

## Acute Spinal Cord Injury, Part I: Pathophysiologic Mechanisms

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**Summary:** Spinal cord injury (SCI) is a devastating and common neurologic disorder that has profound influences on modern society from physical, psychosocial, and socioeconomic perspectives. Accordingly, the present decade has been labeled the Decade of the Spine to emphasize the importance of SCI and other spinal disorders. Spinal cord injury may be divided into both primary and secondary mechanisms of injury. The primary injury, in large part, determines a given patient's neurologic grade on admission and thereby is the strongest prognostic indicator. However, secondary mechanisms of injury can exacerbate damage and limit restorative processes, and hence, contribute to overall morbidity and mortality. A burgeoning body of evidence has facilitated our understanding of these secondary mechanisms of injury that are amenable to pharmacological interventions, unlike the primary injury itself. Secondary mechanisms of injury encompass an array of perturbances and include neurogenic shock, vascular insults such as hemorrhage and ischemia–reperfusion, excitotoxicity, calcium-mediated secondary injury and fluid–electrolyte disturbances, immunologic injury, apoptosis, disturbances in mitochondrion function, and other miscellaneous processes. Comprehension of secondary mechanisms of injury serves as a basis for the development and application of targeted pharmacological strategies to confer neuroprotection and restoration while mitigating ongoing neural injury. The first article in this series will comprehensively review the pathophysiology of SCI while emphasizing those mechanisms for which pharmacologic therapy has been developed, and the second article reviews the pharmacologic interventions for SCI. **Key Words:** Spinal cord injury—Secondary injury—Pathophysiologic mechanisms

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Spinal cord injury (SCI) may be defined as an injury resulting from an insult inflicted on the spinal cord that compromises, either completely or incompletely, its major functions (motor, sensory, autonomic, and reflex). Spinal cord injury remains an important cause of morbidity and mortality in modern society. An estimated 8,000–10,000 people experience traumatic SCI in the United States each year (1–6). In addition to its cost to the individual physically as well as the health care system and society financially, SCI has profound psychosocial effects that are devastating for patients, families, and friends.

A basic understanding of the pathophysiological

mechanisms underlying spinal cord injury is of paramount importance to facilitate comprehension of pharmacological interventions. These pharmacological strategies are largely targeted at attenuating or eliminating the effects of secondary injury mechanisms. Additionally, an appreciation of these pathophysiologic mechanisms in SCI has further relevance, because many, if not all, of these processes are common to other insults of the central nervous system such as head injury, cerebral ischemia, and subarachnoid hemorrhage (7–9).

The pathophysiology of acute SCI comprises both primary and secondary mechanisms of injury. The prognosis for recovery after SCI has been closely examined (10–18). The extent of the primary injury may group patients with SCI into severity categories (neurologic grades). A patient's neurologic grade at admis-

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sion to the hospital has proven to be the strongest prognostic indicator. Nonetheless, for a large majority of patients with SCI, the extent of secondary injury evokes further damage, limits restorative processes, and predicts their long-term morbidity. Therefore, a full understanding of secondary injury mechanisms in SCI facilitates the development of targeted interventions. In the following passages, pathophysiologic mechanisms of spinal cord injury are reviewed, with special attention to secondary injuries against which pharmacologic therapies have been postulated and applied.

### PRIMARY INJURY

There are four characteristic mechanisms of primary injury: (i) impact plus persistent compression; (ii) impact alone with transient compression; (iii) distraction; and (iv) laceration/transection. The first and most common mechanism involves impact plus persistent compression (9,19). This is evident in burst fractures with retropulsed bone fragment(s) compressing the cord, fracture-dislocations, and acute disc ruptures. The second mechanism involves impact alone with only transient compressions as observed with hyperextension injuries in individuals with underlying degenerative cervical spine disease. Distraction, forcible stretching of the spinal column in the axial plane, provides a third mechanism and becomes apparent when distraction forces resulting from flexion, extension, rotation, or dislocation produce shearing or stretching of the spinal cord and/or its blood supply. This type of injury may underlie SCI without radiological abnormality, especially in children where cartilaginous vertebral bodies, underdeveloped musculature, and ligament laxity are predisposing factors (20). This type of injury may also be a causative factor in SCI without radiologic evidence of trauma, which is a syndrome most common in adults with underlying degenerative spine disease (9). Laceration and transection comprise the final primary mechanism of injury. Laceration of the spinal cord may result from missile injury, sharp bone fragment dislocation, or severe distraction. Laceration may occur to varying degrees, from minor injury to complete transection. Thus, primary mechanisms of injury include impact plus persistent compression, impact alone with only transient compression, distraction, and laceration/transection.

