first hour for individuals within the first 8 hours

of injury; treatment is continued (5.4 mg/kg per hour) for the next 23 hours for individuals treated within 0 to 3 hours and for the next 47 hours for individuals treated within 3 to 8 hours of injury. MPSS is not indicated to be administered more than 8 hours after trauma or for acute penetrating SCI (53).

The high steroid dose used in the treatment of SCI is associated with side effects such as increased incidence of gastric bleeding, sepsis, pneumonia, acute corticosteroid myopathy, and wound infection. The elderly are particularly prone to these complications and therefore deserve special consideration (54). Rapid mobilization to rehabilitation is perhaps the most important variable in limiting infectious and skin breakdown complications.

The mechanism by which MPSS acts in acute SCI is unclear but is largely held to reduce the inflammatory cascade. Studies have shown reductions in inflammation, edema, lipid peroxidation, and improvements in blood flow. MPSS treatment also reduces “dieback” of vestibulospinal fibers, enhances axonal sprouting, inhibits tumor necrosis factor- α and nuclear factor- κ B binding activity, inhibits calpain, and reduces the release of excitatory amino acids (47). However, it is difficult to assign mechanisms based on in vivo studies, because any neuroprotective intervention will likely produce many of the above-mentioned observations.

Following primary outcome measures in a preliminary study of monosialotetrahexosylganglioside (GM-1 ganglioside) (55), a prospective, randomized, placebo-controlled, double-blind trial of 2 doses of GM-1 ganglioside versus placebo was evaluated in acute traumatic SCI (56). Treatment with GM-1 had to begin within 72 hours of injury onset; an initial bolus (300 mg IV over 30 minutes in normal saline) was given after MPSS, followed by 56 daily doses (100 mg each). The high-dose group received a 600-mg bolus and 200-mg daily dose. Although not proven in primary outcomes analysis, GM-1 seems to be beneficial in individuals with incomplete SCI, and faster neurologic recovery was achieved in all individuals. There were significant effects in all patients in the primary outcome variable (percentage of marked recovery) at week 8, the end of the dosing period. Consistent positive trends favoring GM-1 were observed in ASIA motor and sensory scores, bowel and bladder function, sacral sensation, and anal contraction.

Unfortunately, GM-1 is not readily available for acute treatment in the United States. GM-1 was available for use in the United States under an open-label trial from Fidia Pharmaceuticals Corporation, but presently all studies have been completed. The Food and Drug Administration has not approved it for general distribution. Presently, it can only be used under an Emergency IND from the Food and Drug Administration on a case-by-case basis and pragmatically can only be obtained for more subacute injuries, where clinical data are not available.

The proposed mechanism of action of GM-1 is also not clear, with studies suggesting multiple effects, including an-

tiexcitotoxic activity, apoptosis prevention, neurite sprouting promotion, and nerve growth factor effects.

Nonetheless, the MPSS and GM-1 ganglioside trials offer encouraging progress in a very difficult clinical research arena, each trial improving on its predecessor. A critical process to enable faster delivery of acute therapies before entry to the emergency room is needed to maximize the effectiveness of any future therapy to prevent secondary injury. The present multihour interval to pharmacologic treatment is too long.

Future acute therapies for SCI are likely to be more mechanistically focused and based on current advances in the pathophysiology of secondary injury. Promising agents include those that protect cells from excess glutamate and excitotoxicity. Recently, white matter oligodendrocytes were discovered to be highly vulnerable to AMPA-type glutamate receptor overactivation (excitotoxicity) (15). This work supports previous data demonstrating a prominent neuroprotective (particularly white matter preservation) and recovery effect of AMPA receptor antagonists in experimental acute SCI (57,58). Only a few early clinical drug trials of AMPA/kainate receptor antagonists have been reported, and most have been completed in stroke. Derivatives of GYKI53655 have apparently been abandoned, but YM90K demonstrated safety and pharmacokinetic profiles compatible with clinical use (59,60). Such compounds offer selective advantages for additional use in the orphan disease SCI, because they are being clinically pursued for treatment of disorders with much larger population bases, including migraine and nausea.

