# Surgical Management of Spinal Cord Injury: Controversies and Consensus

Edited by

## Arun Paul Amar, MD

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Stanford University School of Medicine
Stanford, CA

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# Preface

The Edwin Smith papyrus, a surgical treatise drafted nearly 4000 years ago, recounted the devastation attendant to cervical spine injuries with quadriplegia and categorized them as "ailments not to be treated."[1] The nihilism implied by this proscription has remained the prevailing sentiment over the succeeding millennia. Indeed, relative to the triumphs achieved in some areas of modern medicine, spinal cord injury (SCI) has remained a debacle. It is estimated that traumatic SCI costs American society between 6 and 40 billion dollars annually.[2] As staggering as this economic impact appears, it is overshadowed by the emotional toll and personal tragedy that attend such disabling injuries.

The acute management of the SCI patient begins at the scene of an accident the moment that such an insult is suspected and progresses until the time of discharge to a rehabilitation facility. At each stage along this continuum, the goals of treatment remain identical:[3,4]

**1** To maximize neurological recovery.
**2** To restore normal alignment and correct deformity.
**3** To promote spinal stability and/or fusion.
**4** To minimize pain, both acutely and chronically.
**5** To facilitate early mobilization and rehabilitation.
**6** To minimize hospitalization and cost.
**7** To prevent secondary complications of disability.

Although these tasks can only be accomplished by the concerted efforts of a multidisciplinary team of doctors, therapists, and nurses, the surgeon's role remains preeminent. However, *in vitro* studies, animal models, and clinical outcome analyses have all failed to yield incontrovertible guidelines that define the role of surgery in SCI. As a result, there is no consensus regarding the necessity, timing, nature, or approach of surgical intervention. Intuitive hunches and anecdotal accounts have not been corroborated by scientific studies, and individual or institutional preferences abound. Because of numerous methodological limitations, including ethical concerns about withholding potentially beneficial treatments to victims of SCI, it has not been feasible to subject such theories to prospective, randomized, controlled trials. Thus, the majority of the extant literature consists of retrospective analyses, unrandomized case series, and experimental models that may fail to simulate human SCI.[5–7]

This book reviews the controversies pertaining to the emergency, diagnostic, medical, and surgical management of SCI and summarizes the foundations of rational treatment paradigms. Scrutiny of the scientific data has yielded objective truths, though there remains some latitude for subjectivity and personal experience. Collectively, the insights disclosed within these pages justify a

sense of optimism and compel the practicing surgeon to refute the archaic, defeatist notions of the past. In 2007, SCI is an ailment to be treated.

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# Foreword by Charles H. Tator

In the last two decades the management of spinal cord injuries has changed dramatically, and major improvements have occurred in both the diagnosis and surgical treatment of spinal cord injury. Furthermore, these accomplishments have been underpinned by major advances in the basic science of both spinal injury and spinal cord injury. We now have a much greater understanding of the mechanisms of these injuries, especially improved knowledge of the pathophysiological processes in the acute, subacute, and chronic stages of traumatic spinal cord injury.

As well, it is now apparent that there should be regionalization and specialization in the management of all phases of spinal cord injury, and that all patients with acute injury should reach a specialized unit for definitive management within about two hours of injury. Certainly, this goal can be achieved in most centers in North America, except those in very remote regions. Early triage is essential for improved patient outcomes because we now know that the spinal cord suffers from major vascular impairments that worsen over time, and that best practice guidelines include careful and judicial management of hemodynamic factors as soon as possible after injury in order to prevent progressive posttraumatic infarction of the spinal cord.

Also, it has become apparent that a multidisciplinary approach to the management of spinal cord injury is the best way to ensure optimal outcome in terms of enhancement of neurological recovery, achievement of a stable, pain-free spine, and social and psychological rehabilitation. This team approach in the acute stage must be followed by a similar team approach in the rehabilitation and chronic stages in order to maximize recovery and minimize complications. The tragic passing of Christopher Reeve emphasizes the importance of management of the whole individual to prevent the potential fatal complications of spinal cord injury.

