Spinal Cord Injury - 2009

Neuroplasticity – The ability of the brain and spinal cord to reorganize - sprouting new neural connections throughout life.

Newsletter 1 | 2009

At HyperMED NeuroRecovery we are dedicated to improving the quality of life of individuals suffering neurodegenerative disorders through innovative clinical applications and research. Clinical applications include but not limited to Hyperbaric Oxygenation (HBOT), assertive physical therapies, Lokomat (Robotic Gait Assisted Walking) and emerging stem cell related applications.

HyperMED NeuroRecovery goes 'Beyond Therapy'

NeuroRecovery goes beyond the conservative therapy program a person would normally receive as an 'in-patient' or even attending an out-patients program where the focus is on *coping and adapting to disability*. Most traditional rehabilitation programs are typically designed to get patients as independent as possible and trained on how to take care of themselves after discharge. In contrast HyperMED NeuroRecovery focuses on the full extent and capacity to *re-train and re-learn function*.

Most patients in the chronic phase of their condition become stagnant in their recovery and virtually all aspects of recovery and motivation fade. HyperMED NeuroRecovery is like a 'rigorous boot-camp'; patients attend between 4-6 hours on each day and receive combination therapies designed to challenge immune and physiological responses and facilitate functional change.

At HyperMED NeuroRecovery we make no apology for 'pushing' the patient – the objective is to *penetrate the deeper neurovascular structures, unlock dormant pathways and promote functional changes*. Patients require an initial intensive saturation or start up program, typically 4-6 weeks followed by periodic short blocks of intensive therapies designed to promote neuroplasticity salvage.

Prepare yourself - You have got to WORK!

NewScientist

Do Wheelchairs Hinder Spinal-Cord Recovery?

NewScientist Aug 2008 - INJURED rats strapped to tiny "wheelchairs" that restrict their movements recovered less limb function and coordination than those left to fend for themselves. This might mean that people with a spinal cord injury would recover better if they were encouraged to use their limbs sooner after injury and relied less on wheelchairs.

"Our data suggests that wheelchair restriction definitely impairs functional recovery in rats, and logically it would seem to apply also to humans," says Dr David Magnuson of the Kentucky Spinal Cord Injury Research Center, University of Louisville.

There seems to be an optimal time period following spinal cord injury during which the brain is better able to relearn at least some of the functions that are lost. Missing this *"window of opportunity"* is thought to reduce the amount of movement an injured person can recover, but no one is sure exactly which components are necessary for successful rehabilitation or when that window occurs, says Magnuson. Some studies suggest putting body weight onto the legs is best, while others stress moving the feet, for example.

Lab animals tend to recover from spinal cord damage much more quickly and completely than humans. Magnuson believes this is partly because their movements are less restricted during recovery - they tend to drag themselves around using their undamaged limbs and, being four-legged, have fewer balance problems.

His team created rat-sized wheelchairs attaching four wheels to small plastic platforms. Then they took half of a group of rats with loss of movement in their hind legs and strapped them to the wheelchairs five nights a week for eight weeks. The wheelchairs restricted their hind legs but the rats wheeled themselves around on their forelegs. The other rats were left to move about freely.

'Wheelchair restriction impairs functional recovery in rats, and logically it would seem also to apply to the humans suffering brain and spinal cord injury'. Dr Magnuson Kentucky Spinal Cord Injury Research Center

'HyperMED NeuroRecovery is committed to expanding the therapeutic window promoting worthwhile functional outcomes - gone are days of simply living and coping with disability!'

After another eight weeks, in which all the animals were allowed free movement, their walking and swimming abilities were assessed using standard tests that measure joint movements, weight support, limb coordination, foot placement and gait stability. The team also filmed the rats while they had reflective tape stuck to their joints, so they could analyze their movements in detail. They found that *rats given wheelchairs recovered significantly less function than those left to move about as best they could*. The team presented their results at the National Neurotrauma Society Symposium in Orlando, Florida, earlier this week. "Most people when they see the rat wheelchair, their first response is to chuckle, because it does look comical, but then they realize we are trying to address some pretty important questions," says Magnuson.

While the study points to the importance of movement during spinal cord recovery, and suggests less reliance on wheelchairs might help, it provides no indication of what kind of movements would improve recovery for humans, nor when exactly during rehabilitation these movements should take place. "This study indicates the importance of providing the appropriate feedback to the damaged cord to get the best functional outcome," says Mark Bacon, head of research at Spinal Research, a UK charity. "It remains to be seen what rehabilitation regime will be the most appropriate for humans."

Facts on Spinal Cord and Brain Injury
There are an estimated 50 million Americans affected by diseases or disorders of the spinal cord and brain. The list of disorders includes: spinal cord injury, memory loss, addiction, schizophrenia, learning disability, depression, violence, stroke, brain injury, dementia, suicide and many others. More than 90% of the American population has or will experience the effects of a brain and related disease, disorder or injury at some point in their lives. Spinal cord injuries affect in excess of 250,000 Americans, costing more than $10 billion yearly. Head injuries have disabled two million individuals, costing the country $25 billion annually. Strokes affect 500,000 new people every year, costing the national economy $25 billion yearly. Spinal cord and brain disorders impact the American economy in excess of $400 billion a year, on direct health care costs and additional indirect lifetime costs. Individual suffering and loss to society, however, are almost impossible to quantify. Sources: American Paralysis Association and The Dana Alliance for Brain Initiatives.

Approximately 450,000 people in the United States have sustained traumatic spinal cord injuries, with more than 10,000 new cases of SCI emerging in the U.S. every year. Males account for 82 percent of all SCI's and females 18 percent. Spinal cord injuries are most commonly caused by motor vehicle accidents. The next most frequent causes are falls and acts of violence. Sports-related spinal cord injuries occur more commonly in children and teenagers, while work-related injuries (especially from construction work) predominate in adults.

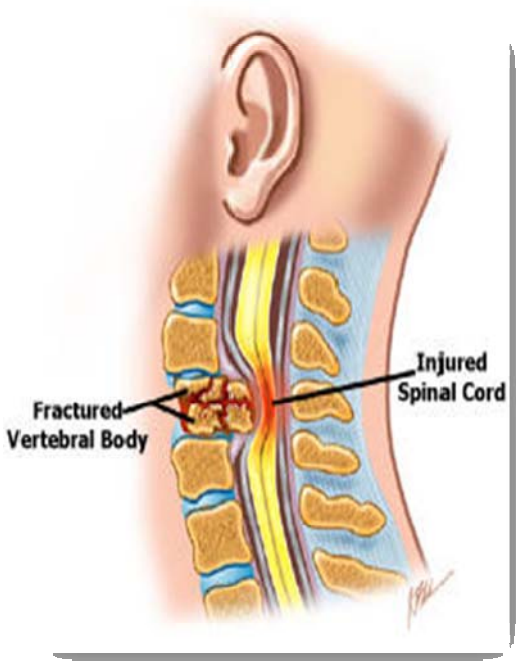
Most spinal cord injury patients are in their teens or twenties - 80% are male. This male preponderance decreases beyond age 65, at which age falls become the most common mechanism of spinal cord injury. More than half of all spinal cord injuries occur in the cervical area, i.e., in the neck. Almost a third occur in the thoracic area (where the ribs attach to the spine). The remainder occur in the lumbar area, i.e., the lower back.

Until recent years it was generally considered that there was no cure for spinal cord injuries. However, ongoing research to test surgical interventions, functional activity based rehabilitation, drug therapies and emerging stem cell applications are progressing rapidly. Christopher Reeve demonstrated to the world that he had recovered a degree of movement and sensation. While he could not walk, did not regain bowel, bladder, or sexual function, nor could he breathe without a ventilator, his limited recovery was significant.

The scientific literature on spinal cord injury predicts that most recovery will occur in the first six months after injury and that it is generally complete within two years. Reeve's recovery, coming five to seven years after his injury, defies these medical expectations and had a dramatic effect on his daily life. Why did he get better so long after his injury? *Reeve believed his improved function was the result of vigorous physical activity to re-train function and awaken dormant nerve pathways – the brain and spinal cord needs to reconnect!* [Source: American Association of Neurological Surgeons, Craig Hospital, Christopher and Dana Reeve Foundation, The National Institute of Neurological Disorders and Stroke].

The University of Alabama National Spinal Cord Injury Statistical Center, Centers for Disease Control and Prevention reports – 'By developing therapies for those who are already spinal cord injured and preventing new injuries, the United States would save as much as $400 billion on future direct and indirect lifetime costs.'

'Christopher Reeve believed his improved function was the result of vigorous physical activity to re-train function and awaken dormant nerve pathways – the brain and spinal cord needs to reconnect!'



Spinal Cord Injuries and Rehabilitation
Most spinal cord injury causes permanent disability or loss of movement (paralysis) and sensation below the site of the injury. Paralysis that involves the majority of the body, including the arms and legs, is called quadriplegia or tetraplegia. When a spinal cord injury affects only the lower body, the condition is called paraplegia.

Spinal cord injury symptoms depend on two factors:

Location of the injury - in general, injuries that are higher in your spinal cord produce more paralysis. For example, a spinal cord injury at the neck level may cause paralysis in both arms and legs and make it impossible to breathe without a respirator, while a lower injury may affect only your legs and lower parts of your body.

Severity of the injury - spinal cord injuries are classified as partial or complete, depending on how much of the cord width is damaged.

In a **partial spinal cord injury**, which may also be called an incomplete injury, the spinal cord is able to convey some messages to or from your brain. So people with partial spinal cord injury retain some sensation and possibly some motor function below the affected area.

A **complete spinal cord injury** is defined by total or near-total loss of motor function and sensation below the area of injury. However, even in a complete injury, the spinal cord is almost never completely cut in half. Doctors use the term 'complete' to describe a large amount of damage to the spinal cord. It's a

key distinction because many people with partial spinal cord injuries are able to experience significant recovery, while those with complete injuries are not. However many spinal patients classified as 'complete' may still re-gain some functional responses. This is evident with *assertive therapeutic interventions designed to activate damaged nerve cells and re-train function*.

What Happens Following Spinal Cord Injury?

- Spinal Injury may result in either complete or incomplete injury
- Laceration, extensive bruising, and massive swelling results in extensive cord *hypoxia (inadequate tissue oxygen) which fosters destructive cellular apoptosis (programmed degeneration)*
- Apoptotic cells from the immune system migrate to the injury site causing further damage to some neurons and death to others that survived the initial trauma. Immediate strategies are must be implemented to minimize this programmed cellular destruction
- Within weeks of the initial injury a fluid-filled cavity surrounded by glial scarring is left behind. Localized myelomalacia emerges *(morbid softening at the injured site due to hypoxic necrosis of the spinal cord)*
- Progressive cord apoptosis due to hypoxia may cause progressive hemorrhagic myelomalacia - *spread of myelomalacia progresses above and below the injured site due to progressive intramedullary hemorrhage of the spinal cord*. This potentially leads to further loss of neurologic function and cord atrophy severely inhibiting the capacity to regenerate. *Comparison MRI post surgical stabilization is critical within the early months – functional improvements does NOT rule out the potential cascade of secondary complications*
- Experiments conducted on spinalized cats demonstrate that spinal circuitry (reflex generators) below the level of injury remains active and functional neuronal properties can respond to peripheral input from *below* the level of injury. Treadmill cats can be trained to walk
- Lack of appropriate stimulation induces functional incapacity called the 'learning non-use'. *Simply stated if you teach the remaining active spinal circuits to sit they will sit!*
- Motor cortex centers in the brain re-allocate functional capacity lost through spinal cord injury – *it is imperative to keep this 'window open'*
- Body Weight Support Treadmill Training (BWSTT) and more recent studies on Lokomat (Robotic Gait Assisted Walking) demonstrate the potential of *functional neuroplasticity - the ability to re-learn and re-organize function*

Spinal Cord. 2008 Mar;46(3):176-80. Epub 2007 Sep 18
Adaptive changes in chronic paraplegic mice: rapid health degradation (apoptosis) after spinal cord injury
Neuroscience Unit, CHUL Research Center, Quebec City, Quebec, Canada.
STUDY DESIGN: Literature review. OBJECTIVE: To describe quantitatively some of most important anatomic, systemic, and metabolic changes occurring soon (one month) after spinal cord trauma in mice. SETTING: University Laval Medical Center. RESULTS: *Significant changes in weight, mechanical and contractile muscle properties, bone histomorphometry and biomechanics, deep-vein morphology, complete blood count, immune cell count, lipid metabolism and anabolic hormone levels were found occurring within 1 month in completely spinal cord transected (Th9/10) mice.* CONCLUSION: These data reveal that many changes in mice and humans are comparable suggesting, in turn, that this model may be a valuable tool for neuroscientists to investigate the specific mechanisms associated with rapid health degradation post-SCI. *HyperMED comment: it is imperative to keep the 'window open'*

Neuroplasticity: The brain's ability to reorganize itself by forming new neural connections throughout life. *Neuroplasticity allows the neurons (nerve cells) in the brain and spinal cord to compensate for injury and disease and to adjust their activities in response to new situations or to changes in their environment.*

- *Neural stem cells (NSCs) migrate* through the parenchyma along non-stereotypical routes in a precise directed manner across great distances to injury sites in the CNS, where they might engage niches harboring local transiently expressed reparative signals
- *Neuronal reorganization takes place by mechanisms such as "axonal sprouting"* in which undamaged axons grow new nerve endings to reconnect neurons whose links were injured or severed. Undamaged axons can also sprout nerve endings and connect with other undamaged nerve cells, forming new neural pathways to accomplish a needed function
- For example, if one hemisphere of the brain is damaged, the intact hemisphere may take over some of its functions. The brain compensates for damage in effect by reorganizing and forming new connections between intact neurons. *In order to reconnect, the neurons need to be stimulated through activity which must be accurate and repeated many thousands of times*
- Neuroplasticity sometimes may also contribute to impairment. For example, people who are deaf may suffer from a continual ringing in their ears (tinnitus), the result of the rewiring of brain cells starved for sound. For neurons to form beneficial connections, they must be correctly stimulated. 'Spinal cord activation often causes increased spasms and uncontrolled movements'
- Neuroplasticity (brain plasticity and or spinal plasticity) is often referred to as *neural malleability*

Slow the cascade - keep the window open (alive)

J Neurosci Res. 2008 Nov 1;86(14):3039-51
A technological platform to optimize combinatorial treatment design and discovery for chronic spinal cord injury
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Chronic spinal cord injury (SCI) is associated with the development of serious medical concerns. In fact, it is increasingly well documented that most SCI patients who survive the first 24 hr will rapidly develop, *within a few months to a few years, cardiovascular problems, type II diabetes, muscle wasting, osteoporosis, immune deficiencies, and other life-threatening problems.* The cellular mechanisms underlying these so-called secondary health complications remain unclear, and no drug or standard approach has been developed to specifically treat these complications. To investigate the cellular and metabolic changes associated with chronic SCI and functional recovery, work mainly from our laboratory recently has led to the characterization of a mouse model of chronic paraplegia. This review reports cellular, systemic, and metabolic changes (associated mainly with secondary health complications) occurring within a few days to a few weeks after SCI in low-thoracic spinal cord-transected mice. We also describe our research platform developed to ease technological transfer and to accelerate drug-screening studies in animals. A global understanding of the many chronic changes occurring after SCI together with efficient tools and approaches for testing new or existing drug candidates is likely to yield the *design of innovative treatments against secondary complications that combine cellular plasticity-modulating agents, locomotor network-activating drugs, hormonal therapy, and exercise training.* (c) 2008 Wiley-Liss, Inc.

