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## *Letter to the Editor*

# Re: Ditunno JF, Little JW, Tessler A, Burns AS. Spinal shock revisited: a four-phase model. *Spinal Cord* 2004; 42: 383–395

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The review of 'spinal shock' by Ditunno *et al*[1] and the commentary by Silver[2] shed new insights into the neurophysiologic basis and clinical presentation of this well-documented phenomenon. Such insights are important for understanding the evolution of 'spontaneous' recovery and 'conversions', that is, progression from one level of neurologic impairment to another. In their model, Ditunno *et al*[1] attribute the initial phase of areflexia, flaccid paralysis and loss of autonomic function to (a) loss of excitatory input to alpha and gamma motor neurons, interneurons and preganglionic sympathetic neurons from supraspinal centers, and (b) increased spinal inhibition as a consequence of reduced descending inhibition of spinal inhibitory pathways. They characterize these effects as 'spinal neuron hyperpolarization'. Elsewhere, Little *et al*[3] acknowledge that resolution of conduction block due to resorption of edema or hematomyelia may contribute to motor recovery following incomplete spinal cord injury.

Advances in understanding immune-central nervous system (CNS) signaling,[4] and the immunological consequence of cord trauma,[5] suggest that other factors may be contributing to early onset and reversible neurologic deficits. In particular, proinflammatory cytokines and other immune mediators, such as nitric oxide (NO), that exhibit increased expression in the injured cord, have now been shown to block conduction in long tract axons of the mammalian neuraxis.[6–8] The conduction blocking effects are dose-dependent.[6,7] As the proinflammatory cytokine levels reduce, so axonal conduction is restored. Several proinflammatory cytokines that are known to be present at elevated concentrations within the CNS following neurotrauma, for example, tumor necrosis factor alpha (TNF$\alpha$), have the capability to induce complete, but reversible, conduction failure.[7] The mechanisms of cytokine and NO action appear to involve modulation of axonal ion channel conductances.[6–9]

Cerebrospinal fluid concentrations of proinflammatory cytokines that reflect the drainage of these cytokines following CNS neuroinflammation, and serum levels, are elevated within minutes of trauma and typically resolve with a time course of days to weeks. This time course bears a striking similarity to that of Phase 1 and the later phases of spinal shock. Moreover, if enhanced $Na^+$ channel conductance is involved, as is thought to be the case in TNF$\alpha$-induced axonal conduction failure,[7] then incomplete elimination of TNF$\alpha$ would be expected to lead to neuronal hyperexcitability. The parallel to the emergence of hyperreflexia is obvious. Variations in the time course of CSF cytokine profiles and the evolution of spinal shock most likely reflect differences in the extent and type of pathology, the acute immunomodulatory management of the trauma and the existence of comorbid polytrauma or medical complications.

Immune-mediated axonal conduction failure that is reversible on resolution of the acute cytokine response thus appears to be a mechanism likely contributing to the Phase 1 of spinal shock. This mechanism of central conduction deficit would predict the type of motor and autonomic dysfunction present below a lesion in the acute stage and the recovery of tone, reflexes and perhaps voluntary function, with varying degrees of 'conversion' in the post acute stage (Phase 2 and beyond). In doing so, it may account for conduction failure that resolves with a time course too early to be attributable to remyelination.[3] As proinflammatory cytokines such as TNF$\alpha$ are also involved in altering the permeability of the blood–spinal cord barrier and the induction of edema, their involvement in spinal shock may be multi-faceted. Much remains to be known about the immunologic processes underlying both spinal shock and neurologic recovery.

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