Surgical treatment has been marvelously improved, and one of the major reasons for the improvement is the accuracy with which the diagnosis of both the spinal and spinal cord injuries can be made. The importance of obtaining early complete definition of both the spinal and spinal cord injuries must be stressed: all patients with spinal cord injuries must have unimpeded access to early and expert imaging with both computerized tomography (CT) and magnetic resonance imaging (MRI). Both modalities are essential for accurate diagnosis and management, and serial imaging is essential for determining the reasons for any early deterioration. It is important to keep in mind that a significant percentage

of patients deteriorate within the first few days of injury, and that the causes can often be detected by serial neurological examination and serial imaging.

The spinal cord injury field has benefited greatly from the efforts to standardize and improve the grading and scoring neurological function. Indeed, careful monitoring of clinical neurological status is just as important today as it was 50 years ago when CTs and MRIs were not available. In contrast, neurophysiologic monitoring, although useful intraoperatively, has been somewhat disappointing because it has proven to be less accurate than careful, serial, clinical neurological examinations. Thus, all practitioners in spinal cord injury must continue to remain expert in performing the clinical neurological examination. Furthermore, this examination should be based on the American Spinal Injury Association (ASIA) system because it is the best available for accurate, serial monitoring. Although it is important for surgeons to teach the neurological examination to other members of the team, especially to nurses, and physical and occupational therapists, it is essential for surgeons to continue to be skilled in this aspect of care.

The advances in our ability to repair the injured vertebral column have been staggering, and it is wonderful to behold the array of surgical approaches, strategies, and devices that are now available for patients with spinal injuries. Furthermore, it is heartening to see the cooperation between the spinal neurosurgeons and the spinal orthopedic surgeons, and the convergence of expertise toward the goal of training spinal surgeons from both training streams. The emphasis must be on training for this difficult and complicated field.

Unfortunately, the medical and surgical treatments available for reconstructing the injured spinal cord have lagged behind those available for the spinal column, and there have been no "breakthroughs" in the past 50 years. We can be proud of the many high-quality clinical trials that have occurred including the nine randomized prospective clinical trials (RPCTs) for neuroprotection, although only one RPCT for the surgical management of spinal cord injury. The lack of these "gold standard" RPCTs for surgical treatment of spinal cord injury is disappointing, and some of the blame must rest with the national funding agencies including the National Institutes of Health that have chosen to deny funds for these trials since the last National Acute Spinal Cord Injury Study (NASCIS) trial ended in approximately 1990. Hopefully, this will be rectified in the future because it is essential to conduct RPCTs of important issues such as the timing and effectiveness of acute surgical decompression of the spinal cord. In my view, almost every patient with an acute spinal cord injury should be entered into a formal clinical trial. If we do not do this, individuals writing Forewords to books such as this, 50 years from now will continue to be faced with a lack of knowledge of important issues in this field. For example, the efforts of the Surgical Treatment for Acute Spinal Cord Injury Study (STASCIS) group that I founded several years ago should be supported.

Arun Amar has performed a real service to the practitioners involved in the surgical management of spinal injuries by putting together this excellent group of chapters, and I am optimistic that the knowledge transfer will result in improved patient outcomes.

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# Foreword by Michael L. J. Apuzzo

## Unraveling a Gordian Knot



Jean-Simon Berthélemy: Alexander durchschlägt den gordischen Knoten (Alexander cuts the Gordian Knot)

The surgical discipline of neurosurgery is replete with challenges, many of which have seemed insurmountable in spite of the dramatic progress in neuroscience and clinically meaningful therapies over the past generation of effort. This collection of disorders will be the focus of intense scrutiny over the next generation. They include, among others, the glia tumor spectrum, cerebral vasospasm, and neural injury, which includes those of the spinal cord.

Functional restoration and capability for neural repair remains a "holy grail" for the investigators of the 21st century.[1] However, during our time, we can appreciate remarkable improvement in the general management of these problematical injuries through refinements in initial and more sustained stabilization techniques as well as the development of probes that offer apertures

to understanding that which will eventually allow the unraveling of the Gordian knot of neural injury.