Watch your weight – every other day fasting promotes neuroplasticity and recovery

Exp Neurol. 2008 Sep;213(1):28-35
Dietary restriction started after spinal cord injury improves functional recovery
International Collaboration on Repair Discoveries, University of British Columbia, Vancouver, British Columbia, Canada V6T 1Z4.
Spinal cord injury typically results in limited functional recovery. Here we investigated whether therapeutic dietary restriction, a multi-faceted, safe, and clinically-feasible treatment, can improve outcome from cervical spinal cord injury. The well-established notion that dietary restriction increases longevity has kindled interest in its potential benefits in injury and disease. When followed for several months prior to insult, prophylactic dietary restriction triggers multiple molecular responses and improves outcome in animal models of stroke and myocardial infarction. However, the efficacy of the clinically-relevant treatment of post-injury dietary restriction is unknown. Here we

report *that "every-other-day fasting" (EODF), a form of dietary restriction, implemented after rat cervical spinal cord injury was neuroprotective, promoted plasticity, and improved behavioral recovery*. Without causing weight loss, *EODF improved gait-pattern, forelimb function during ladder-crossing, and vertical exploration. In agreement, EODF preserved neuronal integrity, dramatically reduced lesion volume by >50%, and increased sprouting of corticospinal axons*. As expected, blood beta-hydroxybutyrate levels, a ketone known to be neuroprotective, were increased by 2-3 fold on the fasting days. In addition, we found increased ratios of full-length to truncated trkB (receptor for brain-derived neurotrophic factor) in the spinal cord by 2-6 folds at both 5 days (lesion site) and 3 weeks after injury (caudal to lesion site) which may further enhance neuroprotection and plasticity. *Because EODF is a safe, non-invasive, and low-cost treatment, it could be readily translated into the clinical setting of spinal cord injury and possibly other insults.*

Task specific activity based rehab promotes BDNF (brain derived neurotrophic factors) and neuronal reorganization

Neurosci Res. 2008 Nov;62(3):147-54
Training improves the electrophysiological properties of lumbar neurons and locomotion after thoracic spinal cord injury in rats
Centre de Recherche, Hôpital du Sacré-Coeur de Montréal, Département de Chirurgie, Université de Montréal, Montréal, Québec, Canada. e-beaumont@crhsc.rtss.qc.ca
The aim of the present study was to evaluate the effect of a stepping-based rehabilitation program in voluntary wheel cages on the functional recovery and electrophysiological properties of neurons in the rat lumbar spinal cord after compressive thoracic (T10) spinal cord injury (SCI). A significant decrease in stance/swing duration and the number of limbs simultaneously in the stance phase was seen in trained compared to sedentary rats at 28 days after SCI ($p<0.05$). These kinematic improvements were associated with a significant increase in the amplitude of extracellular recordings from the tibial motoneuron pool in response to descending neuronal drive as well as significant amelioration of electrophysiological properties assessed from intracellular recordings. In fact, electrophysiological properties were not significantly different between uninjured controls and SCI-trained rats. *Brain-derived neurotrophic factor (BDNF) levels were significantly elevated in the lumbar spinal cord of SCI-trained rats compared to SCI-sedentary controls. The data support a therapeutic role of increased neuromuscular activity in promoting functional recovery and suggest that it might occur via the beneficial effects of neurotrophic factors on neuronal plasticity.*

Neuroscience. 2008 Sep 9;155(4):1070-8
BDNF-exercise interactions in the recovery of symmetrical stepping after a cervical hemisection in rats
Department of Physiological Science, University of California, Los Angeles, CA 90095-1527, USA.
Clinical evidence indicates that motor training facilitates functional recovery after a spinal cord injury (SCI). *Brain-derived neurotrophic factor (BDNF) is a powerful synaptic facilitator and likely plays a key role in motor and sensory functions. Spinal cord hemisection decreases the levels of BDNF below the injury site, and exercise can counteract this decrease* [Ying Z, Roy RR, Edgerton VR, Gomez-Pinilla F (2005) *Exercise restores levels of neurotrophins and synaptic plasticity following spinal cord injury.* Exp Neurol 193:411-419]. It is not clear, however, whether the exercise-induced increases in BDNF play a role in mediating the recovery of locomotion after a SCI. We performed a lateral cervical (approximately C4) hemisection in adult rats. Seven days after hemisection, the BDNF inhibitor trkB IgG was injected into the cervical spinal cord below the lesion (approximately C5-C6). Half of the rats were exposed to voluntary running wheels for 14 days. Sedentary and exercised rats with BDNF inhibition showed a higher level of asymmetry during the treadmill locomotion test than rats not treated with the BDNF inhibitor. In hemisected rats, exercise normalized the levels of molecules important for synaptic function, such as cyclic AMP response element binding protein (CREB) and synapsin I, in the ipsilateral cervical enlargement, whereas the BDNF blocker lessened these exercise-associated effects. *The results indicate that BDNF levels play an important role in shaping the synaptic plasticity and in defining the level of recovery of locomotor performance after a SCI.*

1.5 Tesla MRI reveals structure – 3.5 Functional BOLD (Blood Oxygen Level Dependency) monitors functional changes within structure

Exp Neurol. 2008 Jan;209(1):155-60. Epub 2007 Sep 26.
Reorganization of sensory processing below the level of spinal cord injury as revealed by fMRI
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The adult mammalian CNS undergoes plastic changes in response to injury. To investigate such changes in spinal cord, functional magnetic resonance imaging (fMRI) was applied in rats subjected to complete transection of the mid-thoracic spinal cord. Blood oxygenation level-dependent (BOLD) contrasts were recorded in the distal spinal cord different times after injury (3, 7, and 14 days, and 1, 3, and 6 months) in response to electrical hind limb stimulation. *Functional MRI demonstrated a substantial increase of neuronal activation* in the ipsilateral dorsal horn after injury. Notably, 0.5 mA, which did not evoke activation in the normal spinal cord and was considered a non-painful stimulus, induced significant BOLD responses in the dorsal horn after injury. Increased sensitivity was also seen in response to 1.0 mA stimulation. Our results suggest exaggerated responsiveness of spinal neurons after spinal cord injury. Reorganization in the injured spinal cord has been shown to involve the amplification of peripheral inputs and implicated as one underlying mechanism causing neuropathic pain and autonomic dysreflexia. Since *BOLD signals can demonstrate such plastic changes in spinal cord parenchyma, we propose fMRI as a method to monitor functional reorganization in the spinal cord after injury.* Combining brain and spinal cord fMRI allows the visualization of neuronal activities along the entire neuroaxis and thereby an evaluation of the different plastic responses to CNS injuries that occur in the brain and the spinal cord.

Does your injured cord remember how to walk?

ScientificWorldJournal. 2008 Aug 1;8:757-61
Can the spinal cord learn and remember?
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Learning and memory traditionally have been associated with cellular processes occurring in a specialized region of the brain called the hippocampus. However, recent data have provided strong evidence to suggest that comparable processes are also expressed in the spinal cord. *Experiments performed mainly in spinal cord-transected animals have reported that, indeed, spinal-mediated functions, such as the stretch or flexion reflex, pain signaling, micturition, or locomotion, may undergo plasticity changes associated with partial functional recovery that occur spontaneously or conditionally. Many of the underlying cellular mechanisms strikingly resemble those found in the hippocampus.* This mini-review reports, mainly, animal data that support the idea that other areas of the central nervous system, such as the *spinal cord - can also learn and remember*.

Brain adapts to spinal injury – in time the brain re-allocates 'representation' unless you use it!

Brain. 2007 Nov;130(Pt 11):2951-61. Epub 2007 Oct 3
Cortical sensory map rearrangement after spinal cord injury: fMRI responses
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Cortical sensory maps can reorganize in the adult brain in an experience-dependent manner. We monitored somatosensory cortical reorganization after sensory deafferentation using functional magnetic resonance imaging (fMRI) in rats subjected to complete transection of the mid-thoracic spinal cord. Cortical representation in response to spared forelimb stimulation was observed to enlarge and invade adjacent sensory-deprived hind limb territory in the primary somatosensory cortex as early as 3 days after injury. Functional MRI also demonstrated long-term cortical plasticity accompanied by increased thalamic activation. To support the notion that alterations of cortical neuronal circuitry after spinal cord injury may underlie the fMRI changes, we quantified transcriptional activities of several genes related to cortical plasticity including the Nogo receptor (NgR), its co-receptor LINGO-1 and brain derived neurotrophic factor (BDNF), using in situ hybridization. We demonstrate that NgR and LINGO-1 are down-regulated specifically in cortical areas deprived of sensory input and in adjacent cortex from 1 day after injury, while BDNF is up-regulated. Our results demonstrate that cortical neurons react to sensory deprivation by decreasing transcriptional activities of genes encoding the Nogo receptor components in the sensory deprived and the anatomically adjacent non-deprived area. Combined with the BDNF up-regulation, these changes presumably allow structural changes in the neuropil. Our observations therefore suggest an involvement of Nogo signalling in cortical activity-dependent plasticity in the somatosensory system. In spinal cord injury, cortical reorganization as shown here can become a disadvantage, much like the situation in amblyopia or phantom sensation. *Successful strategies to repair sensory pathways at the spinal cord level may not lead to proper reestablishment of cortical connections, once deprived hind limb cortical areas have been reallocated to forelimb use*. In such situations, methods to control cortical plasticity, possibly by targeting Nogo signalling, may become helpful.

Early functional rehabilitation drives (supraspinal) brain re-organization in spinal cord injury

Exp Neurol. 2008 Feb;209(2):407-16. Epub 2007 Jul 6
Cortical and subcortical plasticity in the brains of humans, primates, and rats after damage to sensory afferents in the dorsal columns of the spinal cord
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The failure of injured axons to regenerate following spinal cord injury deprives brain neurons of their normal sources of activation. These injuries also result in the reorganization of affected areas of the central nervous system that is thought to drive both the ensuing recovery of function and the formation of maladaptive neuronal circuitry. Better understanding of the physiological consequences of novel synaptic connections produced by injury and the mechanisms that control their formation are important to the development of new successful strategies for the treatment of patients with spinal cord injuries. Here we discuss the anatomical, physiological and behavioral changes that take place in response to injury-induced plasticity after damage to the dorsal column pathway in rats and monkeys. Complete section of the dorsal columns of the spinal cord at a high cervical level in monkeys and rats interrupts the ascending axon branches of low threshold mechanoreceptor afferents subserving the forelimb and the rest of the lower body. Such lesions render the corresponding part of the somatotopic representation of primary somatosensory cortex totally unresponsive to tactile stimuli. There are also behavioral consequences of the sensory loss, including an impaired use of the hand/forelimb in manipulating small objects. *In monkeys, if some of the afferents from the hand remain intact after dorsal column lesions, these remaining afferents extensively reactivate portions of somatosensory cortex formerly representing the hand.* This functional reorganization develops over a postoperative period of 1 month, during which hand use rapidly improves. These recoveries appear to be mediated, at least in part, by the sprouting of preserved afferents within the cuneate nucleus of the dorsal column-trigeminal complex. In rats, such functional collateral sprouting has been promoted by the post-lesion digestion of the perineuronal net in the cuneate nucleus. Thus, this and other therapeutic strategies have the potential of enhancing sensorimotor recoveries after spinal cord injuries in humans.

Bladder and bowel function – what to expect

Prog Brain Res. 2006;152:147-62
Plasticity in the injured spinal cord: can we use it to advantage to reestablish effective bladder voiding and continence?
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Micturition is coordinated at the level of the spinal cord and the brainstem. Spinal cord injury therefore directly interrupts spinal neuronal pathways to the brainstem and results in bladder areflexia. Some time after injury, however, dyssynergic bladder and sphincter function emerges. The changes mediating the appearance of bladder function after spinal cord injury are currently unknown. Primary afferent *neurons have been shown to sprout in response to spinal cord injury*. Sprouting primary afferents have been linked to the pathophysiology of centrally manifested disorders, such as autonomic dysreflexia and neuropathic pain. It is proposed that sprouting of bladder primary afferents contributes to disordered bladder functioning after spinal cord injury. *During development of the central nervous system, the levels of specific neuronal growth-promoting and guidance molecules are high. After spinal cord injury, some of these molecules are upregulated in the bladder and spinal cord, suggesting that axonal outgrowth is occurring*. Sprouting in lumbosacral spinal cord is likely not restricted to neurons involved in the micturition reflex. Furthermore, sprouting of some afferents may be contributing to bladder function after injury, whereas sprouting of others might be hindering emergence of function. Thus selective manipulation of sprouting targeting afferents that are contributing to emergence of bladder function after injury is critical. Further research regarding the role that *neuronal sprouting plays in the emergence of bladder function may contribute to improved treatment of bladder dyssynergia after spinal cord injury.*

Brain re-organization coupled with specific locomotor training reactivates function even after long term injury

