Figure 1.

Schematic Representation of a Cut Lesion in the Spinal Cord.

A-B) This particular insult (e.g. stab/cut wound) penetrates the meninges, which is a common occurrence in these types of lesions, thus facilitating the infiltration of a variety of cells into the lesion site. Here, for instance, we see two common types of cellular invasion following CNS injury, fibroblasts and macrophages. In the adult CNS, axons fail to regenerate due to the presence of inhibitory molecules found at the injury epicentre.

Briefly, in the CNS the mechanical insult triggers the following events: a) disruption of BBB; b) cavitation occurs at the lesion site and alteration in ECM; c) astrocytes are activated and produce molecules such as CSPG; d) fibroblast invasion the lesion and express a chemorepellent molecules; e) macrophages infiltration and release inflammatory cytokines; and as a result of these aforementioned factors, f) neurons form bulb-like structure and consequently collapse. Note that there are also many other CNS inhibitors of axons that have not been discussed here. Figure modified from Silver and Miller (2004, p147).

ECM = extracellular matrix, BBB = blood brain barrier, CGSP = chondroitin sulphate proteoglycans.

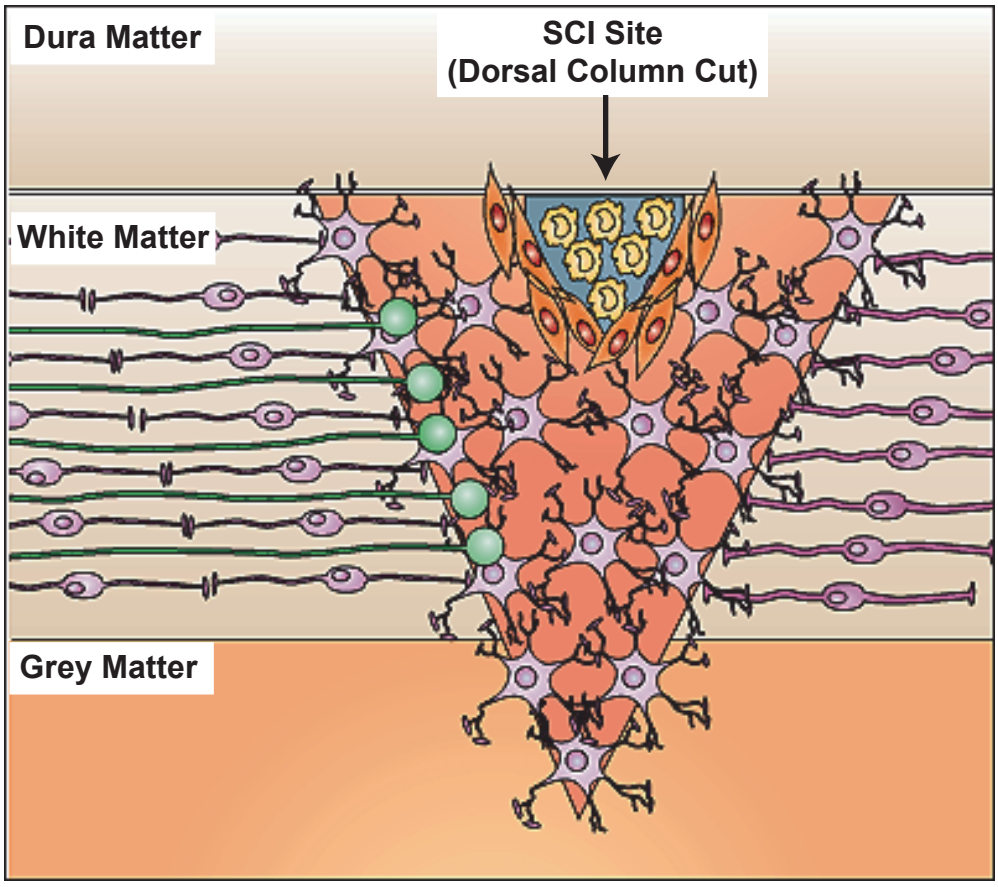
Figure 2.

Comparison of Factors Dictating the Balance Between Detrimental and Beneficial Effects in CNS Repair following Trauma.