It would seem that issues attendant to comprehending the application of molecular and cellular biology will fuel a true evolution of the concept of cellular and molecular neurosurgery in these matters. Nanotechnology, although now a half-century-old concept, is only in its infancy regarding potential application in matters of injury that involve spinal column and neuronal elements.[2–4]

For the time being, we will be required to provide what is considered an optimum milieu for recovery and the creation of the setting for what might be termed, "natural restoration."[5]

Arun Amar has edited a succinct, but substantive presentation of practical issues attendant to this problem, while providing a review of the promising "seminal" concepts that will allow progress to reach the resolution of the central problem – neural injury.

The content of this volume is essential material for all clinical neuroscientists and an important presentation for all those seeking to develop a grasp of modernity of concept and practical action relating to this problem.

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# Pathogenesis of acute spinal cord injury and theoretical bases of neurological recovery

**Arun Paul Amar**

## Introduction

Experimental models and clinical observations of spinal cord injury (SCI) support the concepts of primary and secondary injury, in which the initial mechanical insult is succeeded by a series of deleterious events that promote progressive tissue damage and ischemia. Whereas the primary injury is fated by the circumstances of the trauma, the outcome of the secondary injury may be amenable to therapeutic modulation. This chapter, derived from a more detailed analysis,[1] reviews the pathogenetic determinants of these two phases of injury and summarizes the bases for interventions that may restore neurological function following SCI.

## Pathogenesis

### Models of SCI

Several experimental systems have been employed to investigate the pathophysiology of SCI and to test the effects of neuroprotective agents in the laboratory. Interest in such models dates as far back as the 2nd century AD, when Galen sectioned the spinal cord of monkeys and other animals in order to conduct studies on differential spinal lesions.[2] Current experimental paradigms involve neuronal cell cultures or anatomically intact segments of spinal cord subjected to various mechanical or ischemic insults such as weight drop, focal or circumferential extradural balloon compression, clip pressure, photochemical or thermal injury, distractional forces, or piston trauma.[3–10] The resultant injury can be assessed by histological examination (e.g. light or electron microscopy, special staining, and tracing methods), electrophysiological outcome measures (e.g. evoked potentials), or behavioral assessments (e.g. open field locomotion or postural stability on an inclined plane).[6,8,9,11]

Such studies are susceptible to a number of inherent flaws in experimental design that impair their ability to simulate human SCI. For instance, the weight drop method only mimics the trauma of initial impact and omits the force of persistent compression. Whereas most humans suffer anterior or circumferential

cord compression from fracture dislocations of a closed vertebral system, most animal models create posterior compression through an open laminectomy.[2] Animal models may not account for neurogenic shock or concomitant injuries that produce systemic hypoxia and hypotension, factors which are known to aggravate the extent of injury resulting from any given mechanical stress.[12] Also, these models often fail to analyze the effects of repetitive mechanical trauma to the spinal cord from an unstable fracture.[6] Furthermore, few animal studies examine the same range of injury severity that is encountered in human trials, in which patients with both complete and incomplete deficits are often randomized to the same treatment group.

Because of differences in drug metabolism, results in animal models often fail confirmation in human trials. Other variations in experimental methodology, such as the type of species being studied, may also play a role. Unlike human trials, animal studies all require the use of anesthesia, which may affect the response to the substance being tested. Conversely, in the clinical setting, humans receive myriad drugs besides the one being studied, and adverse pharmacological interactions may antagonize the efficacy of the agent in question. Furthermore, neuroprotective therapies are often administered in the laboratory more promptly after injury than may be feasible in clinical practice.

As a result of these discrepancies in drug kinetics, the inability to extrapolate the results of animal models to the human condition does not necessarily invalidate the potential utility of the agent being tested. However, these factors contribute to conflicting or irreproducible results in the literature and hinder attempts at constructing a unified theory of pathogenesis and treatment in SCI.[13]

Despite these limitations, laboratory models have proven relevant to human SCI. Developments in the fields of basic neuroscience, including studies of the cerebral cortex and spinal cord, support the theory that the central nervous system (CNS) responds to injury in an archetypal fashion, whether the inciting insult represents trauma, hypoxia, hypoglycemia, epilepsy, various toxins, neurodegenerative disorders, or other pathophysiological processes.[14–20] The concepts of primary and secondary injuries, first advanced over 80 years ago, have emerged as an explanation for this phenomenon of a rehearsed mechanism of neuronal death. According to this paradigm, the initial mechanical insult in SCI is succeeded by a series of deleterious events that promote progressive tissue damage, largely mediated by ischemia and aberrant calcium influx into neurons. While the primary injury is fated by the circumstances of the trauma, the outcome of the secondary injury may be amenable to therapeutic modulation.