Prog Brain Res. 2002
Transplants and neurotrophic factors increase regeneration and recovery of function after spinal cord injury
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Earlier studies suggested that while after spinal cord lesions and transplants at birth, the transplants serve both as a bridge and as a relay to restore supraspinal input caudal to the injury (Bregman, 1994), after injury in the adult the spinal cord transplants serve as a relay, but not as a bridge. We show here, that after complete spinal cord transection in adult rats, delayed spinal cord transplants and exogenous neurotrophic factors, the transplants can also serve as a bridge to restore supraspinal input (Fig. 9). We demonstrate here that when the delivery of transplants and neurotrophins are delayed until 2 weeks after spinal cord transection, the amount of axonal growth and the amount of recovery of function are dramatically increased. Under these conditions, both supraspinal and propriospinal projections to the host spinal cord caudal to the transection are reestablished. The growth of supraspinal axons across the transplant and back into the host spinal cord caudal to the lesion was dependent upon the presence of exogenous neurotrophic support. Without the neurotrophins, only propriospinal axons were able to re-establish connections across the transplant. Studies using peripheral nerve or Schwann cell grafts have shown that some anatomical connectivity can be restored across the injury site, particularly under the influence of neurotrophins (Xu et al., 1995a,b; Cheng et al., 1996; Ye and Houle, 1997). Without neurotrophin treatment, brainstem axons do not enter [figure: see text] the graft (Xu et al., 1995a,b; Cheng et al., 1996; Ye and Houle, 1997). Similarly, cells genetically modified to secrete neurotrophins and transplanted into the spinal cord influence the axonal growth of specific populations of spinally projecting neurons (Tuszynski et al., 1996, 1997; Grill et al., 1997; Blesch and Tuszynski, 1997). Taken together, these studies support a role for neurotrophic factors in the repair of the mature CNS. *The regrowth of supraspinal and propriospinal input across the transection site was associated with consistent improvements in hindlimb locomotor function. Animals performed alternating and reciprocal hindlimb stepping with plantar foot contact to the treadmill or stair during ascension. Furthermore, they acquired hindlimb weight support and demonstrated*

appropriate postural control for balance and equilibrium of all four limbs. After spinal cord injury in the adult, the circuitry underlying rhythmic alternating stepping movements is still present within the spinal cord caudal to the lesion, but is now devoid of supraspinal control. We show here that restoring even relatively small amounts of input allows supraspinal neurons to access the spinal cord circuitry. Removing the re-established supraspinal input after recovery (by retransection rostral to the transplant) abolished the recovery and abolished the serotonergic fibers within the transplant and spinal cord caudal to the transplant. This suggests that at least some of the recovery observed is due to re-establishing supraspinal input across the transplant, rather than a diffuse influence of the transplant on motor recovery. It is unlikely, however, that the greater recovery of function in animals that received delayed transplant and neurotrophins is due solely to the restoration of supraspinal input. Recent work by Ribotta et al. (2000) suggests that segmental plasticity within the spinal cord contributes to weight support and bilateral foot placement after spinal cord transection. This recovery of function occurs after transplants of fetal raphe cells into the adult spinal cord transected at T11. Recovery of function appears to require innervation of the L1-L2 segments with serotonergic fibers, and importantly, animals require external stimulation (tail pinch) to elicit the behavior. In the current study, animals with transection only did not develop stepping overground or on the treadmill without tail pinch, although the transplant and neurotrophin-treated groups did so without external stimuli. *Therefore both reorganization of the segmental circuitry and partial restoration of supraspinal input presumably interact to yield the improvements in motor function observed. It is unlikely that the recovery of skilled forelimb movement observed can be mediated solely by reorganization of segmental spinal cord circuitry. We suggest that the restoration of supraspinal input contributes to the recovery observed. It is likely that after CNS injury, reorganization occurs both within the spinal cord and at supraspinal levels, and together contribute to the recovery of automatic and skilled forelimb function and of locomotion.* These findings suggest that opportunity for intervention after spinal cord injury may be far greater than originally envisioned, and that CNS neurons with long-standing injuries may be able to re-initiate growth leading to improvement in motor function.

HyperMED NeuroRecovery Australia

HyperMED NeuroRecovery continues to pioneer the *principles of neuroplasticity* through the application of Hyperbaric Oxygenation (HBOT), Lokomat (Robotic Gait Assisted Walking), Median Nerve Stimulation combined with assertive supportive therapies in the treatment and management of chronic brain and spinal injury.

Hyperbaric Oxygenation simply stated is breathing 100% oxygen at pressures greater than normal. Typically we breathe 21% oxygen (or less in larger populated cities) - Hyperbaric drives greater levels of enriched oxygen into the body enabling the effects of hypoxia (inadequate oxygenated blood) to be corrected.

Hyperbaric acts as a 'catalyst' promoting functional immune responses by correcting deep seated hypoxia in damaged tissue structures. Hyperbaric tissue oxygenation results in increased blood flow by fostering the formation of 'new capillary dynamics' into damaged regions of the body. Hyperbaric tissue oxygenation accelerates neuroplasticity - activating damaged and dormant nerve cells.

Approximately 20-30% of the body's consumption of Oxygen occurs within 3-5% of the body mass - the brain and spinal cord. These structures are extremely sensitive to Oxygen deficiency, and can have the most dramatic results with the use of HBOT. This increased tissue Oxygenation significantly accelerates the rate of healing, stabilization and repair. The central nervous system is mobilized for repair!

'Hyperbaric Oxygenation provides the available fuel and acts as a catalyst to the underlying central issue of damage (hypoxia). HBOT diminishes the further cascade of Apoptosis (programmed cellular degeneration). HBOT activates dormant and inactive nerve cells hastening recovery. HBOT mobilizes and elevates the patient's own circulating neural stem cells that are target specific whilst preparing the body for further stem cell implantation techniques

American Journal Physiology - Heart and Circulatory Physiology (Nov 05)] reports a single 2-hour exposure to HBOT at 2 ATA doubles circulating CD34+ progenitor stem cells (primordial cells targeted to salvage and restore damaged structures); and at approx. At 40-hours HBOT - circulating CD34+ cells increases eight fold (800%)

Lokomat (Robotic Gait Assisted Walking) and other forms of intensive physical therapy including Median Nerve Stimulation drives functional reorganization and recovery – patients with brain and spinal cord injury have the capacity to retrain and reconnect function'

Hyperbaric provides the available fuel and acts as a catalyst to the underlying central issue (hypoxia). Lokomat (Robotic Gait Assisted Walking) and other forms of intensive physical therapy are required to 'drive' neuroplasticity - the ability of the neurons in the nervous system to develop new connections and 'learn' new functions. The rate of neuroplasticity is directly impacted by the levels of continuing hypoxia which blocks recovery! This combined Hyperbaric Lokomat approach 'awakens' dormant neural pathways and provides accurate neurological repetition enhancing and re-training connections and pathways in the brain and spinal cord. Patients have the ability to 'salvage back' what has been damaged improving brain and spinal cord function - to regain walking ability or learn to walk!

Lokomat (Robotic Gait Assisted Walking)

For the past 15-years bodyweight supported treadmill training (BWSTT) has become a prominent gait rehabilitation method in leading rehabilitation centers throughout the world. This type of locomotor training has many functional benefits but the labor costs are considerable. To reduce therapist effort, Robotically Gait Assisted BWSTT (Lokomat) has been shown to be more accurate and financially feasible, compared to the other BWSTT modalities. Currently 45+ Lokomat systems are in use in large Neurorehabilitation hospitals in the USA and approximately 150 Lokomat systems found in 31 Countries.

In December 2006 HyperMED NeuroRecovery located in Melbourne installed Australia's first Adult and Pediatric Lokomat systems (Robotic Gait Assisted Body Weight-Support Treadmill Training) providing opportunity for adults and children with gait impairment due to spinal or cerebral motor disorder to improve functional outcomes.

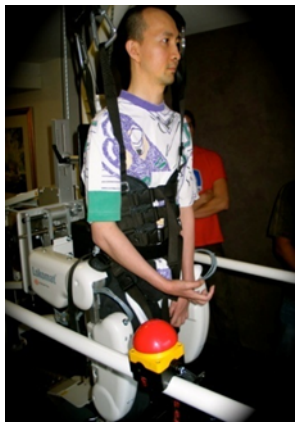
Neural plasticity refers to the natural ability of the neurons in the nervous system to generate and develop new connections aimed at repairing the neuronal damages. In the other word, they can learn new tasks. Based on this fact, locomotor training focuses on retraining the nervous system through simulating and repetition of walking gait, in order to regain their function and/or enhance their existing potentials. By repetitively stimulating the muscles and nerves in the lower body Lokomat Gait Assisted Training works to *awaken dormant neural pathways controlling standing, stepping and balance*. Experiments conducted on spinalized cats demonstrate that treadmill walk was possible suggesting evidence of a *central gait pattern generator which remain active; these spinal generators drive the ability to re-learn function.* When these generators are not activated the spinal circuits remain dormant;

this *inability to realize a movement* combined with the neuroplasticity of the central nervous system may induce a secondary functional incapacity called *"learning non use" – the ability to sit!*

Locomotor Gait Assisted Training refers to an intervention for retraining patients to walk after neurologic injury providing repetitive, intensive and task specific training that induces neuronal plasticity and subsequently cortical reorganization after brain and spinal cord damage. The goals of locomotor training are to capitalize on the intrinsic mechanisms of the CNS that respond to sensory input associated with walking to generate a stepping response and the ability of the CNS to learn through intensive, task-specific repetition and practice. Task specific training such as *gait assisted walking enables repair and reorganization* of processes in the central nervous system. In order to walk or regain functional capacity the injured patient must 're-learn to walk'.

Activity based rehabilitation after neurological injury relies on three principles of motor learning. *Practice* is the first principle. All other things being equal, *more functional learning will occur with more accurate practice*. *Specificity* is the second principle. *The best way to improve performance of a motor task is to execute that specific motor task repeated many times*. *Effort* is the third principle. *Individuals need to maintain a high degree of focus, participation and involvement to facilitate motor learning*. These three principles are critical to promoting activity-dependent plasticity (i.e. altering the efficacy and excitation patterns of neural pathways by activating those pathways). With regards to neurological rehabilitation, it is important to emphasize that plasticity occurs in neural pathways that are *active*.

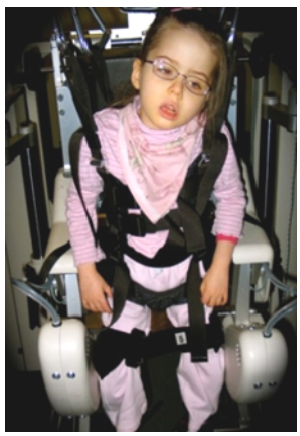
'Practice – greater functional learning occurs with more accurate practice.
Specificity – accurate repetition of the desired task to be acquired repeated many times over.
Effort – you have to focus and be prepared to work!'



Over the past decades, extensive research studies have assessed and evaluated the use and benefits of body weight-supported locomotor training. These studies reveal that BWSTT can effectively improve walking parameters such as speed, limb coordination, distance, and level of independence. It has also been shown that BWSTT in incomplete SCI patients can also lead some positive neurological alterations namely stepping ability, corticospinal tract function, and increased electromyography activity. Manually assisted treadmill training has been used for more than 15-years as a regular training for patients with spinal cord injury and stroke. The most extensive study published to date found that *80% of wheelchair bound patients with chronic incomplete spinal cord injury gained functional walking ability after functional training* Spinal Cord Inj Rehabil 2005. Unfortunately BWSTT has not found prominence in Australian hospitals or private rehabilitation clinics.

What are the limits of Lokomat Gait Training? Patients with spinal cord injuries who have been wheelchair bound for many years are still potentially able to ambulate. Improving a patient to the point that he/she no longer needs a wheelchair to move would definitely lead to reducing the yearly costs of his/her neurological disease as well as the financial burden of wheelchair-associated complications such as; pressure ulcers, circulatory disorders, osteoporosis and attendant care. Lokomat Gait Training also records *improved cardiovascular performance and reductions in spasticity, bone loss and bladder/bowel complications*.

The Lokomat has been suggested to be predestined for patients with complex neurologic disability who are too weak to walk over-ground without external support and thus require the assistance of several therapists to perform body-weight- supported treadmill training. Our experience (HyperMED NeuroRecovery) is that Lokomat Gait Training is highly adaptable for all patients with disability. Lokomat Gait Training can provide numerous accurate repetitions necessary to restore activity especially walking function with neurologic patients. Lokomat Gait Training kinetic settings can be varied and specifically adjusted throughout the training session intensifying functional outcomes. Patients with incomplete spinal lesions and with stroke undertaking Lokomat Gait Training have measurable functional changes; *reflex stiffness and spasticity are significantly reduced; range of motion, peak velocity and acceleration of voluntary movements are increased with patients with incomplete spinal lesions and stroke*. Therefore the walking ability improves as well as functional independence.



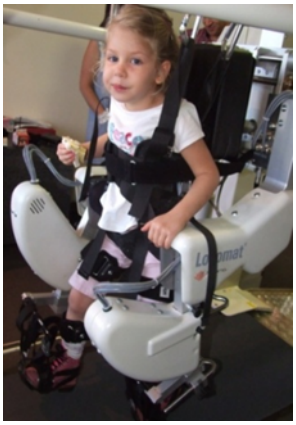
Additionally, it has been revealed that Lokomat Gait Training can lead to functional improvements in patients with different neurological diseases such as; Multiple Sclerosis, Chronic Stroke, Parkinson's Diseases, Cerebral Palsy (CP), as well as the other various types of idiopathic and secondary muscular dystrophies and neurological disorders in adult and children. In stroke hemiparetic patients BWSTT has been shown to *improve balance, lower limb motor recovery, walking speed, endurance, and other important gait characteristics such as symmetry, stride length and double stance time*.

Moreover, a number of research studies have shown that Lokomat Gait Training can not only improve the gait in neurological patients but also positively affect *cardiovascular and general health regulations*. For this reason, to keep a level of maintenance treadmill training after the initial period of intense training is highly recommended.

Cerebral Palsy and Lokomat – Learning to Walk!
The central nervous system develops function through interaction. Activities that we take for granted shape our nervous system developing healthy skills and mental function that ensures a healthy developing child. When the brain and spinal cord suffer 'hypoxic injury' the normal development and the ability to develop normal skills become replaced by abnormal signal leading to disabilities the brain recognizes as 'normal'. Abnormal signals need to be corrected through functional re-organization. Lokomat treadmill training is a task-specific rehabilitation strategy that enhances neurologic re-organization impacting cognitive function and development!

The ability to walk is a complex motor activation pattern organized hierarchically, with the uppermost level (initiation of the movement) mediated through the primary cortex in the brain and the lowest levels (organization and execution of the movement) mediated through the

spinal motor neurons. Hypoxic injury at any level directly affects the ability to walk – the ability to generate the correct movement and the execution of that movement.



Innate pattern generators in the spine produce the newborn stepping. During the first year of development the 'corticospinal tracts' grow which transforms this innate ability towards a normal stepping. Children with disability do not 'learn' this function properly and adult patients suffering neurodegenerative disorders progressively loose this ability and have to re-train and re-learn to walk!

The Pediatric Lokomat has been clinically deployed in our rehabilitation centre (HyperMED NeuroRecovery) since December 2006. Pediatric Lokomat offers opportunity to practice a most physiological gait pattern in a high intensity and frequency for children with gait impairment due to spinal or cerebral motor disorder including cerebral palsy. With this new tool, not only longer distances and therefore "higher dosages" of gait therapy, but also various and higher speeds can be trained, which is not possible to this extent with conventional physiotherapeutic methods. The Pediatric Lokomat raises many new topics of research about the effectiveness, dosage and age related application of this new therapy.