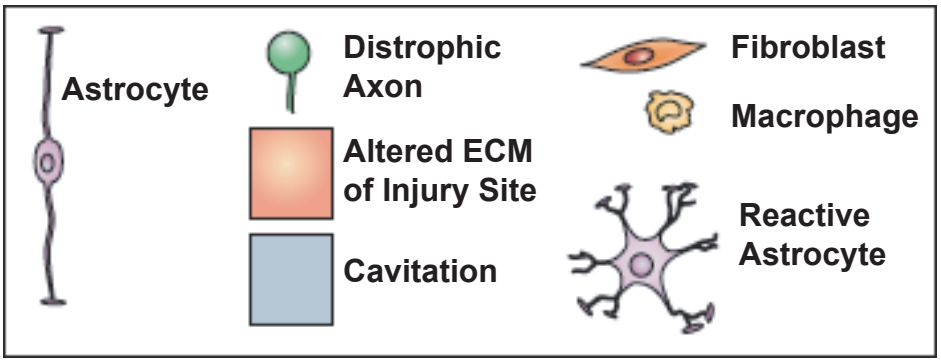
A-B) After trauma to the CNS, several events occur that may lead to further tissue destruction and/or, in contrast, may result in tissue remodelling and repair. Damaging events include acute phenomena such as haemorrhage, oedema, as well as protracted events such as apoptosis, demyelination and degeneration. Reparative processes such as angiogenesis and axon growth also typically occur in the injured spinal cord. Depending on the severity of the injury, functional recovery may be limited to and/or nearly complete. Interestingly, inflammation along with the presence of inflammatory cells such as macrophages, have the ability to precipitate both detrimental and beneficial events after SCI.

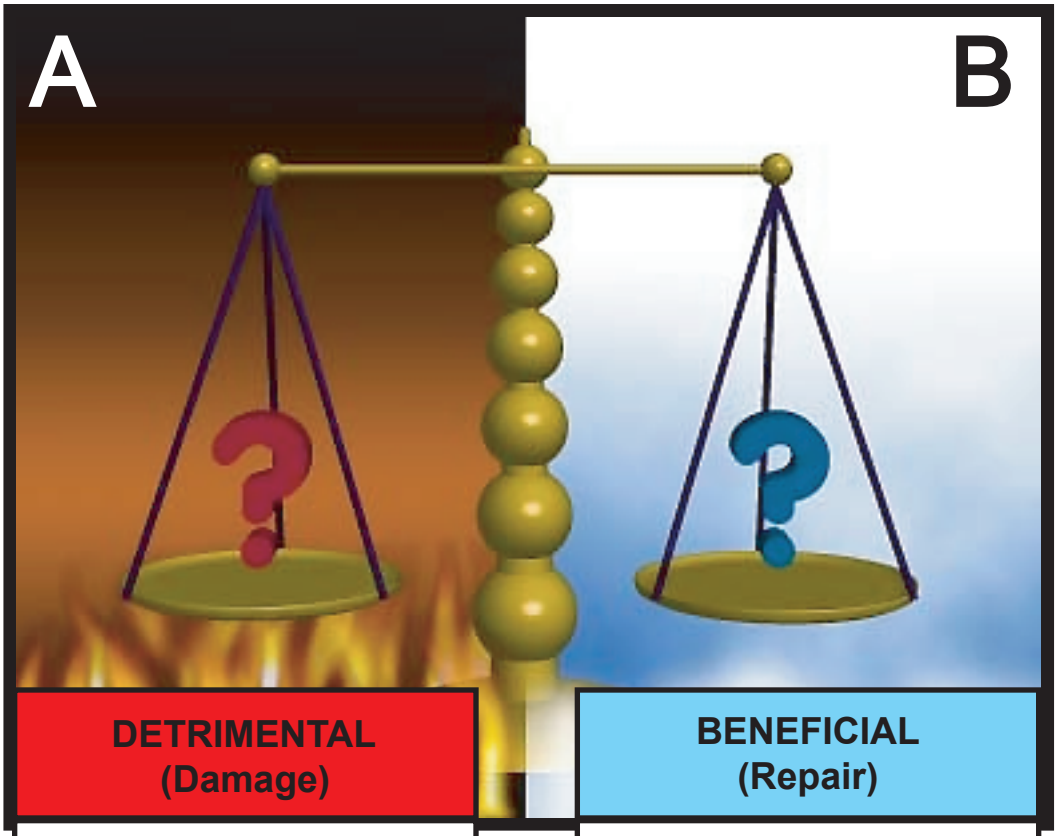
On the one hand, immune cells express pro-inflammatory and neurotoxic molecules (**A**), which likely represent destructive consequences associated with CNS inflammation. On the other hand, immune cells can also express anti-inflammatory and protective molecules including trophic factors (**B**). Therefore, it is likely that the balance between the protective and destructive events following trauma to the CNS, determine the net effect of the inflammatory reaction in a given injury. Figure adapted from McTigue et al., (2000, p4) and Kerschensteiner et al., (2003, p299).