## Determinants of primary injury

SCI may follow many types of trauma to the cord itself or to the surrounding vertebral column, and the extent of subsequent damage depends on several biomechanical factors that may be unrelated to the degree of bony fracturing.[21,22] Distractional forces associated with flexion, extension, dislocation, or rotation can all result in stretching or shearing of the neural elements themselves or

spinal cord vasculature, and damage to either substrate could incur clinical deficit.[3,21,22] Other possible mechanical stresses include compression and contusion from bone fragments, ligaments, and hematoma within the spinal canal. These mechanisms may be responsible for cord injury even when the bony alignment appears normal at the time of admission. For instance, momentary dislocation may occur from ligamentous disruption, resulting in transitory cord compression or distraction. These distortions are substantially greater than what is depicted by initial radiographs, since soft tissue elasticity and postural influences tend to initiate spontaneous recoil, and muscle spasm tends to maintain the reduction by the time such radiographs are taken.

These forces may be operant not only acutely, at the moment of injury, but also chronically, secondary to persistent deformity. Mechanical instability can lead to further structural deformations, such as posttraumatic kyphosis or subluxation, which add additional compressive or distractive forces and result in worsening neurological deficit. Kyphosis, for instance, has been shown to cause tension within axonal tracts and constriction of intramedullary blood vessels.[3,21]

For any force applied to the neural elements, the extent of subsequent injury also depends on the relative dimensions of the spinal canal at that level. Whereas larger canals might provide a buffer for any given mechanical stress, stenotic canals lack such reserve. Thus, 53% of fractures of thoracic spine result in neurological injury compared with only 39–47% in the cervical region.[1,23] Similarly, one study revealed a much higher likelihood of complete injury resulting from lesions of the thoracic region (77.5%) than the cervical (60.4%) or thoracolumbar junction (64.7%) regions.[22] This discrepancy probably relates to the narrower canal of the thoracic spine, such that the degree of cord compression tends to be more severe for any given encroachment, as well as the relative paucity of blood flow to the thoracic cord.[21–23] Likewise, Eismont measured the midsagittal canal diameter in patients with fracture dislocations of the cervical spine and found that those with smaller canals were prone to more significant neurological injury, while larger canal diameters afforded a protective effect.[24] Other studies have shown that the relative stenosis incurred by cervical spondylitic disease predisposes to SCI following minor trauma, even in the absence of detectable bony injury.[3,22]

The anatomic location of injury in relation to the conus medullaris also seems to have some prognostic significance. Cauda equina injuries have a better prognosis for neurological recovery than comparable injuries to the spinal cord itself, since lower motor neurons are inherently more resistant to trauma, with fewer mechanisms of secondary injury and greater regenerative capacity than upper motor neurons and their tracts.

## Determinants of secondary injury

In addition to local forces that potentially compromise spinal cord function, systemic pulmonary and cardiac factors that determine tissue oxygenation and perfusion can profoundly modulate the extent of injury resulting from

any given mechanical stress.[12] Taken together, these considerations of local and systemic influences imply that ischemia underlies much of the mechanism of posttraumatic SCI. While other pathological processes such as edema, intramedullary hemorrhage, axonal degeneration, or demyelination may also play a role, these all have an integral relationship with impaired cord perfusion and bioenergetic failure at the cellular level. Experimental models employing the basic mechanisms of both compression and distraction have confirmed that SCI is associated with long-lasting ischemia that parallels the force of the experimental insult and the severity of the clinical deficit.[3,9,10,25,26] The ischemia is worse in the gray matter and may extend focally for considerable distances rostral and caudal to the injured segment.[3,8,9,12,25,26] The impaired perfusion may be followed by a phase of "hyperemia" or "luxury perfusion" due to the reduction of perivascular pH from accumulation of acid metabolites such as lactate.[26] This tissue reperfusion may increase cellular damage by promoting the influx of free radicals and other toxic byproducts.[18]