The Lokomat produces a constraint-induced movement therapy of a specific task - the gait training enables pattern of muscle activation as physiologic as possible. The alternating 'stance and swing phase' of the Lokomat generates afferent inputs which stimulate the spinal gait generator inducing a motor reorganization and acquisition of forgotten skills or the learning of new ones. The partial body weight support allows patients to stand even with very weak muscles.

It is common practice in physical therapy to move a patient's limbs and joints through natural motion in order to improve function. Gait ability is a complex motor activation pattern organized hierarchically with the upper most level (initiation of the movement) mediated through the primary cortex and the lowest levels (organization and execution of the movement) mediated through the spinal motor neurons. There is evidence that innate pattern generators in the spine produce newborn stepping. During the first year of a child's development there is a transformation of this innate ability towards a normal plantigrade stepping through corticospinal tract development. This process of learning is dysfunctional in children with cerebral palsy and then reinforced over time. Equally patients with progressive neurodegenerative disorders progressively loose this functional ability and have to re-train and re-learns to walk!

The deficit induced by a central nervous system lesion depends on which group of cells is damaged: lesions of the upper motor neuron let some muscle contractions even with an altered highest cortical control. Lesions of the lower motor neuron result in flaccid paresis without the ability to recover some movements. Therefore central nervous system lesions produce different symptoms: paresis, somatosensory deficits which induce inactivity and loss of function. This inability to realize a movement combined with the neuroplasticity of the central nervous system may induce a secondary functional incapacity called the "learning non use". Functional incapacity is challenging for the child, parents and therapist. Acquired deformity results in a cascade effect of adaptation and dysfunction notwithstanding psychological effects.

Children with cerebral palsy have an acquired dysfunction which their central nervous system function deems normal. This is evident when CP children undertake an intensive Lokomat Gait Training protocol. Many of these children demonstrate a 'normal gait' whilst on the Lokomat which raises question of acquired neural pathways and motor function wrongly developed and reinforced over time. When these same children come off the Lokomat they immediately return back to the acquired gait. Intensity and repetition enables the CP child to generate a new functionality which resembles a 'normal gait'. It is a frequent finding to observe the bewilderment of both parents and CP child when the child sees themselves 'walking normal' on the Lokomat. Visualization whilst on the Lokomat is an important paradigm shift for not only the CP child and parent but also the therapist.

Task specific training such as Lokomat Gait Assisted Walking enables *repair and reorganization of innate processes in the central nervous system*. In order to walk or regain functional capacity the injured patient must re-learn to walk. Re-organization of processes refers to the development of the brain to find alternate pathways sending improved electrical signals. It is possible for the brain to transfer function responsibility to another part of the brain. It has also been demonstrated that strength training in children with CP can increase strength as well as result in higher gait velocity. Similar to strength training, treadmill training with partial body weight support, as discussed before, can improve walking speed and endurance of children with CP who can already walk. Furthermore, it has been found that, in some cases, treadmill training with partial body weight support can achieve completely independent mobility for previously non-ambulatory children with CP.

All the above mentioned improvements would lead to positively changing the quality of life of the affected individuals, boost up their physical capacity, their confidence and increase the valuable time they spent in their community.

What the advantages of using Robotically Assisted Gait Training (Lokomat) compared to manual bodyweight supported treadmill training (BWSTT)?

Because manual assisted bodyweight supported treadmill training has high therapist labor requirements, research groups around the world have developed a host of robotic devices to assist treadmill stepping. In manual BWSTT, at least three to four specially trained therapists are required to move the patient's legs and body. The purpose of these robotic machines is to replace therapist manual assistance, increasing the amount of stepping practice and accuracy while decreasing therapist effort.

Manually assisted treadmill training (BWSTT) has several major limitations. The training is labor-intensive and biomechanically challenging to the active therapist; therefore, training duration is usually limited by personnel shortages and therapist, not patient fatigue. Furthermore, therapists often experience back pain because the training is performed in an ergonomically unfavorable seating posture. Consequently, training sessions are shorter than may be required for an optimal therapeutic outcome. The most compelling argument for Lokomat is that manually assisted treadmill training lacks accurate repeatability and objective measures of patient performance and progress. In contrast, the duration and number of sessions in Lokomat Gait Training can be accurately repeated and increased while reducing the number of therapists required for each patient. Indeed, one therapist may be able to train two or more patients at a time in the future.

Lokomat has great advantage providing *intensive task specific repetitive training that induces neuronal plasticity and subsequently cortical reorganization after brain and spinal cord damage*. Patients with high level spasticity causing compensatory gait dysfunction are better suited on the Lokomat than manual BWSTT. *Lokomat parameters can be initially set at very low and controlled setting providing a safe environment for the patient to develop confidence and allow functional reorganization through repetition and patterning.* These parameters can then be built on and individually tailored to the specific requirements and functional responses of the individual patient. Lokomat provides task specific accuracy and repetition stimulating innate central pattern reflexes and higher cortical function.

Robotic training drives brain and spinal neuroplasticity

Neurorehabil Neural Repair. 2005 Dec;19(4):313-24
Functional BOLD MRI changes in cerebellum (supraspinal) following Lokomat in motor-incomplete spinal cord injury
University of Texas Southwestern Medical Center, Department of Physical Therapy, Dallas, USA. patricia.winchester@utsouthwestern.edu
OBJECTIVES: Body weight-supported treadmill training (BWSTT) is a task-specific rehabilitation strategy that enhances functional locomotion in patients following spinal cord injury (SCI). *Supraspinal centers may play an important role in the recovery of over-ground locomotor function in patients with motor-incomplete SCI.* The purpose of this study was to *evaluate the potential for supraspinal reorganization associated with 12 weeks of robotic BWSTT using functional magnetic resonance imaging (fMRI).* METHODS: Four men with motor-incomplete SCI participated in this study. Time since onset ranged from 14 weeks to 48 months post-SCI injury. All subjects were trained with BWSTT 3 times weekly for 12 weeks. This training was preceded and followed by fMRI study of supraspinal activity during a movement task. Testing of locomotor disability included the Walking Index for Spinal Cord Injury (WISCI II) and over-ground gait speed. RESULTS: *All subjects demonstrated some degree of change in the blood-oxygen-level-dependent (BOLD) signal following BWSTT. fMRI results demonstrated greater activation in sensorimotor cortical regions (S1, S2) and cerebellar regions following BWSTT.* CONCLUSIONS: *Intensive task-specific rehabilitative training, such as robotic BWSTT, can promote supraspinal plasticity in the motor centers known to be involved in locomotion. Furthermore, improvement in over-ground locomotion is accompanied by an increased activation of the cerebellum.*

Brain Res Bull. 2009 Jan 15;78(1):4-12
Robotic training and spinal cord plasticity
Department of Physiological Science, University of California, Los Angeles, CA 90095, USA. vre@ucla.edu
What is the potential for recovery of locomotor ability after a spinal cord injury? *Both human and animal studies show that the spinal cord has the potential to reorganize and/or readjust to the loss of supraspinal input and utilize the remaining peripheral input to actually control stepping and standing.* Motor training can be used to provide sensory ensembles within the *spinal circuitry are task-specific*, i.e., *step training improves stepping and stand training improves standing*. A large component of this learning is a function of improved coordination of motor pools within and among limbs. The most successful type of training includes variability in the performed task, i.e., monotonous repetition of the exact same sensorimotor pattern results in "learned disuse". The use of robotics for training specific motor tasks has become more prevalent recently and we report here that using an "assist-as-needed" approach for step training after a severe spinal cord injury provides a high probability of successful rehabilitation. The "assist-as-needed" paradigm allows variability in the step trajectory within specific boundaries such that the robotic arms constrain the deviations in a manner mimicking that observed under normal, intact conditions. Another critical feature of robotic devices or step training seems to be the ability to integrate normal hip and leg motion as occurs during normal stepping. *These types of robotic devices have the potential to aid therapists in the clinical setting and to enhance the ability of spinal cord injured individuals to regain the maximum locomotor ability possible*.

Brain Res Bull. 2009 Jan 15;78(1):22-5
Plasticity properties of Central Pattern Generators circuits in humans: impact on gait recovery
IRCCS Santa Lucia Foundation, Roma, Italy. m.molinari@hsantalucia.it
Recent data on spinal cord plasticity after spinal cord injury (SCI) emphasize the influence of 'task specific training' on determining the functional organization of the spinal circuits that provide the appropriate sequence and intensity of muscular activation needed for gait the so-called central pattern generator (CPG) circuits. This evidence questions the essence of CPG circuits. Are the CPG characteristics innate or are they induced in spinal cord neurons by training? The answer of this question present obvious consequences on the rehabilitative approach to spinal cord injury patients. After briefly reviewing present knowledge on the anatomical and functional organization of spinal CPG in animal models of SCI, data on humans are presented. Evidence indicating that, after SCI, specific functional properties of gait CPG can be induced de novo by specific training in spinal neurons are reported and the hypothesis that CPG circuits may be determined by experience is advanced.

J Spinal Cord Med. 2008;31(5):509-21.
Neuromotor and musculoskeletal responses to locomotor training for an individual with chronic motor complete AIS-B spinal cord injury
Kessler Medical Research and Education Center, West Orange, NJ 07052, USA. gforrest@kmrrec.org
BACKGROUND/OBJECTIVE: To determine the effects of locomotor training (LT) using body weight support (BWS), treadmill, and manual assistance on muscle activation, bone mineral density (BMD), and body composition changes for an individual with motor complete spinal cord injury (AIS B), 1 year after injury. METHODS: A man with chronic C6 AIS B (motor complete and sensory incomplete) spinal cord injury (SCI), 1 year after injury, completed 2 blocks of LT over a 9-month training period (35-session block followed by 8.6 weeks of no training and then a 62-session block). RESULTS: Before training, muscle activation was minimal for any muscle examined, whereas after the 2 blocks of LT (97 sessions), hip and knee muscle activation patterns for the bilateral rectus femoris, biceps femoris, and gastrocnemius were in phase with the kinematics. Mean EMG amplitude increased for all bilateral muscles and burst duration increased for rectus femoris and gastrocnemius muscles, whereas burst duration decreased for the biceps femoris after 62 LT sessions. Before LT, left biceps femoris had a pattern that reflected muscle stretch, whereas after training, muscle stretch of the left biceps femoris could not totally account for mean EMG amplitude or burst duration. After the 62 training sessions, total BMD decreased (1.54%), and regional BMD decreased (legs: 6.72%). Total weight increased, lean mass decreased (6.6%), and fat mass increased (7.4%) in the arms, whereas fat mass decreased (3.5%) and lean mass increased (4%) in the legs. CONCLUSIONS: *LT can induce positive neural and body composition changes in a non-ambulatory person with chronic SCI, indicating that neuromuscular plasticity can be induced by repetitive locomotor training after a motor complete SCI.*

Arch Phys Med Rehabil. 2005 Apr;86(4):672-80.
Effectiveness of automated locomotor training in patients with chronic incomplete spinal cord injury: a multicenter trial
Spinal Cord Injury Center, Balgrist University Hospital, Zurich, Switzerland.
OBJECTIVE: *To determine whether automated locomotor training with a driven-gait orthosis (DGO) can increase functional mobility in people with chronic, motor incomplete spinal cord injury (SCI).* DESIGN: Repeated assessment of the same patients or single-case experimental A-B design. SETTING: Research units of rehabilitation hospitals in Chicago; Heidelberg, Germany; and Basel and Zurich, Switzerland. PARTICIPANTS: *Twenty patients with a chronic (>2 y postinjury), motor incomplete SCI,* classified by the American Spinal Injury Association (ASIA) Impairment Scale with ASIA grades C (n=9) and D (n=11) injury. Most patients (n=16) were ambulatory before

locomotor training. INTERVENTION: *Locomotor training was provided using robotic-assisted, body-weight-supported treadmill training 3 to 5 times a week over 8 weeks.* Single training sessions lasted up to 45 minutes of total walking time, with gait speed between .42 and .69 m/s and body-weight unloading as low as possible (mean +/- standard deviation, 37%+/-17%). MAIN OUTCOME MEASURES: Primary outcome measures included the 10-meter walk test, the 6-minute walk test, the Timed Up & Go test, and the Walking Index for Spinal Cord Injury-II tests. Secondary measures included lower-extremity motor scores and spastic motor behaviors to assess their potential contribution to changes in locomotor function. All subjects were tested before, during, and after training. RESULTS: *Locomotor training using the DGO resulted in significant improvements in the subjects' gait velocity, endurance, and performance of functional tasks.* CONCLUSIONS: *Intensive locomotor training on a treadmill with the assistance of a DGO results in improved overground walking.*

Annu Rev Neurosci. 2004;27:145-67
Plasticity of the spinal neural circuitry after injury
Brain Research Institute, University of California, Los Angeles, California 90095, USA. vre@ucla.edu
Motor function is severely disrupted following spinal cord injury (SCI). The spinal circuitry, however, exhibits a great degree of automaticity and plasticity after an injury. *Automaticity implies that the spinal circuits have some capacity to perform complex motor tasks following the disruption of supraspinal input, and evidence for plasticity suggests that biochemical changes at the cellular level in the spinal cord can be induced in an activity-dependent manner that correlates with sensorimotor recovery. These characteristics should be strongly considered as advantageous in developing therapeutic strategies to assist in the recovery of locomotor function following SCI. Rehabilitative efforts combining locomotor training pharmacological means and/or spinal cord electrical stimulation paradigms will most likely result in more effective methods of recovery than using only one intervention.*

Orthostatic instability improves with Lokomat Training

J Neurotrauma. 2009 Jan 2.
Improvements in Orthostatic Instability with Stand Locomotor Training in Individuals with Spinal Cord Injury
Kentucky Spinal Cord Injury Research Center, Department of Neurological Surgery, University of Louisville , Louisville, Kentucky., 2 Frazier Rehab Institute , Louisville, Kentucky., 3 Department of Neurology and Brain Research Institute, University of California , Los Angeles, California., 4 International Collaboration on Repair Discoveries (ICORD), Division of Physical Medicine and Rehabilitation, and School of Rehabilitation, Department of Medicine University of British Columbia , and Spinal Cord Injury Program, G.F. Strong Rehabilitation Centre, Vancouver, British Columbia, Canada .
Abstract Prospective assessment of cardiovascular control in individuals with spinal cord injury (SCI) in response to active stand training. *Cardiovascular parameters were measured at rest and in response to orthostatic challenge before and after training in individuals with clinically complete SCI.* The goal of this study was to evaluate the effect of active stand training on arterial blood pressure and heart rate and changes in response to orthostatic stress in individuals with SCI. *Measurements were obtained in individuals with SCI (n = 8) prior to and after 40 and 80 sessions of the standing component of a locomotor training intervention (stand LT).* During standing, all participants wore a harness and were suspended by an overhead, pneumatic body weight support (BWS) system over a treadmill. Trainers provided manual facilitation as necessary at the trunk and legs. *All individuals were able to bear more weight on their legs after the stand LT training. Resting arterial blood pressure significantly increased in individuals with cervical SCI after 80 training sessions. At the end of the training period, resting systolic blood pressure (BP) in individuals with cervical SCI in a seated position, increased by 24%* (from 84 +/- 5 to 104 +/- 7 mmHg). Furthermore, orthostatic hypotension present in response to standing prior to training (decrease in systolic BP of 24 +/- 14 mmHg) was not evident (decrease in systolic BP of 0 +/- 11 mmHg) after 80 sessions of stand LT. Hemodynamic parameters of individuals with thoracic SCI were relatively stable prior to training and not significantly different after 80 sessions of stand LT. Improvements in resting arterial blood pressure and responses to orthostatic stress in individuals with clinically complete cervical SCI occurred following intensive stand LT training. *These results may be attributed to repetitive neuromuscular activation of the legs from loading and/or conditioning of cardiovascular responses from repetitively assuming an upright posture.*

MEDICAL UPDATE

Q: What is the future for patients that regain some degree of function?
A: Functional independence

All spinal patients desire 'greater independence' – for some it is to be to be able to sit and transfer better, others to stand; to take a few steps or to continue to do exactly what we were designed to do – to walk! Every spinal patient's ability to recover the ability to walk is dependent on the level of injury. However emerging robotic assisted devices are currently being trialled which will endeavour to enable greater independence among spinal patients.