The initial mechanical insult tends to damage primarily the central gray matter, with relative sparing of the white matter, especially peripherally. This increased propensity for damage to the gray matter has been speculated to be a result of its softer consistency and greater vascularity (21). Evidence of hemorrhage

within the spinal cord develops early, and blood flow within the spinal cord is later disrupted after the initial mechanical injury. Disruption in blood flow results in local infarction caused by hypoxia and ischemia. This is particularly damaging to the gray matter because of its high metabolic requirement. Neurons that pass through the injury site are physically disrupted and exhibit diminished myelin thickness (22). Nerve transmission may be further disrupted by microhemorrhages or edema near the injury site (23–25). It is thought that the gray matter is irreversibly damaged within the first hour after injury, whereas the white matter is irreversibly damaged within 72 hours after injury.(26)

### SECONDARY INJURY

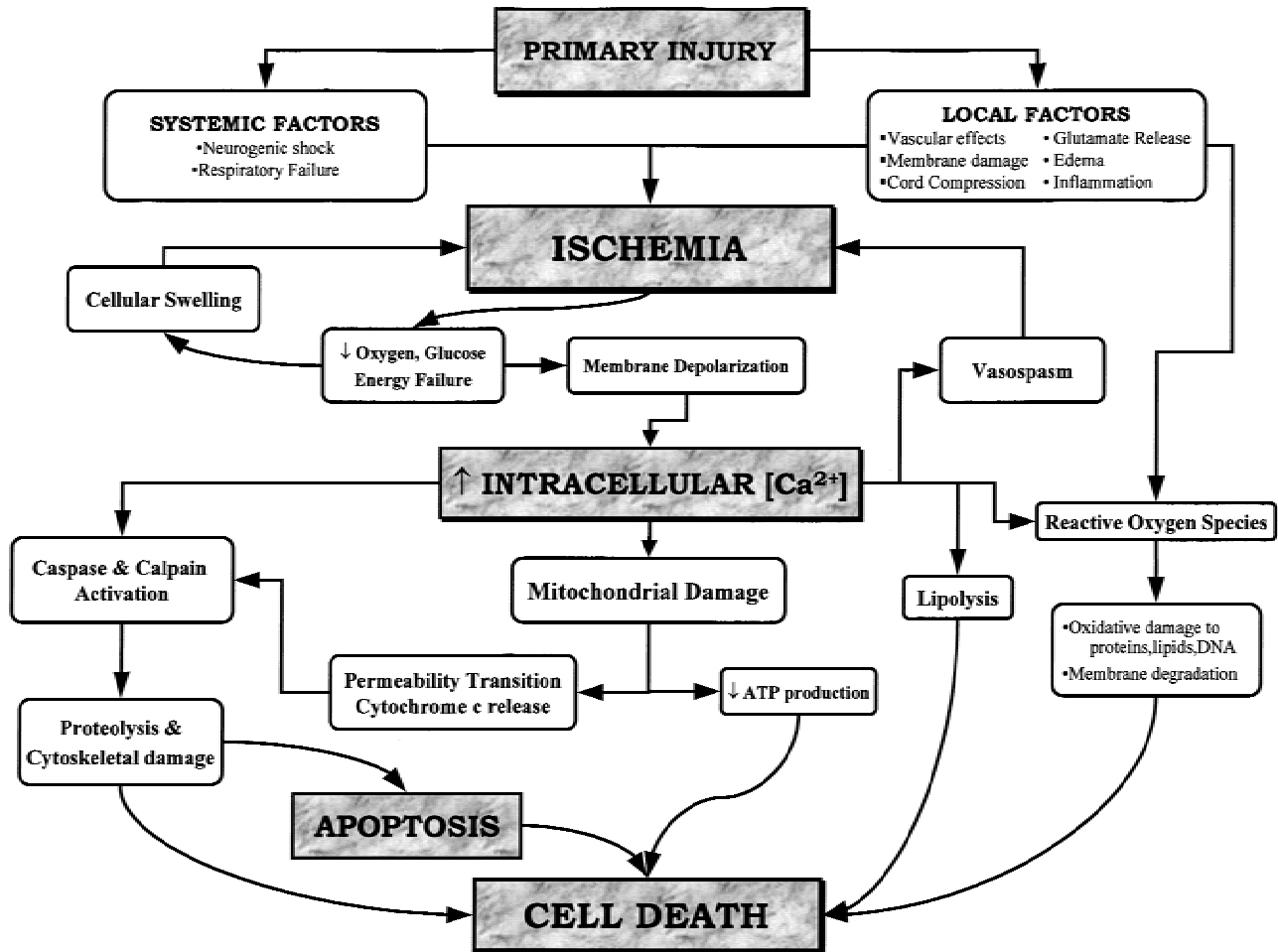
The primary mechanical injury serves as the nidus from which additional secondary mechanisms of injury extend. These secondary mechanisms include neurogenic shock, vascular insults such as hemorrhage and ischemia–reperfusion, excitotoxicity, calcium-mediated secondary injury and fluid-electrolyte disturbances, immunologic injury, apoptosis, disturbances in mitochondrion function, and other miscellaneous processes (Figs. 1, 2).