Other neuroprotective agents of the future might include lipid peroxidase inhibitors, reactive oxygen species derived from nitric oxide, peroxynitrite inhibitors, inhibitors of calpain (which degrades the spinal cord cytoskeleton), and inhibitors of posttraumatic apoptosis of neurons and oligodendrocytes. All of these approaches have been supported by promising animal studies, but translation into clinical trials is a major hurdle.

LONG-TERM TREATMENT

Individuals with incomplete SCIs show substantial functional recovery despite the limited ability of the adult CNS to regenerate spontaneously (61,62). Traditionally, recovery from SCI was managed primarily on an inpatient basis, but it is now transitioning to a life-long process. The old dogma that recovery is limited to the first 2 years after injury is giving way to the understanding that functional improvement can occur for many years. Treating complete and incomplete lesions involves different challenges, however. A primary goal for regeneration after complete SCI is regrowth of connections across the lesion site (8). For incomplete injuries, sprouting and remyelinating intact connections are important therapeutic targets. Another target includes the neurologic complications of SCI that largely result from fragmentation

and distortion of signals crossing the lesion, including chronic pain and spasticity (63).

General principles of inpatient SCI rehabilitation (Table 2) have been the subject of excellent recent reviews (64). Preventing medical complications, which hospitalize up to 30% of individuals with SCI yearly, is of paramount importance. After inpatient rehabilitation, lack of access to specialty centers limits specialist care for most individuals with SCI. However, annual follow-ups should include both medical and functional evaluations and therefore are best performed by neurologists, physiatrists, and other SCI experts. They can help to tailor physical fitness programs for each patient to combat functional loss and adjust therapies to the most current advances in clinical and basic science research.

Expert intervention can also minimize some of the structural and functional adaptations to paralysis. In the peripheral vascular system, a decrease in the diameter of the common femoral artery, reduced capillarization, and diminished blood flow to the legs have been documented. Impaired blood flow and other maladaptive changes can contribute to early fatigue during muscle contractions, including electrically stimulated

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contractions (65,66). Preventing such changes could minimize long-term sequelae.

Spasticity, a positive symptom of the upper motor neuron syndrome encountered frequently in individuals with SCI, can affect function, comfort, self-image, and even care delivery. Moreover, it contributes to development of secondary musculoskeletal complications (trauma, fractures, and pressure ulcerations) and pain. Treatment of spasticity ranges from physical modalities (eg, stretching, positioning, range of motion) to local pharmacologic (chemodenervation with anesthetic agents, phenol, alcohol, botulinum toxin), general, and regional pharmacologic interventions (dantrolene, oral or intrathecal baclofen, tizanidine, clonidine, benzodiazepines, gabapentin) and surgery (posterior rhizotomy).

Chronic pain is also an important problem for people with SCI. The reported incidence varies but conservatively occurs in most individuals, and one third rate their pain as severe (67). Present treatments use a variety of pharmacologic (oral or intrathecal opioids, α -adrenergic agonists, antidepressants, anticonvulsants, local anesthetics, N-methyl-D-

Table 2.