To become an eligible candidate for emerging robotic assisted devices ultimately requires upper limb function. The immediate objective for injured cervical spinal patients is to regain and improve upper limb functionality. Upper limb functional control is required for upper spinal cord patients in order to be able to operate robotic assisted devices. Lower spinal cord injury i.e. T12/L1 have greater capacity to regain walking independence.

Re*Walk*™ is part of the future!

The novelty of Re*Walk*™ is in the unique manner in which the user is actively involved in the walk-restoration and other mobility functions, through the control processes. Utilizing sophisticated algorithms, upper-body motions are analyzed and used to trigger and maintain walk (gait) patterns and other modes of operation (such as stair-climbing and shifting from sitting to standing), leaving the hands free for self support and/or other functions.

Re*Walk*™ is a wearable, motorized quasi robotic suit. Partially concealable under clothing, ReWalk provides user-initiated mobility - leveraging advanced motion sensors, sophisticated robotic control algorithms, on-board computers, real-time software, actuation motors, tailored rechargeable batteries and composite materials.

Re*Walk*™ works with users – not just for them. Users walk with the assistance of crutches, controlling suit movement through subtle changes in center of gravity and upper-body movements. In addition to simplifying suit control, this user participation in mobility brings tangible health and emotional benefits. Re*Walk*™ is not just a vertical wheelchair – Re*Walk*™ restores the element of control over mobility so lacking for wheelchair users.

As any sedentary wheelchair user can attest, life in a wheelchair carries a hefty healthcare price tag. Serious problems with the urinary, respiratory, cardiovascular and digestive systems are common, as well as osteoporosis, pressure sores and other afflictions. By maintaining users upright on a daily basis, and exercising even paralyzed limbs in the course of movement, Re*Walk*™ alleviates many of the health-related problems associated with long-term wheelchair use. In addition to relieving suffering, this has a real impact on healthcare costs – cutting yearly expenses almost in half, and enabling both insurers and individuals to redirect funds to other avenues.

Adoption of Re*Walk*™ by wheelchair users results in significant cost saving at both institutions and private homes. Re*Walk*™ makes standing devices, stair lifts, bed lifts, and other mobility assistance apparatus redundant. Similarly, Re*Walk*™ users don't require expensive powered wheelchairs – or the oversize vehicles and devices required to handle them. With Re*Walk*™, users require only minimal additional mobility assistance – saving tens of thousands of dollars yearly.

Re*Walk*™ can serve as a robotic therapeutic or physical training device, used for intensive functional locomotion therapy. By replacing or supplementing expensive mechanized gait trainers, for example, Re*Walk*™ allows institutions to redirect significant budget resources for other therapeutic activities.

Functionality:

- All day usage
- *Mobility – walking, sit-to-stand, stand-to-sit, climb stairs, driving*
- Training – replacing other training equipment at home and at rehabilitation center

Prerequisites:

- Ability to use hand and shoulders (walking with crutches)
- Healthy cardiovascular system and bone density

Re*Walk*™ is schedule for commercial release 2010 – approximate cost US 25,000!

MEDICAL UPDATE
Honda Walking Assistance Device

Honda has also ventured in the robotic walking assistance space however the target market appears to be more directed towards the aging population and work hardening environments. Honda Assisted Walking (pictured above right) demonstrations can be viewed on You Tube.

Brain Res Bull. 2008 Jul 30;76(5):459-63. Epub 2008 Mar 25
Body weight supported gait training: from laboratory to clinical setting
Dietz V. University Hospital Balgrist, Spinal Cord Injury Center, Forchstr. 340, CH-8008 Zurich, Switzerland. volker.dietz@balgrist.ch
After spinal cord injury (SCI) of the cat or rat neuronal centres below the level of lesion exhibit plasticity that can be exploited by specific training paradigms. In individuals with complete or incomplete SCI, human spinal locomotor centers can be activated by appropriate afferent input. This includes to facilitate and assist stepping movements of the legs and to provide body weight support (BWS) standing on a moving treadmill. *Individuals with incomplete SCI benefit from such a locomotor training such that they improve the ability to walk over ground.* Load- and hip-joint-related afferent input seems to be of crucial importance for both the generation of a locomotor pattern and the effectiveness of the training. It appears to be a critical combination of afferent signals that is needed to generate and improve a locomotor pattern after SCI. Mobility of individuals after a SCI can be improved by taking advantage of the plasticity of spinal neuronal circuits and can be maintained with persistent locomotor activity. Since several years driven gait orthoses can provide a standardized locomotor training. In the future, if regeneration approaches can successfully be applied in human SCI, even individuals with complete SCI may recover walking ability with locomotor training. *Presently, individuals with complete SCI, spinal neuronal circuits undergo a degradation of their function 1 year after injury evidenced by progressive cord degeneration.*

HyperMED Patient Update
Isabella Del Castillo – Chronic T6 incomplete - Mexico

From: VERONICA P VAZQUEZ DE DEL CASTILLO veronicadelcastillo@gmail.com
Date: May 3, 2008 2:20 PM
Subject: ISABEL DEL CASTILLO
To: 'Dr Mal Hooper'
CC: raymundo del castillo raymundodelcastillo@googlemail.com

Isabella injured her spine in 2006 after a horse riding accident; classified T7/8 incomplete she has massive spasticity of her legs held fixed rigid.

'Dear Dr. Hooper,

Raymundo, Isabel and my-self wish you are doing great! It´s been almost a year since we were in Melbourne, and many small great things have been happening around Isabel´s well being, and we will like to share with you what Isabel has been going through, for we would like if possible to come back to Melbourne this coming July and August for our summer vacations and while there have Isabel working on the Lokomat and the hyperbaric chamber.

We have been considering either Switzerland or Australia for this summer, taking in consideration that Isabel even during vacations has to keep on with her rehab process, and the Lokomat and hyperbaric combination seem to us the most beneficial option for her.

In October 2007, Isabel was accepted at the Guttman Institute in Barcelona for a three month rehab protocol which included 45-minutes Lokomat each day. Her physiotherapist noticed after time that she was able to make a random step with one leg and encouraged her to start in parallel bars with a harness to support herself and with the aid of electroestimulators to enable the step in the other limb and to help whenever the steps couldn't come out properly. Since then she kept on working and improving little by little.

Currently she can walk (pictured right) without the electrostimulators almost 250.meters! Doctors say that her walking is because of reflex movement that has been activated by Lokomat. Isabel is also able to stand up, still supporting herself in the parallel bars, and without any harness. She is working very hard to improve tone in dorsal muscles in order to get stability, and keeps up with the self walking exercise now with the help of a wheeled walking device. She is gaining tone and confidence. We are aware that there is still a lot of time and effort involved in order for Isabel to keep improving, but we are positive and sure that at this stage there is a very optimistic panorama for her better being and we are strongly convinced that the Lokomat and hyperbaric combination have been decisive in her improvements.

Spasticity is still a big issue for her independent life but it has lessened considerably considering what you saw while we were in Melbourne, we have observed that now the more she moves the less spasticity she now has which has greatly improved her day to day life!

In this process there have been many other small, but great improvements, which we would like to share with you. Isabel and ourselves are very happy, confident and hopeful that she will keep on improving and very much aware that she has to put a great deal of effort and work very hard in order to achieve positive results, and above all she is completely certain and confident about the benefits of the hyperbaric and Lokomat combination.

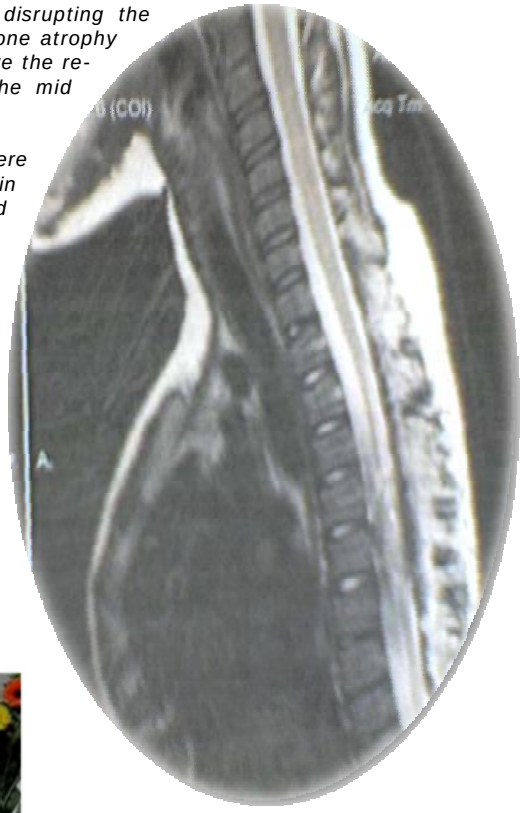
We take this opportunity, to thank you and hope to continue with your protocol; please let us know if it is possible for Isabel to come for 6 weeks this coming summer, so that we can start making our trip arrangements.

Our best regards - Veronica and Raymundo del Castillo

HyperMED Patient Update
Isabel Martin – Spinal Tumour – Chronic T4 complete - Melbourne

Isabel was born a normal healthy baby. 'At the age of 8 months Isabel was diagnosed with a large spinal tumor located in her mid upper spine. There was no way to know if the tumor was benign or malignant; as much of the tumor was removed however the radical surgery left Isabel completely paralyzed from the waist down. Over the years Isabel has also developed severe scoliosis and kyphosis curvature of her spine.

MRI prior to commencing at HyperMED revealed a large mass re-growth completely disrupting the thoracic spinal cord. The spinal cord immediately above and below the mass has undergone atrophy (wasting); in addition cord syringomyelia extends an additional 3-vertebral segments above the re-growth. In addition there is evidence of subtle T2 hyperintensity extending up into the mid cervical spinal cord.



'Today we are more optimistic and hopeful than ever that Isabel will regain function! We were considering a trip to the USA to take advantage of Lokomat Robotic Walking to help retrain neurological function when we read about HyperMED and that the Lokomat had arrived Melbourne!

After only 40-hours in the hyperbaric chamber and 8-hours on the Lokomat the changes Isabel began experiencing were amazing, and as parents we are thrilled. Isabel can now initiate movement in her pelvis and both legs. She can now lift both her legs up and down repeatedly and continues to demonstrate increasing functional changes and greater independence.

Isabel is very excited about the changes she sees and feels. We can see she is much happier that we are doing something proactive to help her regain as much function as possible. – She has always asked, "When do you think I will be able to walk?" Of course we don't know the answer but it feels tangible.' Cathryn (mother)

You can also see Isabel in action by visiting the HyperMED Media file section at www.hypermed.com.au or visit You Tube under 'Spinal Cord Injury HyperMED NeuroRecovery'.

Channel 7 NEWS Spinal Cord Injury

Spinal Cord Injury - Isabel NOW moving her legs!

HyperMED Patient Update
Dion McCafferty – Chronic T6 incomplete – South Africa

Posted by Dion McCafferty at http://myprojecttowalk.blogspot.com/
Hi I'm Dion; in Feb 07 I suffered a T6 spinal injury in a car accident in Cape Town, South Africa. I was the passenger - this is my journey to walk again!

South Africa offers very little as far as activity based spinal rehabilitation; you're told very early after the accident that this is as good as it gets and to learn to accept your disability! I have never been one to sit back and wait for a miracle; I have constantly pursued many forms of rehab that may help; I also spent time at Project Walk in the USA and over time I have made incredible gains.

I am now able to walk with a walker but with a great deal of spasticity. I am very active in the gym and I spend a lot of time on a stationary spin bike. I have come to Australia because of the intensive program offering Hyperbaric and Lokomat. My desire is to get more function and realize my dreams and be able to run on the beach again with my kids.

From: Dion McCafferty [mailto:dion.mccafferty@gmail.com]
Sent: Tuesday, 17 February 2009 6:56 PM
To: 'Dr Mal Hooper'
Subject: De KAFF - Cape Town

'Hi Doc - I just wanted to give you a quick note to say thanks a mil for everything. I can without a doubt say that the Hyperbaric and Lokomat training has changed my life. My functional gain after just three weeks of being at HyperMED is nothing short of mind blowing. My standing ability had increased to the point where I can now stand unaided for up to two minutes. My body is fighting me in my chair to 'get up' all the time. My wheel chair has become the most uncomfortable place in the world – (which is a problem because I am a para). I also managed to leg press 120kg at gym on Friday – not bad for someone who was told they would never walk hey!

My Biokinetisis where blown away at the changes after such a short period on intense rehab with you. I am also walking short distances with regularity using my walker around the house and with mates. (I was able to stand with ease and have a couple of beers with my mates over the weekend and confidently know that I would only fall over if I was pissed. Ha ha!)

There has been one down side and that is that my spasticity and neuropathic pain has increased tremendously, I get a lot of hot flushes and burning in my legs and feet. But I also realize from previous function return that these are very good signs despite the discomfort. Thank again!