#### Neurogenic Shock

Spinal cord injury may result in neurogenic shock. Although there are several interpretations of this term, it is defined in this context as inadequate tissue perfusion caused by serious paralysis of vasomotor input (thereby producing deleterious disruption of the balance of vasodilator and vasoconstrictor influences to the arterioles and venules). It is characterized by bradycardia and hypotension with decreased peripheral resistance and depressed cardiac output (27). These effects have been linked to underlying abnormalities such as decreased sympathetic tone, depressed myocardial function from increased vagal tone, and possibly secondary changes in the heart itself (27,28). If untreated, the systemic effects of neurogenic shock (namely, ischemia of the spinal cord and other organs) may exacerbate neural tissue damage.

#### Vascular Insults: Hemorrhage and Ischemia–Reperfusion

As alluded to previously, vascular insult has deleterious effects on the spinal cord, both initially at the time of injury and subsequent to this. These vascular injuries produce both hemorrhagic and ischemic damage. The microcirculation, especially venules and capillaries,



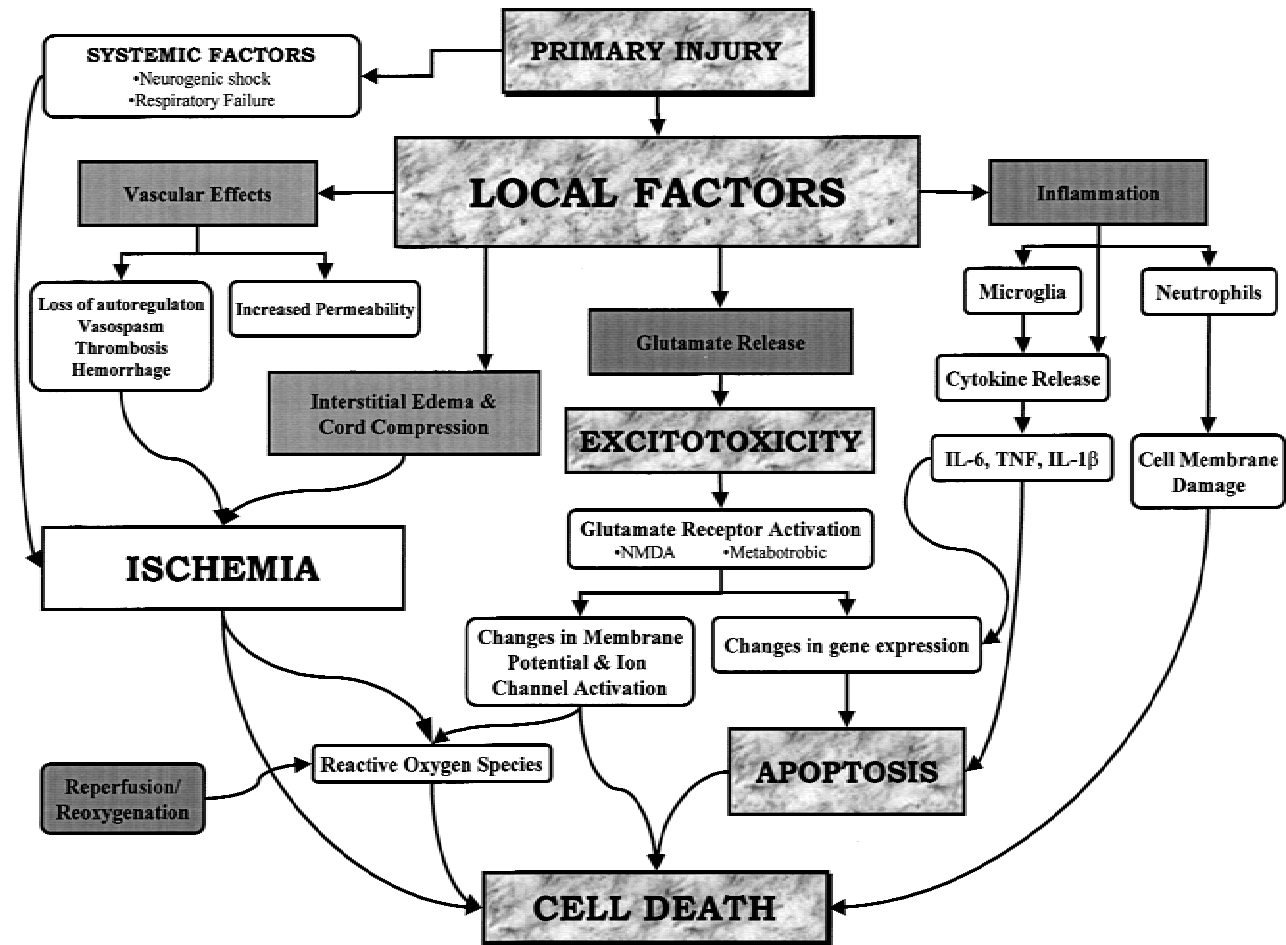
**FIG. 1.** The mechanisms underlying injury after spinal cord trauma are depicted, emphasizing the central importance of ischemia, increased intracellular calcium, and apoptosis in cell death. Each of these boxes represents potential avenues for pharmacologic intervention.