Traditional Treatment for Patients With Spinal Cord Injuries

Medical	Surgical	Rehabilitative
Cardiovascular: Hemodynamic instability Autonomic dysfunction Thromboembolism	Spinal stabilization: Internal fusion/instrumentation External orthoses	Management of chronic hemodynamic issues, Autonomic dysreflexia
Respiratory dysfunction: Respiratory failure Atelectasis Pneumonia Vent-dependent care	Tracheostomy	Preventive respiratory care, Respiratory conditioning program
Gastrointestinal: Ileus Impaction, constipation Gastric/duodenal ulcers Gastrointestinal reflux disease, cholelithiasis		Establish predictable bowel continence program, Preventive gastrointestinal care
Urological: Urinary tract infection Hydronephrosis Cycto/nephrolethiasis	Urinary system augmentation, diversion procedures, penile implants, lithotripsy, sphincterotomy	Establish bladder continence program, Preventive genitourinary care, sexual dysfunction program
Dermatological: Pressure ulcers	Pressure ulcer repair	Establish skin integrity program, Prevention/management of pressure ulcers
Musculoskeletal: Osteoporosis Heterotopic ossification Fractures Overuse syndromes Acute and chronic pain	Treatment of delayed neurologic/spine complications: syringomyelia, focal nerve entrapments, central pain, spasticity, spinal instability, implantation of intrathecal drug delivery systems	Prevention/management of musculoskeletal complications: contractures, spasticity, postural abnormalities, skeletal deformities, long-term maintenance of intrathecal drug therapy
		Functional retraining programs in self-care, mobility, psychosocial adaptation, vocational/ recreational skills, adaptive equipment/orthotic devices

aspartate (NMDA) receptor antagonists, and Baclofen), surgical (dorsal root entry zone lesion), physical, and psychological approaches (68–77). However, there is limited scientific evidence for the efficacy for many of these treatments.

Fertility and sexual function need to be addressed for individuals undergoing SCI rehabilitation. The anatomic location and extent of injury can only partially predict sexual dysfunction, and treatment demands a systematic clinical approach. Described are impairments of male and female sexual responses, such as erectile function, lubrication, ejaculation, and orgasm as well as issues of childbearing for women and issues of parenting for men and women (78,79). Major advances in the areas of sperm retrieval and complex reproductive technologies have made biologic parenthood for men with spinal cord injuries a realistic option. Penile vibratory stimulation (PVS) and electroejaculation (EEJ),

combined with intrauterine insemination or in vitro fertilization, may be encouraging options for men with SCI and their partners to achieve successful pregnancies (80,81).

Rehabilitation must include reintegration into a gainful employment, although only a few patients will achieve this goal. Long-term support in job seeking and intensive re-education, including switching to a less physically demanding job, are very important (82).

Several advanced therapeutic options can enhance patients' ability to function at home and in the workplace. They include tendon transfers, partial weight-supported walking (PWSW), and functional electrical stimulation (FES). The loss of hand function, which is perceived by most tetraplegic individuals as the greatest loss related to their injury, can be partially regained by tendon transfer. Tendons of muscles that are under volitional motor control and that have a redundant

role (eg, both the biceps brachii and brachioradialis can flex the elbow) are surgically rerouted to allow the muscles to take over lost motor functions. It requires sufficiently strong (4–5/5) muscles, which must be trained to assume their new roles. The most frequent tendon transfers are performed to restore voluntary thumb pinch, improve grip strength, and regain active elbow and wrist extension (83,84).

PWSW may improve gait in individuals with incomplete SCI (85,86). PWSW consists of walking on a treadmill while supported by a harness and a pneumatic suspension device. Some pilot studies have provided an adequate basis for a larger, controlled clinical trial comparing PWSW with conventional gait training. However, this potential treatment is only applicable to a small subset of individuals with SCI, primarily ASIA C/D classification (Table 1).

FES and evolving neuroprostheses are dramatically changing therapeutic strategies for patients with SCI (87). However, muscles can be safely electrostimulated directly or transcutaneously only by activating a functional nerve ending, which requires the lower motor neuron and peripheral nerve to be intact. FES cannot be applied to denervated muscle because injurious currents would be required.

FES can strengthen muscles, condition the heart, pace the diaphragm, enhance bowel and bladder function, facilitate erection and ejaculation, and control pain. Some FES systems reproduce walking, but engineering complexities and high human energy requirements preclude their routine use. However, using FES to facilitate standing can greatly improve quality of life and increase the cross-sectional area of large conduit arteries, improving blood flow into the paralyzed leg (88).

Involuntary exercise by electrically stimulated contractions of the paralyzed limbs is used for strength training. Muscle strengthening can partially reverse neurologic muscle weakness, slow or reverse osteopenia, and improve muscle mass and blood flow. It is possible that FES systems can be used to effectively decrease spasticity, provide cardiovascular conditioning, and reduce medical complications such as venous thrombosis and skin breakdown (89–92).