Regards, Dion'

Video of Lokomat in action

posted by dion mccafferty at 11:51 am 1 comments

Posted by Dion McCafferty - Thurs, Jan 15, 2009 - myprojecttowalk.blogspot.com/

'Howzit! Just an update, for this week at HyperMED. The training on the Lokomat seems to have turned the corner, my legs today seemed to have stopped fighting the Lokomat machine as much and I did last week. I have had huge amounts of spasticity in my legs since using the machine as my body has been fighting the 'new patterns' it is learning through the repetitive walking motion. I have up until today been causing the machine to reset quite often as my leg spasms have been so strong. Today I did two one hour sessions where they were able to increase my walking speed and I was also able to walk almost 3km of on the Lokomat. So today was pretty damn good! Dion'

Dion in Hyperbaric Chamber

HyperMED Comment – Dion has experienced considerable functional changes over the past 2-years using a 'spin bike' however when he walks his gait resembles the motion as though he is on a *spin bike!* Neural response 'learn' what they are being programmed. Dion has been programmed to spin bike NOT walk so part of our approach is to break down the inappropriate spin bike gait and teach a more 'normal walking gait'. Lokomat retrains supraspinal (brain and brainstem control centres) and corticospinal tracts (spinal circuits) which are required to accomplish a walking gait! However, activity based rehabilitation is better than simply sitting in a wheelchair but remember – 'what you train is what you accomplish'. Activity based rehabilitation must be accurate!

Hyperbaric impacts hypoxia (lack of oxygen) due to edema (chronic swelling)

J Neurosurg. 1981 Oct;55(4):501-10.
Effects of hyperbaric oxygen therapy on long-tract neuronal conduction in the acute phase of spinal cord injury.
To study the acute effects of hyperbaric oxygen ventilation (HBO) on long-tract function following spinal cord trauma, the authors employed a technique for monitoring spinal cord evoked potentials (SCEP) as an objective measure of translesion neuronal conduction in cats subjected to transdural impact injuries of the spinal cord. Control animals subjected to injuries of a magnitude of 400 or 500 gm-cm occasionally demonstrated spontaneous return of translesion SCEP within 2 hours of injury when maintained by pentobarbital anesthesia and by ventilation with ambient room air at 1 atmosphere absolute pressure (1 ATA). Animals sustaining corresponding injuries but receiving immediate treatment with HBO at 2 ATA for a period of 3 hours following impact demonstrated variable responses to this treatment modality. Animals sustaining injuries of 400 gm-cm magnitude showed recovery of translesion SCEP in four of five cases, while animals sustaining injuries of 500 gm-cm magnitude responded to HBO treatment by recovery of SCEP no more frequently than did control animals. The observations suggest that *HBO treatments can mediate preservation of marginally injured neuronal elements of the spinal cord long tracts during the early phases of traumatic spinal cord injury. These protective effects may be based upon the reversal of focal tissue hypoxia, or by reduction of tissue edema.*

Hyperbaric slows the rate of mitochondrial degeneration due to hypoxia

Neuroscience. 2003;120(1):113-20
Hyperbaric oxygen therapy protects against mitochondrial dysfunction and delays onset of motor neuron disease in Wobbler mice
Department of Neurology, D4-5, University of Miami School of Medicine, P.O. Box 016960, Miami, FL 33101, USA.
The Wobbler mouse is a model of human motor neuron disease. Recently we reported the impairment of mitochondrial complex IV in Wobbler mouse CNS, including motor cortex and spinal cord. The present study was designed to test the effect of hyperbaric oxygen therapy (HBOT) on (1) mitochondrial functions in young Wobbler mice, and (2) the onset and progression of the disease with aging. HBOT was carried out at 2 atmospheres absolute (2 ATA) oxygen for 1 h/day for 30 days. Control groups consisted of both untreated Wobbler mice and non-diseased Wobbler mice. The rate of respiration for complex IV in mitochondria isolated from motor cortex was improved by 40% ($P<0.05$) after HBOT. The onset and progression of the disease in the Wobbler mice was studied using litters of pups from proven heterozygous breeding pairs, which were treated from birth with 2 ATA HBOT for 1 h/day 6 days a week for the animals' lifetime. A "blinded" observer examined the onset and progression of the Wobbler phenotype, including walking capabilities ranging from normal walking to jaw walking (unable to use forepaws), and the paw condition (from normal to curled wrists and forelimb fixed to the chest). These data indicate that the onset of disease in untreated Wobbler mice averaged 36+/-4.3 days in terms of walking and 40+/-5.7 days in terms of paw condition. *HBOT significantly delayed* ($P<0.001$ for both paw condition and walking) *the onset of disease* to 59+/-8.2 days (in terms of walking) and 63+/-7.6 days (in terms of paw condition). *Our data suggest that HBOT significantly ameliorates mitochondrial dysfunction in the motor cortex and spinal cord and greatly delays the onset of the disease in an animal model of motor neuron disease.*

Surgical stabilization – is you're spinal canal still compromised? Poor neurologic outcomes if the canal remains compromised

Spine. 1999 Aug 15;24(16):1623-33
The influence of spinal canal narrowing and timing of decompression on neurologic recovery after spinal cord contusion in a rat model
Department of Orthopaedic Surgery, University of Louisville, Kentucky, USA.
STUDY DESIGN: The effect of spinal canal narrowing and the timing of decompression after a spinal cord injury were evaluated using a rat model. OBJECTIVE: To evaluate whether progressive spinal canal narrowing after a spinal cord injury results in a less favorable neurologic recovery. Additionally, to evaluate the effect of the timing of decompression after spinal cord injury on neurologic recovery. SUMMARY OF BACKGROUND DATA: Results in previous studies are contradictory about whether the amount of canal narrowing or the timing of decompression after a spinal cord injury affects the degree of neurologic recovery. METHODS: Forty adult male Sprague-Dawley rats were equally divided into a control group, in which spacers of 20%, 35%, and 50% were placed into the spinal canal after laminectomy, and an injury group in which the spacers were placed after a standardized incomplete spinal cord injury. After spacer removal, neurologic recovery in both was monitored by Basso, Beattie, Bresnahan (BBB) Locomotor Rating Scale (Ohio State University, Columbus, OH) motor scores and transcranial magnetic motor evoked potentials for 6 weeks followed by histologic examination of the spinal cords. Subsequently, 42 rats were divided into five groups in which, after spacer placement, the time until decompression was lengthened 0, 2, 6, 24, and 72 hours. Again, serial BBB motor scores and transcranial magnetic motor evoked potentials were used to assess neurologic recovery for 6 weeks until the animals were killed for histologic evaluation. RESULTS: Spacer placement alone in the control animals resulted in no neurologic injury until canal narrowing reached 50%. All of the control groups (spacer only) exhibited significantly better ($P < 0.05$) motor scores compared with the injury groups (injury followed by spacer insertion). Within the injury groups the motor scores were progressively lower as spacer sizes increased from the no-spacer group to the 35% group. The results in the 35% and 50% groups were not statistically different. The results of the time until decompression demonstrated that the motor scores were consistently better the shorter the duration of spacer placement ($P < 0.05$) for each of the time groups (0, 2, 6, 24, and 72 hours) over the 6-week recovery period. Histologic analysis showed more severe spinal cord damage as both spinal canal narrowing and the time until decompression increased. CONCLUSION: *The results in this study present strong evidence that the prognosis for neurologic recovery is adversely affected by both a higher percentage of canal narrowing and a longer duration of canal narrowing after a spinal cord injury. The tolerance for spinal canal narrowing with a contused cord appears diminished, indicating that an injured spinal cord may benefit from early decompression. Additionally, it appears that the longer the spinal cord compression exists after an incomplete spinal cord injury, the worse the prognosis for neurologic recovery.*

Blood flow recovery imperative for recovery – Hyperbaric fosters capillary networks in injured spinal cord (neovascularization)

Spine. 2007 Aug 15;32(18):1955-62
Real-time direct measurement of spinal cord blood flow at the site of compression: relationship between blood flow recovery and motor deficiency in spinal cord injury
Department of Orthopaedic Surgery, Ehime University School of Medicine, Tohon city, Ehime, Japan.
STUDY DESIGN: An in vivo study to measure rat spinal cord blood flow in real-time at the site of compression using a newly developed device. OBJECTIVES: To evaluate the change in thoracic spinal cord blood flow by compression force and to clarify the association between blood flow recovery and motor deficiency after a spinal cord compression injury. SUMMARY OF BACKGROUND DATA: Until now, no real-time measurement of spinal cord blood flow at the site of compression has been conducted. In addition, it has not been clearly determined whether blood flow recovery is related to motor function after a spinal cord injury. METHODS: Our blood flow measurement system was a combination of a noncontact type laser Doppler system and a spinal cord compression device. The rat thoracic spinal cord was exposed at the 11th vertebra and spinal cord blood flow at the site of compression was continuously measured before, during, and after the compression. The functioning of the animal's hind-limbs was evaluated by the Basso, Beattie and Bresnahan scoring scale and the frequency of voluntary standing. Histologic changes such as permeability of blood-spinal cord barrier, microglia proliferation, and apoptotic cell death were examined in compressed spinal cord tissue. RESULTS: The spinal blood flow decreased on each increase in the compression force. After applying a 5-g weight, the blood flow decreased to <40% of the precompression level. Complete ischemia was reached using a 20-g weight. After decompression, the blood flow level in the 20-minute complete ischemia group was significantly higher than that in the 40-minute complete ischemia group. The hind-limb motor function in the 40-minute complete ischemia group was significantly less than that in the sham group (without compression), while no significant difference was observed between the 20-minute ischemia group and the sham group. In the 20-minute ischemia group, the rats whose spinal cord blood flow recovery was incomplete showed significant motor function loss compared with rats that completely recovered blood flow. Extensive breakdown of blood-spinal cord barrier integrity and the following microglia proliferation and apoptotic cell death were detected in the 40-minute complete ischemia group. CONCLUSION: *Duration of ischemia/compression and blood flow recovery of the spinal cord are important factors in the recovery of motor function after a spinal cord injury.*

Hyperbaric – is it the break-through in all neurologic disorders?

Adv Ther. 2005 Nov-Dec;22(6):659-78.
Hyperbaric oxygen in the treatment of patients with cerebral stroke, brain and spinal cord trauma and neurologic disease.
Life Support Technologies, Inc., and NewTechnologies, Inc., The Mount Vernon Hospital, New York Medical College, New York, USA.
Hyperbaric oxygen (HBO) therapy has been used to treat patients with numerous disorders, including stroke. This treatment has been shown to *decrease cerebral edema, normalize water content in the brain, decrease the severity of brain infarction, and maintain blood-brain barrier integrity*. In addition, *HBO therapy attenuates motor deficits, decreases the risks of sequelae, and prevents recurrent cerebral circulatory disorders, thereby leading to improved outcomes and survival*. Hyperbaric oxygen also *accelerates the regression of atherosclerotic lesions, promotes antioxidant defenses, and suppresses the proliferation of macrophages and foam cells in atherosclerotic lesions*. HBO therapy has *improved the function of damaged cells, attenuated the effects of hypoxia on the neonatal brain, enhanced gross motor function and fine motor control, and alleviated spasticity*. In the treatment of patients with migraine, HBO therapy has been shown to reduce intracranial pressure significantly and abort acute attacks of migraine, reduce migraine headache pain, and prevent cluster headache. In studies that investigated the effects of HBO therapy on the damaged brain, the treatment was found to *inhibit neuronal death, arrest the progression of radiation-induced neurologic necrosis, improve blood flow in regions affected by chronic neurologic disease as well as aerobic metabolism in brain injury, and accelerate the resolution of clinical symptoms*. Hyperbaric oxygen has also been reported to *accelerate neurologic recovery after spinal cord injury by ameliorating mitochondrial dysfunction in the motor cortex and spinal cord, arresting the spread of hemorrhage, reversing hypoxia, and reducing edema*. HBO has *enhanced wound healing in patients with chronic osteomyelitis*. The results of HBO therapy in the treatment of patients with stroke, atherosclerosis, cerebral palsy, intracranial pressure, headache, and brain and spinal cord injury are promising and warrant further investigation.

Hyperbaric arrests the spread of hemorrhage, resolves edema causing spinal hypoxia

Magn Reson Imaging. 1991;9(3):423-8.
Magnetic resonance imaging of hyperbaric oxygen treated rats with spinal cord injury: preliminary studies.
Department of Radiology, University of Texas Medical School, Houston 77030.
Magnetic resonance imaging (MRI) has been performed to assess the efficacy of hyperbaric oxygen (HBO) treatment on experimental spinal cord injury in a rat animal model. A moderately severe injury, similar to Type III injury seen in humans (Kulkarni et al. Radiology 164:837;1987) has been chosen for these studies. An improvement in the neurologic recovery (based on Tarlov scale) has been observed following HBO treatment over a period of 72 hr. *Based on MRI, HBO treatment appears to arrest the spread of hemorrhage and resolve edema causing spinal hypoxia.*

Hyperbaric promotes target specific neural stem cells in response to injury – neurogenesis

Undersea Hyperb Med. 2008 Mar-Apr;35(2):113-29.
Hyperbaric oxygen induces endogenous neural stem cells to proliferate and differentiate in hypoxic-ischemic brain damage in neonatal rats.
Division of Neonatology, Department of Pediatrics, Xiang Ya Hospital, Central South University.
BACKGROUND AND PURPOSE: Studies suggest that after brain injury, *hyperbaric oxygen (HBO2) is neuroprotective by stimulating neural cell proliferation. HBO2 promotes neural stem cells (NSC) to proliferate and differentiate in neonatal hypoxic-ischemic (HI) rats*. METHODS: Seven-day-old rat pups were subjected to unilateral carotid artery ligation followed by 2 hours of hypoxia (8% O2). HBO2 was administered (2 ATA (atmospheres absolutes), once daily for 7 days) within 3 hours after HI. The proliferating neural stem cells in the subventricular zone (SVZ) and dentate gyrus (DG) were dynamically examined by 5-bromo-2-deoxyuridine (BrdU)/nestin immunofluorescence. Nestin protein was detected by western blot analysis at various time points (from 6 hours to 14 days) after HI. The migrating NSC were examined by BrdU/doublecortin (DCX) immunofluorescence 7 and 14 days after HI. The phenotype of the newborn cells was identified by BrdU/beta-tubulin, BrdU/ glial fibrillary acidic protein (GFAP) and BrdU/O4 (oligodendrocyte marker) immunofluorescence. Myelin basic protein (MBP) was examined by immunohistochemistry and pathological changes of the brain tissue were detected 28 days after HI. RESULTS: In neonatal HI rats treated with HBO2, the proliferation of endogenous NSC was observed in the SVZ and DG. Cell numbers peaked 7 days after HI and proliferating NSC migrated to the cerebral cortex at 14 d after HI. Twenty-eight days after HI, an increase in newly generated neurons, oligodendrocytes and MBP was observed in the HBO2 group compared to the untreated and HI-treated rats. CONCLUSIONS: *This study suggests that HBO2 treatment promotes 'target specific neurogenesis' of the endogenous NSC in neonatal HI rats, contributing to repair of the injured brain.*

Hyperbaric slows the cascade of neural degeneration caused by hypoxia

Neuroreport. 2004 Oct 25;15(15):2369-73.
Effects of hyperbaric oxygen on GDNF expression and apoptosis (programmed cellular degeneration) in spinal cord injury.
Department of Orthopaedic Surgery, Nagoya University School of Medicine, 466-8500 Nagoya, Japan. yuyimin@med.nagoya-u.ac.jp
The effects of hyperbaric oxygen treatment on the progress of secondary damage following traumatic spinal cord injury were investigated. *The early onset of hyperbaric oxygen treatment significantly diminished the number of apoptotic cells 1 day after the injury.* However, hyperbaric oxygen did not influence the proliferation of macrophages or activated microglia. The gene expression of glial cell line-derived neurotrophic factor (GDNF) and inducible nitric oxide synthetase (iNOS) was significantly attenuated 1 day after the injury in the hyperbaric oxygen groups compared with the control group. The down-regulation was confirmed by immunohistochemical staining. *Early hyperbaric oxygen treatment was shown to effectively suppress the progress of apoptosis* perhaps via the inhibition of iNOS gene despite the down-regulation of the GDNF gene.