appears to be damaged at the site of injury and for some distance rostrally and caudally because of initial mechanical trauma. There appears to be a relative sparing of larger vessels such as the anterior spinal artery from direct mechanical injury (29–33). This damage results in small areas of hemorrhage, or petechiae, that progress to hemorrhagic necrosis with time.

Numerous experimental studies have documented a progressive “posttraumatic ischemia” as measured by various methods of spinal cord blood flow determination (32,33). Vasospasm resulting from direct trauma and possibly some other inciting agent(s) (32,33) has been demonstrated to occur (30,31). Additionally, intravascular thrombosis may also contribute to this posttraumatic ischemia (34,35). Other investigators have noted abnormalities in autoregulatory homeostasis (*i.e.*, a decreased ability to maintain constant blood flow over a wide range of pressures) that may worsen ischemia resulting from systemic hypoperfusion (neurogenic shock) or may worsen hemorrhage with gross

elevations in systemic blood pressure (9). Therefore, vascular insult in SCI results in hemorrhage, likely from underlying mechanical disruption of vessels and loss of microcirculation and disruption of autoregulation. Ischemia is also a product of this vascular insult and is likely secondary to diminished blood flow from thrombosis, vasospasm, and loss of microcirculation or systemic hypoperfusion with loss of autoregulatory homeostasis.

The stage of reduced perfusion discussed above may precede a period of hyperemia or “luxury perfusion”. This is postulated to arise from a reduction in perivascular pH from accumulation of acidic metabolites such as lactate (36). Such reperfusion may exacerbate injury and cellular death through the genesis of deleterious free radicals and other toxic byproducts (37,38). Oxygen-derived free radicals (including superoxide, hydroxyl radicals, and nitric oxide and other high-energy oxidants (including peroxynitrite) are produced during ischemia (39–52) with a most pronounced rise during



**FIG. 2.** The mechanisms underlying spinal cord injury are illustrated, with emphasis on the role of local influences. The role of vascular disturbances, interstitial edema and cord compression, glutamate release, and inflammation are demonstrated. These boxes represent foci that may be particularly amenable to pharmacologic modulation.

the early reperfusion period (47–49,52–55). These highly reactive oxygen and nitrogen species contribute to oxidative stress, a pathological mechanism that contributes to the secondary injury of spinal cord trauma. They are generated via multiple cellular pathways including nitric oxide synthases, calcium-mediated activation of phospholipases, xanthine oxidase, inflammatory cells, and the Fenton and Haber-Weiss reactions (37). When oxidative stress exceeds the protective cellular antioxidant capacity, as can be the case in neurotrauma, the net production of these reactive molecules subsequently gives rise to oxidation of proteins, lipids, and nucleic acids (37,43). More specifically, such molecules mediate the inactivation of mitochondrial respiratory chain enzymes, inactivation of glyceraldehyde-3-phosphate dehydrogenase, inhibition of  $\text{Na}^+\text{-K}^+$  ATPase, inactivation of sodium membrane channels, and other oxidative perturbations of key proteins, in addition to initiation of lipid peroxidation and its deleterious sequelae. Oxidative stress has commonalities with other pathogenic mechanisms imparting injury

from spinal cord trauma. It has been linked to calcium overload, mitochondrial cytochrome c release, caspase activation, apoptosis, and excitotoxicity (43). In summary, it is clear that oxidative stress resulting from the generation of reactive oxygen and nitrogen molecules contributes to SCI and is intimately related to other mediators of secondary injury.