Individuals who sustain an injury at the cervical level have a high incidence of respiratory compromise; approximately 20% will require mechanical ventilatory support and 5% will require chronic mechanical ventilation (93). Mechanical ventilation has a high number of complications, such as increased risk of infection, interference with speech, increased need for assistance, and high costs. In the last two decades, the alternative therapy of choice was bilateral phrenic nerve stimulation, which requires intact bilateral phrenic nerve function (94). Combined intercostals and unilateral phrenic nerve pacing can also provide long-term ventilatory support in patients with only a single functional phrenic nerve. The potential morbidity associated with traditional phrenic nerve pacing may soon be replaced by a simple outpatient procedure that allows direct pacing of the diaphragm using intramuscular electrodes attached to the motor end points (95).

Loss of neurocontrol after SCI has many different aspects: dysphagia, difficulty breathing, loss of bowel and bladder control, and control of limb movement. Perhaps the function that individuals with SCI would most like to regain is bowel and bladder control. FES technology is designed to achieve this goal. Benefits of a FES bladder system include urination on demand, elimination of catheters, improved continence, fewer urinary tract infections, improved quality of life and social ease, and long-term cost savings (96,97).

Neuroprosthesis that uses FES technology for tetraplegic individuals can help to restore hand grasp and release. Multichannel, implanted FES systems are being used or evaluated for their ability to improve motor function of the upper extremities (98,99). Several systems that use FES technology are presently undergoing clinical trials (100–102). Through the latest developments in cortical neuroprosthetics, for example, it may be feasible to reconstruct voluntary motor activity in paralyzed patients. These implantable devices that interface parts of the brain with a computer can bypass damaged motor pathways and could one day be used to restore sensory and motor functions lost through injury or disease (103–106). Present efforts to develop smaller electrodes, recording techniques, control systems, and hardware should eventually make such systems smaller, less expensive, and easier to implant (107). However, these are early days.

RESTORING FUNCTION STEP BY STEP

Targets

Pragmatic approaches to the treatment of SCI are needed to improve quality of life. A clear understanding of the hierarchy of needs for individuals with SCI is therefore necessary. Although needs vary according to the level and severity of injury, most affected individuals prioritize bowel and bladder function, sexual function, hand function, and breathing; walking is a distant competitor.

The management to restore these functions should be designed in a stepwise manner. It is important to explain to the individual that a discovery of a cure will not occur in the near-term and that a cure is not the goal, but only partial restoration is required. Restorative therapies should focus on multiple targets and be applied at different intervals after injury. Important strategies should include limiting secondary injury and promoting regeneration.

What is feasible?

To recover function and improve quality of life, the injured spinal cord does not have to be entirely reconstructed. Disproportionate functional benefits can result from minor anatomic gains. We know from SCI models in cats that effective locomotion can recover with the maintenance of a small proportion (10%) of the original axonal population. These axons are largely concentrated in a doughnut-like rim of white matter remaining at the injury level (108). Defective myelination of the remaining axons in this outer rim will

contribute to functional deficits (34). Consequently, to improve function, remyelination of the exposed axons is one practical approach. It probably will not allow patients with severe SCI to walk, but they might regain some neurocontrol over such domains as bowel and bladder function, breathing, and hand grasp. Thus, it is useful to consider that secondary injury prevention is more feasible than rebuilding damaged spinal tissue.

Present regenerative research efforts are aimed at genetic expression of nerve growth factors and molecules that suppress inhibitors of axonal growth to promote the regrowth of interrupted nerve fibers (109). In rodent models, oligodendrocytes have been enticed to remyelinate axons and improve axonal conduction. Thus, it seems that restoring the integrity of existing neuronal circuits is the most feasible method of enhancing recovery. Neither in rodents nor in humans has long-tract rebuilding of functional neuronal circuits with establishment of appropriate neuronal reconnections been demonstrated. However, there is evidence for partial construction of local nonspecific neuronal connections. For example, human fetal striatal tissue has been transplanted into humans and animals with Huntington's disease, showing establishment of afferent and efferent connections and functional benefits (110,111). Transplantation of human embryonic dopamine neurons into the striatum of patients with Parkinson's disease has proved beneficial in open clinical trials, and transplanted cells have been monitored to store and

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release dopamine for more than a decade (112–115). Focal epilepsy, stroke, and SCI are other applications for neural transplantation in humans (116–118). Greater discussion of the different regenerative strategies is warranted.