Neurol Res. 2007 Mar;29(2):156-61.
Hyperbaric oxygenation in fluid microembolism.
James PB. Wolfson Hyperbaric Medicine Unit, University of Dundee, Dundee, Scotland, UK. p.b.james@dundee.ac.uk
Because clinicians require objectively demonstrable neurological deficits to confirm a diagnosis, the recognition of embolic events in the nervous system is generally restricted to the effects of ischemic necrosis produced by arterial occlusion. However, magnetic resonance imaging (MRI) has shown that lesser degrees of damage associated with small emboli are common, especially in the mid brain, and are usually clinically silent. They are frequently associated with atheromatous embolism in the elderly, but microembolic debris, such as fat, is common in the systemic venous return of healthy people and generally trapped in the microcirculation of the lung being removed by phagocytosis. However, pulmonary filtration may fail and microemboli may also pass through an atrial septal defect in so-called 'paradoxical' embolism. Studies of bubbles formed on decompression in diving have demonstrated the importance of pulmonary filtration in the protection of the nervous system and that filtration is size dependant, as small bubbles may escape entrapment. Fluid and even small solid emboli, arresting in or passing through the cerebral circulation, do not cause infarction, but disturb the blood-brain barrier inducing what has been termed the 'perivenous syndrome'. The nutrition of areas of the white matter of both the cerebral medulla and the spinal cord depends on long draining veins which have been shown to have surrounding capillary free zones. Because of the high oxygen extraction in the microcirculation of the gray matter of the central nervous system, the venous blood has low oxygen content.

When this is reduced further by embolic events, tissue oxygenation may fall to critically low levels, leading to blood-brain barrier dysfunction, inflammation, demyelination and eventually, axonal damage. These are the hallmarks of the early lesions of multiple sclerosis where MR spectroscopy has also shown the presence of lactic acid. Significant elevation of the venous oxygen tension requires oxygen to be provided under hyperbaric conditions. Arterial tension is typically increased ten-fold breathing oxygen at 2 atmospheres absolute (ATA), but this results in only a 1.5-fold increase in the cerebral venous oxygen tension. The treatment of decompression sickness, and both animal and clinical studies, have confirmed the value of oxygen provided under hyperbaric conditions in the restoration and preservation of neurological function in the 'perivenous' syndrome.

Hyperbaric corrects spinal syndromes associated with abscess and infection

Mt Sinai J Med. 2005 Nov;72(6):381-4.
Successful treatment of cervical spinal epidural abscess by combined hyperbaric oxygenation.
Department of Neurosurgery and Division of Hyperbaric Medicine, University Hospital of Occupational and Environmental Health, Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan. k-kohshi@clnc.uoeh-u.ac.jp
A 49-year-old man underwent hyperbaric oxygen (HBO) therapy for the treatment of primary spinal epidural abscess. Although the epidural abscess was initially treated with antibiotic (cefozopran) for 5 days, he subsequently developed motor weakness, paresthesia and urinary retention. MRI demonstrated spinal cord compression at the C1-C4 level. HBO therapy was added to the antibiotic regimen, and three days later we found clinical evidence of a response to treatment. Neurological symptoms were relieved 13 days after HBO therapy. This case suggests that *HBO therapy is an effective therapeutic adjunct for the treatment of spinal epidural abscess.*

Hyperbaric pre-conditioning minimizes the risks associated with spinal injury

Life Sci. 2007 Feb 27;80(12):1087-93. Epub 2006 Dec 5.
Preconditioning with hyperbaric oxygen induces tolerance against oxidative injury via increased expression of heme oxygenase-1 in primary cultured spinal cord neurons.
Department of Aerospace Hygiene and Health Service, School of Aerospace Medicine, Fourth Military Medical University, Xi'an, Shaanxi, 710032, China.
Hyperbaric oxygen (HBO) preconditioning can induce ischemic tolerance in the spinal cord. The effect can be attenuated by the administration of an oxygen free radical scavenger or by inhibition of antioxidant enzymes. However, the mechanism underlying HBO preconditioning of neurons against ischemic injury remains enigmatic. Therefore, in the present study primary cultured spinal cord neurons were treated with HBO and then subjected to a hydrogen peroxide (H(2)O(2)) insult. The results show that H(2)O(2) stimulation of the cultured spinal neurons caused severe DNA damage and decreased cell viability, and that these neurons were well protected against damage after a single exposure to HBO preconditioning (0.35 MPa, 98% O(2), 37 degrees C, 2 h). The protective effect started 4 h after pretreatment and lasted for at least 24 h. The cultured neurons after HBO treatment also exhibited increased heme oxygenase-1 (HO-1) expression at both the protein and mRNA levels, which paralleled the protective effect of HBO. Treatment with tin-mesoporphyrin IX (SnMP), a specific HO-1 inhibitor, before HBO pretreatment abolished the HBO-induced adaptive protection noted in the cultured spinal neurons. In conclusion, *HBO preconditioning can protect primary cultured spinal cord neurons against oxidative stress, and the upregulation of HO-1 expression plays an essential role in HBO induced preconditioning effect.*

Multiple hyperbaric expands the therapeutic window

J Neurosurg. 2003 Sep;99(2 Suppl):198-205.
The role of multiple hyperbaric oxygenation in expanding therapeutic windows after acute spinal cord injury in rats.
Department of Anesthesiology, University of Mississippi Medical Center, Jackson, Mississippi, USA.
OBJECT: *Hyperbaric oxygenation (HBO) therapy has been reported to improve neurological recovery after spinal cord injury (SCI)*. In the present study, the authors examined whether *multiple HBO therapy can expand the therapeutic window after acute SCI*. METHODS: Seventy rats were randomly assigned to seven groups: sham surgery; SCI without treatment; single HBO treatment beginning at 30 minutes, 3 hours, and 6 hours after SCI; and multiple HBO treatments starting at 6 and 24 hours postinjury. Mild SCI was induced by adjusting the height of a weight drop (10 g) to 6.25 mm above the exposed spinal cord. A single HBO administration was performed at 2.82 ata for 1 hour. The multiple HBO treatment modality was performed once daily for 1 week. All rats underwent behavioral testing with the Basso-Beattie-Breshnahan locomotor rating scale twice a week. Rats were killed on Day 42 postinjury and specimens comprising the lesioned area were histopathologically examined. Those rats that received single HBO intervention beginning at 30 minutes and 3 hours and those that received multiple HBO treatment starting at 6 hours following injury made significantly greater neurological recoveries than those in the nontreatment SCI group. These rats also retained more sparing tissue than controls. CONCLUSIONS: *The results of this study demonstrate that multiple HBO treatments can expand the therapeutic window for acute SCI to 6 hours after injury.*

Hyperbaric combined with stem cells increase nerve regeneration

Neurochem Res. 2009 Jan 17.
Human Amniotic Fluid Mesenchymal Stem Cells in Combination with Hyperbaric Oxygen Augment Peripheral Nerve Regeneration
Department of Neurosurgery, Taichung Veterans General Hospital, Taichung, Taiwan.
Purpose: Attenuation of pro-inflammatory cytokines and associated inflammatory cell deposits rescues human amniotic fluid mesenchymal stem cells (AFS) from apoptosis. *Hyperbaric oxygen (HBO) suppressed stimulus-induced pro-inflammatory cytokine production in blood-derived monocyte-macrophages.* Herein, we evaluate the *beneficial effect of hyperbaric oxygen on transplanted AFS in a sciatic nerve injury model.* Methods Peripheral nerve injury was produced in Sprague-Dawley rats by crushing the left sciatic nerve using a vessel clamp. The AFS were embedded in fibrin glue and delivered to the injured site. Hyperbaric oxygen (100% oxygen, 2 ATA, 60 min/day) was administered 12 h after operation for seven consecutive days. Transplanted cell apoptosis, oxidative stress, inflammatory cell deposits and associated chemokines, pro-inflammatory cytokines, motor function, and nerve regeneration were evaluated 7 and 28 days after injury. Results Crush injury induced an inflammatory response, disrupted nerve integrity, and impaired nerve function in the sciatic nerve. However, crush injury-provoked inflammatory cytokines, deposits of inflammatory cytokines, and associated macrophage migration chemokines were attenuated in groups receiving hyperbaric oxygen but not in the AFS-only group. No significant increase in oxidative stress was observed after administration of HBO. In transplanted AFS, marked apoptosis was detected and this event was reduced by HBO treatment. Increased nerve myelination and improved motor function were observed in AFS-transplant, HBO-administrated, and AFS/HBO-combined treatment groups. Significantly, the AFS/HBO combined treatment showed the most beneficial effect. *Conclusion AFS in combination with HBO augment peripheral nerve regeneration, which may involve the suppression of apoptotic death in implanted AFS and the attenuation of an inflammatory response detrimental to peripheral nerve regeneration.*

Hyperbaric induces angiogenesis (formation new capillary networks) due to radiation damage

Cancer Lett. 2003 Feb 28;191(1):59-65.
Prophylactic hyperbaric oxygen treatment and rat spinal cord re-irradiation.
Department of Radiation Oncology, VU University Medical Center, Van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands,
Normal tissue injury may lead to severe, life threatening, late side effects after therapeutic use of irradiation. *Neurological complications caused by radiation of the spinal cord are ascribed to progressive, irreversible damage to the vasculature. Hyperbaric oxygen (HBO) is known to induce angiogenesis in irradiated tissue and has been proven to reduce late radiation injury in several normal tissues when applied during the latent period before complications become manifest.* In the present study: (1). the prophylactic potential of HBO; (2). optimal timing of HBO therapy after spinal cord irradiation, i.e. during the latent period; and (3). effect of HBO on the re-irradiation tolerance of the spinal cord were investigated. The rat cervical spinal cord was locally X-ray irradiated with ten fractions of 6.5 Gy in 11 days. Five treatment groups (n=10) included: irradiation alone and irradiation followed by 30 HBO treatments (100% oxygen at 240 kPa for 90 min) during latency, with HBO starting either immediately, 5, 10 or 15 weeks after the primary irradiation course. One year after the primary treatment, the same spinal cord volume was re-irradiated with 20 Gy single dose. During life span, the animals were observed on the incidence of myelitis and the duration of the latent period. The actuarial analysis revealed no significant difference in neurological complications free survival between the irradiation alone and the irradiation+HBO treatment groups. A tendency towards radiosensitization was found in the group in which the primary irradiation course was immediately followed by the HBO treatment course. The data show that HBO applied during the latent period of progressively developing irradiation damage to the spinal cord does not increase the re-irradiation tolerance of this tissue.

Hyperbaric spinal injury accepted protocol Neurosurgical Unit Tokyo - Japan

Spinal Cord. 2000 Sep;38(9):538-40.
Hyperbaric oxygen (HBO) therapy for acute traumatic cervical spinal cord injury.
Department of Neurosurgery, Tokyo Metropolitan Ebara Hospital, Tokyo, Japan.
STUDY DESIGN: A retrospective study of spinal cord injury (SCI) treated with and without hyperbaric oxygen (HBO) therapy. OBJECTIVES: To report on the use of HBO in spinal cord injury. SETTING: Neurosurgical Unit, Tokyo, Japan. METHODS: Thirty-four cases of hyperextension spinal cord injury without bone damage and previous history of surgical intervention were divided into two groups, with (HBO) or without (non-HBO) therapy. The neurological findings at admission and their outcomes were evaluated by means of Neurological Cervical Spine Scale (NCSS)1 and the average improvement rates in individual groups were compared. RESULTS: The improvement rate ranged from 100% to 27.3% with the mean value of 75. 2% in the HBO group, while these values were 100%, 25.0% and 65.1% respectively in the non HBO group. CONCLUSION: *In the HBO group, the improvement rate indicated effectiveness in acute traumatic cervical spinal cord injury.*

Spinal cord injury causes T2 signal changes on MRI – T2 signal indicates extensive tissue hypoxia.

Spine. 1996 Jan 15;21(2):166-73.
Experimental acute dorsal compression of cat spinal cord: correlation of magnetic resonance signal intensity with spinal cord evoked potentials and morphology.
Department of Orthopaedic Surgery, Tottori University, Yonago, Japan.
STUDY DESIGN: Acute dorsal compression of the spinal cord was applied to adult cats, and magnetic resonance signal intensity, spinal cord evoked potentials, and morphologic changes of the spinal cord were examined after 5 hours. OBJECTIVES: The present study investigated the correlation of magnetic resonance signal intensity with spinal cord evoked potentials and spinal cord morphology after 5 hours of spinal cord compression in cats. SUMMARY OF BACKGROUND DATA: Neurologic prognosis of the injury might be predicted by an analysis of magnetic resonance signal intensity pattern. Little information is available on relationships between magnetic resonance images and functional or morphologic damage of spinal cord in acute animal experiments. METHODS: Acute dorsal compression of the spinal cord was performed in 24 anesthetized cats. After laminectomy, the L2 segment was compressed for 5 hours. Spinal cord evoked potentials were recorded by electrodes placed in the epidural space at L4, and the spinal cord was stimulated at T12. The animals were divided into four groups based on changes in the amplitude of spinal cord evoked potentials. Immediately after compression for 5 hours, magnetic resonance images were obtained. Signal intensity of the spinal cord was measured on sagittal midline images. Morphologic changes were assessed. RESULTS: Spinal compression significantly increased the signal intensity of the L1, L2, and L3 segments on T2-weighted and proton density-weighted images. The increase in signal intensity was remarkable in the animals whose spinal cord evoked potentials were reduced greatly (< 40% of the control group). Histologically, *edema was present in the high intensity area on T2-weighted and proton density-weighted images causing tissue hypoxia.* CONCLUSIONS: In summary, the present study documents that *spinal compression causes tissue edema, which produces high signal intensity on magnetic resonance imaging leading to wide spread hypoxia*. The magnetic resonance signal intensity is correlated closely with decreased amplitude of spinal cord evoked potentials.