### Excitotoxicity

Biochemical derangements and concomitant fluid–electrolyte disturbances appear to assume a central role as a secondary mechanism of injury in acute SCI. Excitatory neurotransmitters are released and accumulate (56), and this has been hypothesized to produce direct damage to spinal cord tissue (57–59) in addition to indirect damage from production of reactive oxygen and nitrogen species and from alterations in microcirculatory function and secondary ischemia. Glutamate, the major excitatory neurotransmitter of the central nervous system (CNS) (60), is released excessively after

injury. This accumulation may result in direct and indirect damage as described above. However, others have asserted that glutamate cell receptor activation (especially activation of the *N*-methyl-D-aspartate [NMDA] and AMPA-kainate ( $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionate-kainate) receptor subtypes (61,62) may be critical in the production of ischemic damage (28). Olney (63) introduced the term "excitotoxicity" to describe those processes resulting from excessive activation of glutamate receptors leading to neuronal injury. Excitotoxicity has assumed a central position in the description of mechanisms of CNS injury. Glutamate receptor activation appears to result in early accumulation of intracellular sodium (64), producing subsequent cytotoxic edema and intracellular acidosis. Failure of the  $\text{Na}^+\text{-K}^+$  ATPase may further exacerbate the intracellular accumulation of sodium and water and the extracellular loss of potassium (65). Additionally, intracellular calcium accumulates [in part, through activation of the  $\text{Na}^+\text{-Ca}^{2+}$  exchanger (66)] which, in turn, produces profound alterations in physiology and subsequent damage. In fact, accumulation of intracellular calcium has been denoted the "final common pathway of toxic cell death" in the CNS (67,68). Glutamate neurotoxicity is also mediated by the generation of reactive oxygen and nitrogen species. Excitotoxicity, particularly mediated by the NMDA receptor, initiates a complex cascade of events that ultimately results in the genesis of reactive molecules that contribute to neuronal death through a variety of mechanisms including initiation of lipid peroxidation, inhibition of  $\text{Na}^+\text{-K}^+$  ATPase activity, inactivation of membrane sodium channels, direct inhibition of mitochondrial respiratory chain enzymes, inactivation of glyceraldehyde-3-phosphate dehydrogenase, and other oxidative modifications of important proteins (37,69–77).

### Calcium-Mediated Secondary Injury and Fluid–Electrolyte Disturbances

High intracellular calcium concentrations contribute to secondary damage through various mechanisms. One of these mechanisms entails interference with mitochondrial function (78,79). This interference inhibits cellular respiration, which has already been impaired by the hypoxia and ischemia secondary to the initial injury. Increased intracellular calcium also stimulates an array of calcium-dependent proteases and lipases, such as calpains, phospholipase A2, lipoxygenase, and cyclooxygenase (1). Calpain activity and expression is increased in activated glial and inflammatory cells in the penumbra of SCI lesions in experimental SCI (80). Calpains can degrade important structural constitu-

ents in the CNS including structural proteins of the axon–myelin unit (80). Additionally, other calcium-dependent proteases and kinases destroy cell membranes and result in dissolution of certain components of the cell ultrastructure such as neurofilaments. Lipase, lipoxygenase, and cyclooxygenase activation results in the conversion of arachidonic acid into certain thromboxanes, prostaglandins, and leukotrienes, and increased levels of these metabolites may occur in association with spinal cord trauma within minutes of injury (81–83). There also appears to be a delayed rise in arachidonic acid approximately 24 hours after injury that is associated with inhibition of the  $\text{Na}^+\text{-K}^+$  ATPase and tissue edema (84). There appears to be a persistent accumulation of cyclooxygenase-1 (COX-1) expressing microglia/macrophages and upregulation of COX-1 expression by the endothelium after experimental SCI (85). These substances produced by the conversion of arachidonic acid contribute to reduced blood flow by causing platelet aggregation and vasoconstriction (78). They can also contribute to an inflammatory response and lipid peroxidation. In addition to the obvious damage to cellular membranes, lipid peroxidation results in a repetitive cycle that involves the production of free radicals. These radicals continue to damage membranes, resulting in further lipid peroxidation and free radical formation. This cycle continues unless stopped by endogenous antioxidants such as  $\alpha$ -tocopherol (vitamin E) and superoxide dismutase (78).