A


Dura Matter
SCI Site
(Dorsal Column Cut)
White Matter
Grey Matter

B


Astrocyte
Distrophic
Axon
Altered ECM
of Injury Site
Cavitation
Fibroblast
Macrophage
Reactive
Astrocyte



DETRIMENTAL (Damage)	BENEFICIAL (Repair)
Haemorrhage	Angiogenesis
Oedema	Synaptogenesis
Degeneration	Regeneration
Demyelination	Remyelination
Inflammation	Inflammation
Apoptosis	Functional Recovery
Th-1 Cytokines	Th-2 Cytokines
Macrophages	Macrophages
Oxygen Radicals	TGF
IL-1	IL-4
Glial Scar Formation	BDNF
TNF	NGF
Nitric Oxide	NT-3, 4/5
MMP	GDNF
IL-6	LIF

Table 1. *Events of Secondary Neuronal Injury After SCI*

Vascular Events	BBB Breakdown
	Oedema Formation
	Ischaemia and Hypoxia
	Release of Vasoactive Substances
	Alteration of Spinal Cord Perfusion
Biochemical Events	Excitotoxicity
	Formation of Free Radicals and Nitric Oxide
	Release of Proteases
	Damage of Mitochondria
	Energy Depletation
Cellular Events	Invasion of Neutrophils
	Activation of Microglia
	Infiltration of Peripheral Macrophages
	Infiltration of Lymphocytes
	Activation of Astrocytes
	Apoptosis of Oligodendrocytes
	Wallerian Degeneration

Modified from Hausmann (2003) *Spinal Cord* **41**: 369-378

Table 2. *Rodent Studies of Promising Human Interventions for SCI Repair*

Intervention	Action	Delivery/Compound
Bridges: Polymers, conduits	Fill cavity; May contain growth substances and cells	Injection of alginate or smart biodegradable fibres may release cells and factors
OEGs	Migrate to surround axons	Injection jus above or below the lesion or within a matrix into a cyst area
Schwann cell graft	Align axons, migrate, produce neurotrophins	Quantity and quality of cells, associated matrix, ability of axon to travel beyond a bridge are uncertain
Bone marrow stromal, stem cells, progenitor cells, foetal spinal cord	Differentiate into matrix cells, neurons, and oligodendroglia; repopulate grey and white matter, provide trophins	Cell type needed may not differentiate or integrate; ethical issues for human studies with foetal tissue
Nogo myelin inhibitor (Nogo-A antibody)	Binds to Nogo to block inhibition of axon growth	Injected locally by osmotic CSF pump; immunisation with CNS myelin component or injection of activated macrophages
Nogo peptide antagonist	Bind to Nogo receptor, blocking inhibition of axon growth by Nogo, MAG, OMGP	Potential for oral administration CSF pump; possible intravenous route
Proteoglycan inhibitor Chondroitinase	Digests inhibitors to foster axon growth in white matter	Infuse locally above and below edge of injury site
Growth cone signalling cAMP, cGMP, Rho GTPases	Overcomes growth cone inhibitors; Higher ratio of cAMP/cGMP for axon extension; Block inhibitory effect of MAG, OMGP, Nogo A	Must be taken up by the neuron (potential for oral administration); Provide soon after injury for brief time by local infusion near injury site
Neurotrophic factors: BDNF, NT-3	Limited neuronal apoptosis, aid axonal regeneration and guidance to targets; aid dendritic sprouting and learning mechanisms	Inject engineered fibroblasts that secrete a trophin; inject or pump factor into CSF
Electrical stimulation	Activates axonal growth cone	Methods and efficacy in humans uncertain
Oligodendrocyte precursors	Abundant in adult brain	Activated in situ precursors may inhibit growth cone

Modified from Dobkin and Havton (2004) Annual Reviews in Medicine **55**: 255-282