Enhancing regeneration – Regenerative sprouting occurs spontaneously but is short lived and diminishes within weeks after SCI (119). A potential reason for this phenomenon could be local production of specific inhibitory proteins that block neurite outgrowth (120). Early successful attempts to neutralize these factors include specific antibodies (eg, inhibitor neutralizing antibody) that counteract the myelin protein NOGO-A (121). Other strategies use neurotrophic factors, such as neurotrophin-3, which can actively promote axonal growth (122). Today's research is focused on NOGO-A blocking agents and other inhibitory proteins, including the

development of antibodies against these molecules, their receptors, or signal pathways (123). The role of guidance proteins (netrins and semaphorins) as molecular cues in regeneration of the spinal cord is under close observation. Their signaling pathway may play a key role in limiting or channeling the regeneration of certain neurons (124,125).

Gene therapy – Transferring therapeutic genes directly into cells surrounding a lesion could enhance the ability of resident cells to produce large quantities of neurotrophic factors such as nerve growth factor, brain derived neurotrophic factor, glial cell line derived neurotrophic factor, platelet derived growth factor, and neurotrophin 3 (126,127). Genetically modifying cells to express neurotrophins or growth factors within the damaged spinal cord increases neuronal survival, sprouting, and regeneration (128). Overexpression of these factors most likely increases the intrinsic ability of axons to grow and potentially compensates for elevated levels of inhibitory molecules surrounding a lesion (129). Long-term expression of these genes can be achieved primarily by viral vector systems (129). Animal studies indicate that intraspinal administration of the antiapoptotic gene *Bcl-2* can prevent retrograde cell loss and reduce atrophy of axotomized red nucleus and Clarke's nucleus neurons after SCI (130). For now, though, efficient gene transfer and appropriate gene expression are still major challenges.

Bridging scars – In the adult CNS, both glial substrates and the extracellular matrix influence axonal regeneration after injury. Numerous groups claiming functional recovery have used therapeutic spinal cord grafting procedures. It has been known for many years that Schwann cell grafts can promote axonal regeneration in the central nervous system (131–134). They are capable of ensheathing and myelinating regenerating axons (135). Olfactory ensheathing cell transplantation points to the neuroprotective mechanism of reducing astrocytic gliosis and cystic cavitations (136). Solid human embryonic spinal cord xenografts transplanted into a cavity in the adult injured spinal cord produce beneficial morphologic effects (137). Delayed cotransplantation of fetal cerebral tissue and nerve tissue can achieve anatomic remodeling and long-term functional recovery in rats (138). Polymer scaffolds that contain nerve growth factors and other small molecules or neural stem cells were transplanted into the lesion site to form a growth-permissive environment with limited success. A primary concern of these grafting approaches is induction of additional scar formation that might inhibit axon growth (109,139).

Replacing cells – Cellular transplantation has been used as a primary strategy for replacing cells lost after injury. Endogenous stem cells isolated from spinal cord, fetal spinal cord, and embryonic stem cells have been used successfully for transplantation in animal SCI models, some showing promising results (125,140,141). Neural precursor or stem cells derived

from the brain have the capacity to renew themselves and to generate progeny that can differentiate into multiple distinct cell lineages of neurons and glia (117–120,142–144). Transplantation of human neural stem cells obtained from embryonic tissue can lead to neuron and astrocyte differentiation (145–147) (Figure 3). Neural precursor cells derived from adult human brain and transplanted into demyelinated rodent spinal cords reportedly achieve remyelination and recover impulse conduction (148). However, the relative inaccessibility of these cells limits such potential therapies. The ultimate goal is harnessing the potential of endogenous stem cells to replace without transplantation those lost.