Cyclooxygenase-2 (COX-2) has been studied recently as a putative contributor to secondary injury. Cyclooxygenase-2 mRNA and protein expression is induced after experimental SCI (86). It may represent a common substrate linking membrane damage and excitotoxicity in SCI. It is well known that  $\text{Ca}^{2+}$  influx can elicit activation of membrane-associated phospholipases and the liberation of arachidonic acid. Increased extracellular excitatory neurotransmitters evoke neuronal activation and results in the induction of COX-2 expression in cortical neurons (87). Consequently, neuronal death may result by direct toxicity. Indeed, selective inhibition of COX-2 improves outcome after spinal cord insult in preliminary animal investigation (25,86).

Electrolyte changes, such as the accumulation of intracellular sodium and calcium, have been outlined above. Increased extracellular potassium appears to result in excessive depolarization of neurons, which adversely affects neuronal conduction and may, in fact, be the critical causative factor underlying spinal shock (88). Another electrolyte disturbance that has received less attention is magnesium depletion. Depletion of intracellular magnesium can have a deleterious effect on metabolic processes such as glycolysis, oxidative phos-

phorylation, and protein synthesis, as well as adversely affecting certain enzymatic reactions in which magnesium serves as a cofactor. Magnesium depletion can also further contribute to intracellular calcium accumulation and the associated pathophysiological processes outlined above (78). Magnesium is thought to also protect neuronal cells by blocking the NMDA receptor of the excitatory amino acid neurotransmitter ion channel, thereby theoretically diminishing excitotoxicity (8). Additionally, magnesium can modulate the binding of endogenous opioids and may alter the resulting aberrations in physiology (89).

### Immunologic Secondary Injury

SCI also evokes changes in activity of certain cells of the CNS. Some classes of glial cells help to maintain homeostasis in the CNS by various mechanisms including regulation of excitatory amino acid levels and pH. After SCI, regulation of homeostasis by these glial cells fails, possibly contributing to tissue acidosis and the excitotoxic process (90). Other glial cells may release certain compounds that can affect neural outgrowth. These compounds include neurotrophic growth factors that can reestablish the disrupted neuronal network by stimulating the reactive sprouting of spared neurons (91) and inhibitory factors that can counteract this activity. Still other glial cells, which function in removing cellular debris after CNS injury, have increased activity of certain oxidative and lysosomal enzymes that can cause further cellular damage (90).

There is a biphasic leukocyte response after trauma to the spinal cord. Initially, infiltration of neutrophils predominates. The subsequent release of lytic enzymes by these leukocytes may exacerbate injury to neurons, glia, and blood vessels (92). The second phase involves the recruitment and migration of macrophages, which phagocytose damaged tissue.

There are data to suggest that immunologic activation promotes progressive tissue injury and/or inhibits neural regeneration after injury to the CNS. However, the functional significance of some immune cells within the lesioned spinal cord is controversial (93). Macrophages and microglia have been regarded as integral components of neural regeneration, whereas others propose that these cells contribute to oligodendrocyte lysis (by a process involving tumor necrosis factor- $\alpha$  and nitric oxide production) (94), neuronal death, and demyelination (8). It has been shown that direct contusion to the spinal cord results in sensitization of the host immune system to a component of CNS myelin (93). It is postulated that the two aforementioned phases of leukocyte infiltration (and the pathophysiological processes that accompany this) contribute to

the demyelination of spared axons beginning within the first 24 hours after the primary insult and peaking during the next several days (92). This process contributes to discernible areas of cavitation within the gray and white matter. Wallerian degeneration also becomes apparent and scarring subsequently ensues. Scarring is primarily mediated by astrocytes and other glia in addition to fibroblasts (92).