The intrinsic mechanisms occurring during SCI have been well documented and are schematically diagrammed in Figure 1.1.[1] In the initial phase, petechial hemorrhages develop within the spinal cord substance due to rupture of postcapillary venules or sulcal arterioles, either from mechanical disruption by the inciting force itself or from intravascular coagulation due to fibrin and platelet thrombi leading to venous stasis and distension.[8,10,12,21,27] Leakage of proteinaceous fluid from the intrinsic vessels of the cord then leads to edema at the injury site and surrounding tissues.[8,26] Because the spinal cord is contained within a relatively inelastic pial membrane, edema produces increased interstitial pressure that may diminish local spinal cord blood flow.[2] Vasoactive substances released by injured cells, including endothelin released from damaged capillaries, and other mechanical, biochemical, or neurogenic mechanisms may also play a role in impairing cord perfusion.[8,12,26–28] Focal narrowing, disruption, aneurysmal dilation, or occlusion of sulcal arterioles and intramedullary capillaries have all been demonstrated with the use of microangiographic techniques and three-dimensional vascular corrosion casts.[27,28] These changes may represent the morphological correlates of microvascular spasm, thrombosis, and rupture that underlie regional impairments in spinal cord perfusion. This focal ischemia is compounded by hypotension or hypoxia, since autoregulation is lost in SCI and spinal cord blood flow passively follows alterations in systemic hemodynamics.[8,9,12,21,26]

Ischemia initiates a cascade of secondary pathogenetic mechanisms collectively known as excitotoxicity because of their dependence on endogenous excitatory amino acid (EAA).[15,20] Ischemia depletes the supply of adenosine triphosphate (ATP), leading to dysfunction of energy-dependent processes such as the sodium–potassium pump that preserves cellular homeostasis. Ionic species then move passively across the cell membrane according to concentration gradients previously maintained between the intracellular and extracellular spaces, leading to a net efflux of potassium and a large influx of sodium, chloride, and calcium into the cell. Acute cellular swelling results. Furthermore,
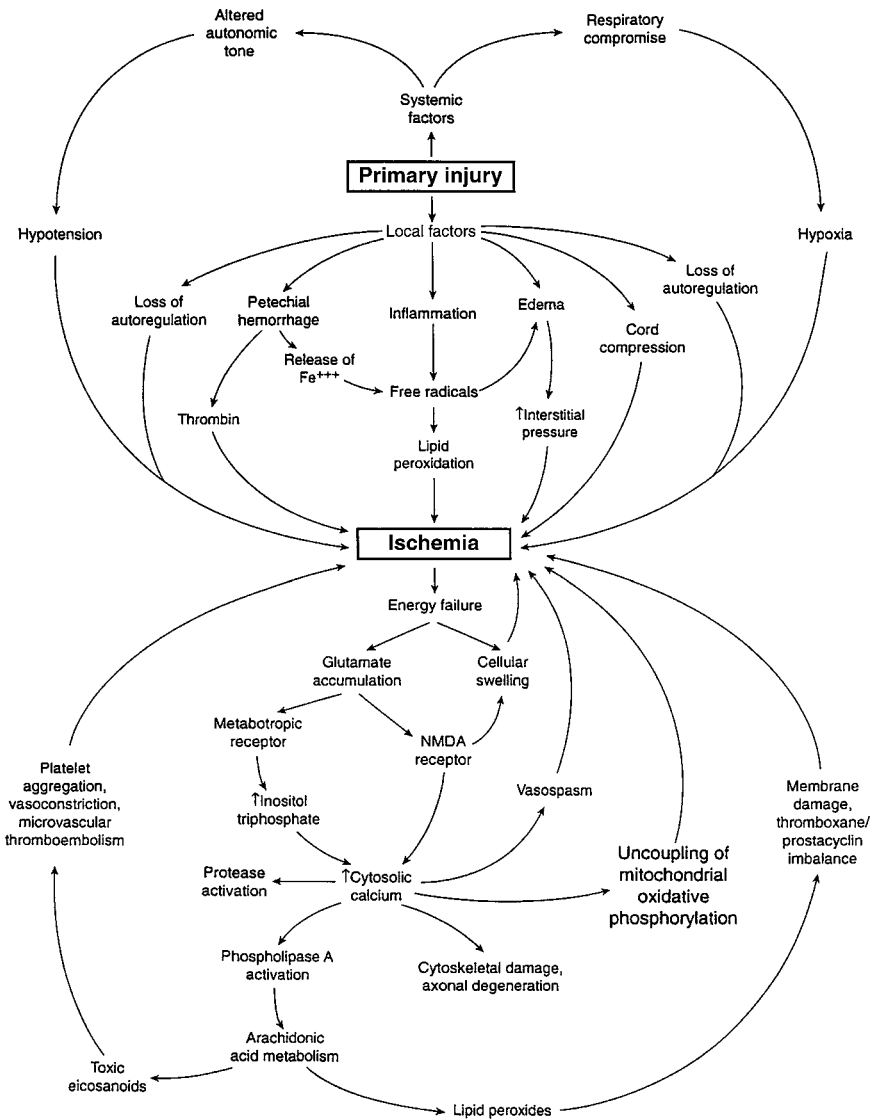
**Figure 1.1**  Schematic representation of key mechanisms, molecular species, and interrelationships underlying the pathogenesis of acute SCI. Principal pathways of secondary injury that converge upon ischemia are emphasized, while others have been omitted for simplicity. These pathogenetic determinants represent the logical targets for therapeutic modulation (reprinted with permission from Ref. [1]).