Adult oligodendrocyte precursor cells, which make up 5% to 8% of the glial cell population in the CNS (149), divide in response to demyelination and are thought to differentiate and replace oligodendrocytes lost through injury (150). However, remyelination fails during the later stages of multiple sclerosis, and it is not clear whether this failure results from depletion of adult oligodendrocyte progenitors or damage to axons (151–153). Adult oligodendrocyte progenitors become activated and proliferate after other forms of CNS damage, such as mechanical injury, excitotoxicity, and viral

infection (154). They also produce several chondroitin sulfate proteoglycans (155) that might inhibit axon regeneration (156).

Recent work demonstrates that stromal cells from bone marrow can differentiate into astrocytes when injected into lateral ventricles of neonatal mice (157). When cultured under appropriate conditions, they can also differentiate into neurons (158). Transplanting bone marrow into the demyelinated rat spinal cord results in rather extensive remyelination (159). However, the concept of transdifferentiation, the ability of non-CNS lineage stem cells to redefine themselves into neural lineage cells, has recently met with substantial controversy with the suggestion that apparent transdifferentiation may simply reflect the effects of long-term *in vitro* propagation (160,161).

The concept of cell replacement has risen to an entirely new level since embryonic stem (ES) cells have become available. These pluripotent cells, which can be expanded in culture for an apparently indefinite period, maintain a normal karyotype and have the potential to generate any cell type in the body. They therefore represent an incredible resource for repairing diseased or damaged tissues (162). Based on these