Given this preamble, processes underlying recruitment of leukocytes to the site of injury is particularly relevant from a putative therapeutic standpoint. Recruitment of immune cells to the injured CNS is orchestrated by multiple families of proteins. One such mediator is intercellular adhesion molecule 1 (ICAM-1). ICAM-1 contributes to immune responses by promoting infiltration of neutrophils into tissues. However, its role in the secondary damage after acute SCI has not been well defined. ICAM-1 involvement in secondary injury after SCI is implicated by the demonstration that a specific monoclonal antibody against ICAM-1 significantly suppressed myeloperoxidase activity, reduced spinal cord edema, and also improved spinal cord blood flow (95). Further evidence supporting a contribution of ICAM-1 in secondary SCI is raised by experiments involving ICAM-knockout mice. In these studies, neutrophil recruitment is reduced (96) and motor function recovery is enhanced after spinal cord contusional injury (97). Other important mediators of immune cell recruitment, and thus further targets for intervention in treating secondary injury in SCI, include other adhesion molecules such as P-selectin, and cytokines including interleukin-1 $\beta$ , interleukin-6, and tumor necrosis factor (97–99). Importantly, interleukin-10 has been shown to reduce production of tumor necrosis factor and thereby exert an inhibitory influence on activation of monocytes and other immune cells after SCI (100,101). Other chemotactic agents such as chemokines and their receptors are upregulated after SCI and contribute to cellular infiltration and secondary injury (102). Chemokine antagonism therefore may represent another area for intervention to reduce the inflammatory response and its associated deleterious effects (102). Another intriguing line of investigation has demonstrated that traumatic SCI induces nuclear factor-kappaB activation (103). Nuclear factor-kappaB represents a family of transcription factors that are required for the transcriptional activation of a variety of genes regulating inflammatory, proliferative, and cell death responses of cells (103). Further elucidation of the precise immune mechanisms and their relative contributions to secondary injury after SCI is warranted. Modulation of the immune response elicited by SCI is important as a potential therapeutic target in attenuating secondary injury.

### Apoptosis

In recent years, programmed pathways of neuronal death have been implicated in the pathobiology of multiple neurologic disorders including SCI. Apoptosis can be triggered by a variety of insults including cytokines, inflammatory injury, free radical damage, and excitotoxicity. Recently, the existence of apoptosis after traumatic human SCI was confirmed (104). In addition, recent data from experimental rodent models of SCI lends credence to the assertion that apoptosis (particularly activation of caspases) contributes significantly to SCI (105–108).

The apoptotic cascade in SCI is activated in neurons, oligodendrocytes, microglia, and perhaps, astrocytes. Apoptosis in microglia contributes to inflammatory secondary injury (109). Experimental work suggests that apoptosis in oligodendrocytes contributes to postinjury demyelination developing during the first several weeks after SCI (110,111). Apoptosis in neurons contributes to cell loss that has a clear negative impact on outcome (112). Apoptosis in neurons after SCI occurs via both the extrinsic, mediated by Fas ligand and Fas receptor (99,113) and/or inducible nitric oxide synthase production by macrophages (114), and intrinsic, via direct caspase-3 proenzyme activation (115) and/or mitochondrial damage, release of cytochrome c and activation of the inducer caspase-9,(108) pathways of caspase-mediated apoptotic death (112). Furthermore, recent evidence suggests that caspase inhibitors may be yet another target for therapeutic intervention in SCI secondary injury (112).

Two main pathways of apoptosis—extrinsic or receptor-dependent and intrinsic or receptor-independent—have been well characterized, and both appear to be active in SCI. Receptor-dependent apoptosis is evoked by extracellular signals, the most significant of which is tumor necrosis factor, hence the designation of “extrinsic” pathway. Tumor necrosis factor is known to rapidly accumulate in the injured spinal cord, and activation of the Fas receptor of neurons, microglia, and oligodendrocytes induces a programmed sequence of caspase activation involving caspase-8 as the inducer caspase and caspase-3 and caspase-6 as the effector caspases (116). Activation of effector caspases results in the demise of the affected cell. An alternative inducer of the extrinsic pathway is inducible nitric oxide synthase, which also ultimately brings about caspase-3 activation to effect programmed cell death (114). The receptor-independent pathway is activated by intracellular signals, and is thus termed the “intrinsic” pathway. Activation of the receptor-independent pathway has been described in neurons after SCI wherein high intraneuronal calcium concentrations induce mito-

chondrial damage, cytochrome c release, and subsequent activation of an alternative programmed sequence of caspase activation (116). In this sequence, cytochrome c couples with apoptosis activating factor-1 to activate caspase-9, the inducer caspase, which, as in the extrinsic pathway, activates caspase-3 and caspase-6 as the effector caspases, likewise culminating in the death of the affected neuron (117,118). Apoptotic secondary injury in SCI has only recently come under close scrutiny, and the precise contribution and potential therapeutic implications of apoptosis in SCI await further clarification.