the altered composition of the extracellular and intracellular spaces leads to changes in membrane polarization that promote the release of EAA neurotransmitters such as glutamate and aspartate from synaptic vesicles. This release is compounded by impaired cellular uptake mechanisms in neurons and glia,

which depend on the presence of high-energy phosphates and are inactivated by the ATP depletion accompanying hypoxia.[14,29,30] As a result of these two mechanisms, the local concentration of glutamate in the extracellular space can increase by a factor of eight following an ischemic insult.[14,30]

Extracellular accumulation of glutamate may also occur through non-ischemic mechanisms. The intracellular glutamate concentration in brain tissue is approximately 10 mmol/l, while its extracellular concentration is normally only 0.6 μmol/l.[18] Excitotoxic damage to neurons can occur when the latter concentration reaches 2–5 μmol/l.[18] Thus, ambient glutamate concentrations are precariously close to those that can destroy neurons, and the injury of even a single cell from direct traumatic mechanisms could produce a local accumulation of glutamate that places neighboring cells at risk for excitotoxic damage.[18] Although the glutamate concentrations within the spinal cord are less well documented, they may approximate those found in the brain. Glutamate receptors have been demonstrated in both the dorsal and ventral horns, and many pathways mediating locomotion and nociception, including the corticospinal and rubrospinal tracts, appear to rely on EAA neurotransmitters.[31] Extracellular EAA concentrations within the spinal cord have been shown to reach toxic levels 15 min after experimental SCI.[31]

Glutamate may act upon several families of receptors, each with distinct pharmacological and electrophysiological properties.[18,20,29] These receptor classes are named for the agonist compounds that selectively activate them. Some of these receptors, such as the N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA), and kainate receptors, are collectively termed "ionotropic" because they comprise ligand-gated ion channels. Others are termed "metabotropic" and comprise transmembrane proteins coupled with changes in the concentration of intracellular second messengers such as cyclic nucleotides or phosphoinositol through GTP-binding proteins.