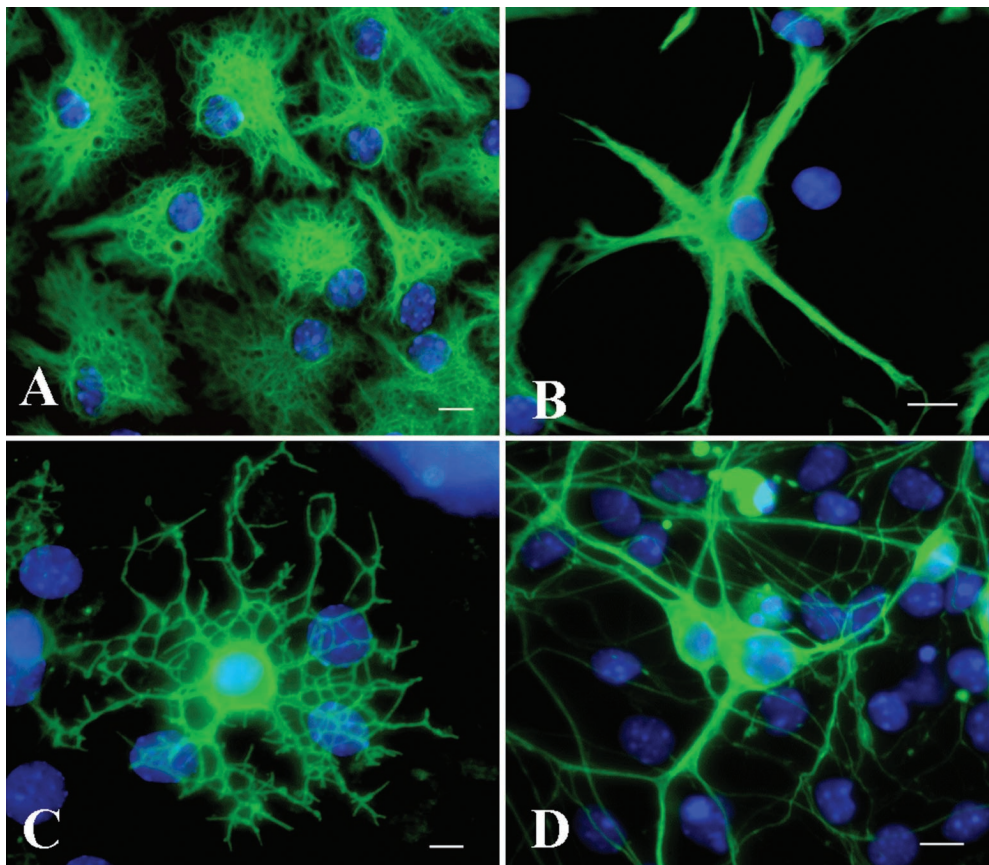


Figure 3. A through D, Three principal cell types in the central nervous system that are important for function and are damaged after injury. The astrocytes type 1 and 2 (A and B), oligodendrocyte (C), and neuron (D) were derived from mouse embryonic stem cells that had been induced to become neural cells with retinoic acid and cultured for 14 days (scale bars=10 μ m).

findings and the fact that they are very amenable to genetic manipulation, ES cells are becoming an invaluable research tool. Harnessing their potential is a major goal now that the Bush administration has made federal funding available for human ES cell research (163). Mouse ES cells have been studied for more than 20 years, but research on human ES cells is still in its earliest stages.

TOWARD THE FUTURE

It is impossible to predict the success of any one approach, but it is important to understand the relative feasibility of each strategy and for science to put efforts into short-, intermediate-, and long-range therapeutic goals.

The discovery that the CNS of adult vertebrates, including humans, contains endogenous progenitor cells capable of making new neurons and glia raises the distinct possibility of someday harnessing this potential for replacing cells lost during nervous system injury (164). It was not long ago that we believed the adult human CNS was hardwired and unable to mend. Now, with each passing year, there is a growing understanding of the increasing regenerative potential of the adult CNS. It is possible that the adult CNS has a much greater capacity of repair than we realize and that perhaps we have not optimized the setting for regeneration to be maximized. It is just a matter of time, resources, and scientific effort before we learn how to program and optimize functional recovery of the human CNS. The old statements too often stated by the bedside that most recovery will occur within 6 months and it will be complete by two years will certainly be giving way to allow hope for some recovery long after an injury (5 to 10 years).

Meanwhile, we can focus on other important ways of improving the lives of individuals with SCI. One is to develop new pharmacologic strategies to minimize CNS injury and optimize recovery. Animal studies have identified numerous neuroprotective agents, such as AMPA receptor antagonists, anandamide (endogenous cannabinoid receptor ligand), dehydroascorbic acid (potent blood brain barrier penetrating antioxidant), and hydroxy-fasudil (Rho-kinase inhibitor), that may protect the spinal cord from injury and ischemia (165–167). Also, reevaluation of clinically available drugs that have shown early promise at the basic science level is a pragmatic approach. For example, topiramate, an antiepileptic drug, can promote neurite outgrowth in vitro and recovery of nerve function in vivo (168). However, there is only limited evidence for the efficacy of these agents (169). Moreover, the clinical effects of such drugs might vary according to the severity and location of a lesion.

The neuroregenerative field has seen impressive advances during the last 20 years. It is now time to unlock the door to repairing the nervous system and minimizing the catastrophic consequences of SCI. Additional investigations into the molecular and cellular mechanisms of spinal cord damage, perseverance in moving potential interventions from bench to

bedside, and advances in rehabilitation techniques should help us achieve these goals. The concept of replacing lost cells via transplantation or activation of endogenous stem cells is exciting, and progress is speeding forward faster than ever. Understanding the factors important for optimizing spontaneous recovery and regeneration will be important (170,171). It is nearly impossible to know where we will be in 10 years, but it promises to surprise us all.

In 2500 BC, Edwin Smith's papyrus stated that SCI is "an ailment not to be treated." Four thousand five hundred years later, we unlocked mechanisms dealing with cellular protection and neuroregeneration, but clinically we are still providing mostly supportive care to individuals with SCIs. It is time to aggressively evaluate and transition the gains obtained in the laboratory at cellular and animal levels to patient care so that the dream of getting out of a chair and walking again can become more of a rule than an exception.

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