### Role of the Mitochondrion in Secondary Injury

Mitochondria may represent a central contributor to cellular death after SCI. A multitude of previously discussed mechanisms of secondary injury involve the mitochondrion in some capacity. In health, mitochondria are critical in cerebral metabolism and in maintenance of cellular  $\text{Ca}^{2+}$  homeostasis. The mitochondria also serve as hosts to a vast array of oxidation-reduction reactions using oxygen and hence, also comprise the primary intracellular source of reactive oxygen species. The orchestration of cellular metabolic flux (neuronal-astrocyte trafficking) is also critically dependent on mitochondria (79). Compromise in any of these functions served by mitochondria can lead to death directly or indirectly by diminishing tolerance to cellular stress. Trauma to the CNS perturbs the ability of mitochondria to carry out cellular respiration and oxidative phosphorylation (119–123). Traumatic injury to the CNS also alters respiration-dependent  $\text{Ca}^{2+}$  uptake/sequestration by inhibiting mitochondrial  $\text{Ca}^{2+}$  transport and hence disturbs intracellular  $\text{Ca}^{2+}$  homeostasis (119–121,123). Additionally,  $\text{Ca}^{2+}$ -induced permeability changes of the mitochondrial inner membrane are observed in cellular death. Such changes reduce the mitochondrial membrane potential and may contribute to osmotic swelling and mitochondrial lysis (124). Moreover, this change in  $\text{Ca}^{2+}$  permeability represents a potential therapeutic target. For example, cyclosporine A, an agent capable of inhibiting  $\text{Ca}^{2+}$ -induced mitochondrial permeability changes, is neuroprotective as discussed in Part II of this series (124,125). Mitochondria appear to be important in cellular damage from accumulation of excitatory neurotransmitters after traumatic injury. A burgeoning body of evidence demonstrates that mitochondria actively sequester the majority of  $\text{Ca}^{2+}$  entering neurons with excitotoxicity. Indeed, excessive mitochondrial  $\text{Ca}^{2+}$  accumulation as opposed to simply increased cytosolic  $\text{Ca}^{2+}$ , is the principal cause of excitotoxic cell death

(126–130). In addition to excitotoxicity, mechanical stress, inflammatory reactions, and altered trophic signal transduction appear to contribute to mitochondrial damage with CNS trauma. In addition, increased permeability of the mitochondria's outer membrane to apoptogenic proteins facilitates their release into the cytosol, thereby representing a key mechanism in the induction of apoptosis and neuronal death. Overall, the mitochondrion is increasingly becoming recognized as an integral mediator of traumatic neural injury. Myriad potential therapeutic points of intervention may be extracted from knowledge of the mitochondrion's contribution to secondary injury.

### Other Contributors to Secondary Injury

Levels of certain peptides and neurotransmitters change following the primary injury. In particular, there is a rise in endogenous opioids after injury. Opioid receptor activation can contribute to the excitotoxic process described earlier (131). Activation of  $\mu$  and  $\delta$  opioid receptors can prolong the excitotoxic process. Activation of  $\kappa$  receptors can exacerbate decreases in blood flow and promote the excitotoxic process (65). Levels of certain neurotransmitters, such as acetylcholine and 5-hydroxytryptamine (5-HT, serotonin), also rise. 5-HT may contribute to secondary damage by causing vasoconstriction and promoting platelet activation and endothelial permeability (90).

### CONCLUSION

In summary, the pathophysiology of acute SCI involves both primary and secondary mechanisms of injury. Treatment of primary injury has not proven to be amenable to pharmacologic methods of treatment at present. However, prevention and education through programs such as the Think First program, show promise for reducing the incidence of SCI and the enormous associated morbidity and mortality. Secondary mechanisms of injury encompass an array of pathophysiologic processes including neurogenic shock, vascular insults such as hemorrhage and ischemia-reperfusion, excitotoxicity, calcium-mediated secondary injury and fluid-electrolyte disturbances, immunologic injury, apoptosis, disturbances in mitochondrion function, and other miscellaneous processes. The secondary mechanisms of injury are currently the target of pharmacologic management. An understanding of the basic secondary pathophysiologic processes outlined above provides the basis for current pharmacotherapy, and in addition, provides a framework for the development of new pharmacologic treatment strategies.

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