Although activation of the AMPA and kainate receptors results primarily in the influx of sodium from the extracellular space, some subtypes may be permeable to calcium as well. In contrast, the NMDA receptor principally mediates calcium entry. The NMDA receptor contains a binding site for glycine, which acts as an obligate co-agonist. Furthermore, at resting membrane potential, inward current through the NMDA receptor is prevented by voltage-dependent blockade of its ion channel by magnesium, even if the glutamate and glycine sites are occupied. However, the degree of this magnesium blockade is reduced as the neuron becomes depolarized. Thus, any process which impairs the neuron's ability to maintain its normal membrane potential, such as bioenergetic defects or simultaneous activation of the AMPA receptor, can lead to electrophysiological decoupling that causes additional calcium influx through the NMDA receptor, even in the face of ambient glutamate concentrations. Membrane depolarization also promotes calcium entry through activation of voltage-dependent calcium channels. Finally, glutamate can trigger the accumulation of intracellular calcium through activation of metabotropic receptors, leading to the metabolism of inositol phospholipids and mobilization

of intracellular calcium stores as well as inactivation of energy-dependent calcium transporters that pump cytosolic calcium across the cell membrane or sequester it within intracellular compartments such as the mitochondria and endoplasmic reticulum.[14,18–20,29]

These aberrant calcium fluxes trigger a myriad of calcium-dependent processes, such as activation of phospholipase A2, mobilization of free fatty acids, synthesis of toxic eicosanoids, generation of free radicals, further depletion of energy reserves through activation of calcium-dependent ATPase, covalent modification of receptor proteins, modification of the microtubular and neurofilament components of the cytoskeleton, impairment of mitochondrial oxidative phosphorylation, axonal degeneration, and activation of lytic enzymes such as proteases, phosphatases, and endonucleases.[14,18–20,25] This sustained elevation of cytosolic calcium concentration is postulated to be the final common pathway mediating cell death in many tissue types.[14–16,18–20]

Potentiating factors in this sequence of events include increased phospholipase activity, either from direct mechanical stimulation or from mobilization of calcium, resulting in the liberation of free arachidonic acid from membrane phospholipids.[25,32] This substrate is rapidly metabolized by cyclo-oxygenase to prostanoids such as thromboxane and prostacyclin. Thromboxane stimulates platelet adherence to endothelium, intravascular platelet aggregation, microvascular occlusion, vascular stasis, microvascular thromboembolism, and vasoconstriction; prostacyclin has the opposite effects on the microcirculation. Other byproducts of the cyclo-oxygenase pathway include free radicals such as lipid peroxides. These latter molecules selectively inhibit prostacyclin production, and the resultant thromboxane–prostacyclin imbalance contributes to an environment favoring thromboembolism and a tendency toward further ischemia.[25,32]

In addition to altering the ratio between thromboxane and prostacyclin production, lipid peroxides interact with polyunsaturated fatty acid components of the cell membrane to cause a chain reaction of phospholipid peroxidation that compromises the structural and functional integrity of the cell membrane and, ultimately, produces cell death.[25,33] Free radicals may also directly damage the nervous tissue's vascular integrity, cellular proteins, and nucleic acids. Besides cyclo-oxygenase, other enzymatic sources of free radicals include xanthine oxidase, which catalyzes production of the superoxide anion and hydrogen peroxide in response to CNS ischemia.[34] Because this enzyme is located primarily in the endothelial cells, the oxygen-derived free radicals induced by the xanthine oxidase system act primarily at the capillary level, altering vascular permeability and worsening posttraumatic edema.[34] Reactive iron species contained within the hemoglobin of extravasated blood may also act as a catalyst of free radical formation and lipid peroxidation reactions.[2] The subsequent release of these substances into the local environment as the cellular and vascular barriers disintegrate can impair neighboring cells and result in progression of deficit.

One limitation of this paradigm is that the excitotoxic model cannot directly account for injury to the white matter and glial elements of the CNS. Although

ischemic damage is commonly observed in this tissue, most studies have failed to demonstrate that axons, myelin, astrocytes, and oligodendrocytes are endowed with NMDA receptors or are vulnerable to glutamate administration.[29] However, the concept of a "bad neighborhood" resulting from the local accumulation of lytic enzymes, free radicals, and other toxic factors derived from glutamate-mediated injury in adjacent neuronal tissue may explain the pervasive effects of focal CNS ischemia.[15,25] Furthermore, some studies suggest that periaxonal astrocytes may express certain subtypes of the AMPA and kainate receptors on their surface, thus implicating these cells in glutaminergic white matter injury.[35]

In the ensuing phases of SCI, inflammation and demyelination prevail. Two waves of peripheral leukocytic influx occur. In the early peak, neutrophils predominate, and their lytic enzymes may further damage vascular, neuronal, and glial cell populations.[2] Later, macrophages participate in the phagocytosis of hemorrhagic and necrotic tissue. Both phases of inflammation have been implicated in the demyelination of spared axons, which starts within the first 24 h after injury and increases over the next several days.[2] Well-demarcated areas of cavitation within the gray and white matter, extensive Wallerian degeneration, and scarring represent the final stages of histopathological evolution.[2] Although this scar is predominantly comprised of astroctyes and other glia, fibroblasts also make a significant contribution.

## Theoretical bases of neurological recovery

Although the propensity for neurological improvement following both complete and incomplete SCI has been verified by experimental models and clinical observations, the biological basis of such recovery remains enigmatic. As Tator has suggested, functional restoration probably involves a combination of several different processes acting upon numerous anatomical substrates, including nerve roots at the level of injury, gray and white matter, and spinal cord vasculature.[11] Neural regeneration, the regrowth of lesioned neural elements with the restoration of functional synaptic connections, may account for late recovery occurring months to years after injury.

### Root recovery

Several studies have confirmed that the peripheral nervous system is more resistant to injury and has a greater capacity for repair than the CNS.[2,11] This resilience is manifested by the frequency with which improved nerve root function is detected among patients with acute SCI. Re-establishment of segmental function at the site of injury, reflecting recovery in one or more nerve roots at that level, may restore innervation to particular muscle groups, organs or dermatomes, although motor roots generally have increased vulnerability to injury and decreased capacity for recovery than sensory roots.[11] Root recovery is expected in both complete and incomplete lesions in 66–90% of patients.[36] However, the greatest proportion of total neurological recovery occurs caudal

to the level of injury, reflecting improvements in the function of long spinal tracts themselves.

## Resolution of cord ischemia

Surrounding the zone of irreparable ischemic damage is a penumbra of hypoxic tissue, whose cells may remain viable, even while lacking the capacity to maintain normal neuronal function. This tissue may be marginally supported by collateral circulation. If the ischemia exceeds a critical level, or persists beyond a certain threshold of time, irreversible damage will ensue and the zone of infarction will extend. If, however, blood flow can be restored before the onset of permanent injury, normal physiological function may be re-established.

Salvage of the ischemic penumbra can result from both medical and surgical interventions. Autopsy reports have shown that in most cases of SCI, including complete injuries, the cord remains anatomically intact.[2,9] Furthermore, animal studies of SCI suggest that preservation of a small proportion of spinal axons can support neurological recovery.[2,10,37] In a rat model, for instance, persistence of only 12% of the normal number of axons following clip compression injury conferred substantial maintenance of inclined plane performance and open field walking.[5] Thus, any manipulation that increases the fraction of functional axons traversing the injury site above this threshold, or that enhances the response of lower motor neurons to the attenuated input from those axons, can have a significant impact on neurological recovery.[10,37] Alternatively, since injured vasculature of the CNS tends to lose its autoregulatory response to hypertension, spinal cord blood flow could be increased passively by improving systemic hemodynamic parameters or selective infusion of CNS vasodilators.[8,12,26]

The central gray matter of the spinal cord is inherently more susceptible to trauma because it has higher metabolic activity and because it contains neuronal bodies whose machinery for biomolecular repair may be directly damaged. In contrast, the circumferential white matter tracts at the site of injury have a lower metabolic rate and have intact cell bodies that are distant from the locus of injury.[37] Thus, delayed pharmacological and physiological interventions are more likely to restore function to the white matter elements of the cord. Metabolic factors may also underlie the fact that motor tracts have increased vulnerability to injury and decreased propensity for recovery than sensory ones.[11]

## Resolution of other injury events

Abnormalities of membrane polarization and excitability may accompany acute SCI. These changes in ionic equilibrium could result from the leakage of potassium into the interstitial fluid or from alterations in sodium permeability across the axolemma.[38,39] Such electrolyte shifts might underlie the early neuronal dysfunction associated with spinal shock and may account for the immediate inability to conduct action potentials across the injury segment.[38,39]