Hyperbaric improves spinal cord central cystic necrosis

Cent Nerv Syst Trauma. 1984 Winter;1(2):161-5.
The use of hyperbaric oxygen to modify the effects of recent contusion injury to the spinal cord. Yeo JD**.**
Studies on the experimental spinal contusion injury in animals confirm that *posttraumatic ischemia contributes to central cystic necrosis or fibrosis occurring at the level of the spinal cord lesion. Hyperbaric oxygen (HBO) modifies the degree and extent of the pathology in the spinal cord of the experimental animals.* HBO has been used for 45 patients with recent spinal cord injuries. The extent of recovery in 27 patients with upper motor neuron lesions treated with adequate HBO is reported. *Fifteen of the 27 patients had useful functional recovery.*

Supplement: Taurine – neural protection and regeneration

Role of taurine in spinal cord injury
2008: SASRD, Nagaland University, Medziphema 797106, India. rameshgupta1954@yahoo.com
Taurine is a sulfur amino acid. It is found endogenously in human and several others tissues. It is significantly in high concentration in mammals. Human body contains about 0.1% of body weight as taurine. It has a number of physiological and pharmacological actions. It is also used in the therapy of important organs dysfunctions. In spinal cord it has inhibitory effects; like antiepileptic and anti-nociceptive. Taurine also inhibits substance p induced biting and scratching behavior. In spinal cord injury elevated level of taurine has been observed. Higher level of taurine has been also recorded in SCI therapy using, known clinical agent methyl prednisolone (MP). *The increased taurine concentration seems to be involved in protection and regeneration of tissues following injury.* In SCI along with physical injury secondary activities also takes place which are complex in nature. Secondary activity includes vascular events and activation of neutrophils, resulting endothelial damage. Activated neutrophils; release a variety of inflammatory mediators such as myeloperoxidase (MPO), reactive oxygen species (ROS), and some others. It is believed that taurine exert its protective action through scavenging of ROS and down regulating several other inflammatory mediators like tumor necrosis factors (TNFalpha). The inside of mechanism reveals toxic substance HOCl is

produced by MPO is converted to less toxic substances through scavenging action of taurine. Amino acid therapy has its own limitations and to over come such situation there is a need to develop small, simple lipophilic analogs of taurine. Use of taurine analogs has provided better results; for example, *N- chloro taurine (NCT) which is a taurine derivative has exhibited therapeutic advances over taurine*. Taurine and its analogs with sound experimental and clinical support may constitute a new class of therapeutic agents for SCI., and perhaps this review may provide enough material to think of this.

Eksp Klin Farmakol. 2005 Nov-Dec;68(6):45-8.
The neuroprotector effect of a new taurine derivative on a model of compression spinal cord trauma in rats
The neuroprotector effect of a new taurine derivative, 2-(1-phenylethyl)-aminoethanesulfonyl-2-propylamide hydrochloride, has been studied in rats with model compression spinal cord trauma. The taurine derivative favored *restoration of the motor function of posterior extremities in rats with the model spinal cord trauma and significantly decreased the lethality in test animals. The taurine derivative normalized the energy metabolism, lipid peroxidation and antioxidant system in animals with spinal cord trauma.* The neuroprotector effect of the new taurine derivative significantly exceeds the action of cerebrolysine.

Methylprednisolone combined with Taurine more effective assisting tissue reorganization

Brain Res. 2001 Mar 2;893(1-2):292-300
Spinal taurine levels are increased 7 and 30 days following methylprednisolone treatment of spinal cord injury in rats
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The amino acid taurine serves many functions in the nervous system serving as inhibitory neurotransmitter/neuromodulator, neurotrophin, antioxidant, and osmolyte. Taurine levels are increased following brain injury and glucocorticoid administration. Thus, the *purpose of this study was to examine spinal taurine concentrations following spinal cord injury (SCI) and methylprednisolone (MP) treatment of SCI*. A total of 44 adult male Sprague-Dawley rats were divided into control and lesion groups. Control rats received a T6 vertebral laminectomy while lesioned rats received a laminectomy followed by complete spinal transection. Half of the animals in each group received MP intravenously following sham-operation or SCI. Rats survived for 7 or 30 days and concentrations of taurine in spinal gray and white matter, in spinal segments both near and distant from the injury epicenter, were resolved by HPLC analysis. Taurine levels were increased 7 and 30 days following transection in spinal segments immediately adjacent to the lesion and were further elevated by MP treatment. No increases were seen in far rostral/caudal segments, and MP treatment alone had no effect on spinal taurine levels. *These findings demonstrate that spinal injury results in increased taurine concentrations in spinal segments undergoing the greatest degree of cellular reactivity and tissue reorganization and that MP therapy potentiates these increases. These findings are significant in that they further characterize the effects of acute MP therapy in spinal tissue. Since taurine is thought to be involved in neuroprotection and/or regeneration following injury, the potentiation of taurine levels by MP treatment may relate to its therapeutic properties.*

Stem cell therapy acts as a 'chaperone' – not a magic bullet!

Cell Prolif. 2008 Feb;41 Suppl 1:94-114
Stem cells and neurological diseases
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Cells of the central nervous system were once thought to be incapable of regeneration. This dogma has been challenged in the last decade with studies showing *new, migrating stem cells in the brain and spinal cord* in many rodent injury models and findings of new neurones in the human hippocampus in adults. Moreover, there are reports of *bone marrow-derived cells developing neuronal and vascular phenotypes and aiding in repair of injured brain.* These findings have fuelled excitement and interest in regenerative medicine for neurological diseases, arguably the most difficult diseases to treat. There are numerous proposed regenerative approaches to neurological diseases. These include cell therapy approaches in which cells are delivered intracerebrally or are infused by an intravenous or intra-arterial route; *stem cell mobilization approaches in which endogenous stem and progenitor cells are mobilized by cytokines such as granulocyte colony stimulatory factor (GCSF) or chemokines such as SDF-1; trophic and growth factor support, such as delivering brain-derived neurotrophic factor (BDNF) or glial-derived neurotrophic factor (GDNF) into the brain to support injured neurones; these approaches may be used together to maximize recovery*. While initially, it was thought that cell therapy might work by a 'cell replacement' mechanism, a large body of evidence is emerging that *cell therapy works by providing trophic or 'chaperone' support* to the injured tissue and brain. Angiogenesis and neurogenesis are coupled in the brain. *Increasing angiogenesis with adult stem cell approaches in rodent models of stroke leads to preservation of neurones and improved functional outcome*. A number of stem and progenitor cell types has been proposed as therapy for neurological disease ranging from neural stem cells to bone marrow derived stem cells to embryonic stem cells. Any cell therapy approach to neurological disease will have to be scalable and easily commercialized if it will have the necessary impact on public health. Currently, bone marrow-derived cell populations such as the marrow stromal cell, multipotential progenitor cells, umbilical cord stem cells and neural stem cells meet these criteria the best. Of great clinical significance, initial evidence suggests these cell types may be delivered by an allogeneic approach, so strict tissue matching may not be necessary. The most immediate impact on patients will be achieved by making use of the trophic support capability of cell therapy and not by a cell replacement mechanism.

Umbilical derived CD34+ stem cells improve cord vascular angiogenesis and neural cell responses

Shock. 2008 Jan;29(1):49-55
Human umbilical cord blood-derived CD34+ cells may attenuate spinal cord injury by stimulating vascular endothelial and neurotrophic factors
Center for General Education, Southern Taiwan University of Technology, Taiwan.
Human umbilical cord blood-derived CD34(+) cells were used to elucidate the mechanisms underlying the beneficial effects exerted by cord blood cells in spinal cord injury (SCI). Rats were divided into four groups: (1) sham operation (laminectomy only); (2) laminectomy + SCI + CD34(-) cells (5 x 10(5) human cord blood lymphocytes and monocytes that contained <0.2% CD34(+) cells); (3) laminectomy + SCI + CD34(+) cells (5 x 10(5) human cord blood lymphocytes and monocytes that contained approximately 95% CD34(+) cells); and (4) laminectomy + SCI + saline (0.3 mL). Spinal cord injury was induced by compressing the spinal cord for 1 min with an aneurysm clip calibrated to a closing pressure of 55 g. CD34 cells or saline was administered immediately after SCI via the tail vein. Behavioral tests of motor function measured by maximal angle an animal could hold to the inclined plane were conducted at days 1 to 7 after SCI. The triphenyltetrazolium chloride staining and terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate-biotin nick end labeling assay were also conducted after SCI to evaluate spinal cord infarction and apoptosis, respectively. To elucidate whether glial cell line-derived neurotrophic factor (GDNF) or vascular endothelial growth factor (VEGF) can be secreted in spinal cord-injured area by the i.v. transplanted CD34(+) cells, analysis of spinal cord homogenate supernatants by specific enzyme-linked immunosorbent assay for GDNF or immunofluorescence for VEGF was conducted. It was found that systemic administration of CD34(+), but not CD34(-), cells significantly attenuated the SCI-induced hind limb dysfunction and spinal cord infarction and apoptosis. Both GDNF and VEGF could be detected in the injured spinal cord after transplantation of CD34(+), but not CD34(-), cells. *The results indicate that CD34(+) cell therapy*

may be beneficial in reversing the SCI-induced spinal cord infarction and apoptosis and hindlimb dysfunction by stimulating the production of both VEGF and GDNF in a spinal cord compression model.

Hyperbaric significantly elevates the patient's own circulating CD34+ neural stem cells

Am J Physiol Heart Circ Physiol. 2006 Apr;290(4):H1378-86.
Stem cell mobilization by hyperbaric oxygen
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We hypothesized that exposure to *hyperbaric oxygen (HBO(2)) would mobilize stem/progenitor cells from the bone marrow by a nitric oxide (*NO) -dependent mechanism*. The population of CD34(+) cells in the peripheral circulation of humans doubled in response to a single exposure to 2.0 atmospheres absolute (ATA) O(2) for 2 h. Over a course of 20 treatments, *circulating CD34(+) cells increased eightfold*, although the overall circulating white cell count was not significantly increased. In mice, HBO(2) increased circulating stem cell factor by 50%, increased the number of circulating cells expressing stem cell antigen-1 and CD34 by 3.4-fold, and doubled the number of CFCs. Bone marrow *NO concentration increased by 1,008 +/- 255 nM in association with HBO(2). Stem cell mobilization did not occur in knockout mice lacking genes for endothelial *NO synthase. Moreover, pretreatment of wild-type mice with a *NO synthase inhibitor prevented the HBO(2)-induced elevation in stem cell factor and circulating stem cells. *We conclude that HBO(2) mobilizes stem/progenitor cells by stimulating *NO synthesis.*

Specialized Umbilical cord stem cells effective – no ethical debate!

Chin Med J (Engl). 2009 Jan 20;122(2):225-31
Human umbilical cord mesenchymal stem cells and the treatment of spinal cord injury
Department of Orthopaedics, General Hospital of Tianjin Medical University, Tianjin 300052, China.
OBJECTIVE: To review the recent studies about *human umbilical cord mesenchymal stem cells (hUCMSCs)* and advances in the treatment of spinal cord injury. Data sources Published articles (1983 - 2007) about hUCMSCs and spinal cord injury were selected using Medline. Study selection Articles selected were relevant to development of *mesenchymal stem cells (MSCs) for transplantation in spinal cord injury* therapy. Of 258 originally identified articles 51 were selected that specifically addressed the stated purpose. RESULTS: Recent work has revealed that hUCMSCs share most of the characteristics with MSCs derived from bone marrow and are more appropriate to transplantation for cell based therapies. CONCLUSIONS: Human umbilical cord could be regarded as a source of MSCs for experimental and clinical needs. In addition, hUCMSCs may play an important role in the treatment of spinal cord injury.

Umbilical neural stem cells refill cord cavity after spinal injury

Tissue Eng Part A. 2009 Jan 27.
Generation of Functional Neural Artificial Tissue from Human Umbilical Cord Blood Stem Cells
1 Department of Neurorepair, Medical Research Institute Warsaw, Poland, 2 Department of Neuropeptide, Medical Research Institute , Warsaw, Poland, 3 Industrial Chemistry Research Institute, Warsaw, Poland, 4 Institute for Health and Consumer Protection, JRC, European Commission, Ispra, Italy, 5 Department of Cell Ultrastructure, Medical Research Institute, Warsaw, Poland.
Stem cell-based regenerative neurology is an emerging concept for treatment of diseases of central nervous system. Among variety of proposed procedures, one of the most promising is *refilling of cystic cavities of injured brain parenchyma with artificial neural tissue*. Recent studies revealed that after allogenic transplantation in rodents these tissue-engineered entities were shown efficient in repair of hypoxic/ischemic brain injury. *Human umbilical cord blood (HUCB) was recognized to be an efficient and noncontroversial source of neural stem cells (NSC)*.

Hyperbaric improves Autism

Med Hypotheses. 2006;67(2):216-28. Epub 2006 Mar 22
Hyperbaric oxygen therapy may improve symptoms in autistic children
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Autism is a neurodevelopmental disorder that currently affects as many as 1 out of 166 children in the United States. Recent research has discovered that some autistic individuals have decreased *cerebral perfusion, evidence of neuroinflammation*, and increased markers of oxidative stress. *Multiple independent single photon emission computed tomography (SPECT) and positron emission tomography (PET) research studies have revealed hypoperfusion to several areas of the autistic brain, most notably the temporal regions and areas specifically related to language comprehension and auditory processing.* Several studies show that diminished blood flow to these areas correlates with many of the clinical features associated with autism including repetitive, self-stimulatory and stereotypical behaviors, and impairments in communication, sensory perception, and social interaction. Hyperbaric oxygen therapy (HBOT) has been used with clinical success in several cerebral hypoperfusion syndromes including cerebral palsy, fetal alcohol syndrome, closed head injury, and stroke. *HBOT can compensate for decreased blood flow by increasing the oxygen content of plasma and body tissues and can even normalize oxygen levels in ischemic tissue. In addition, animal studies have shown that HBOT has potent anti-inflammatory effects and reduces oxidative stress. Furthermore, recent evidence demonstrates that HBOT mobilizes stem cells from human bone marrow, which may aid recovery in neurodegenerative diseases.* It is hypothesized that HBOT will improve symptoms in autistic individuals.

Hyperbaric impacts and slows the rate and spread of malignant cancers – Hypoxia drives tumorgenesis and proliferation

Hyperbaric oxygen therapy for malignancy: a review
Daruwalla, Christophi. World J Surg 2006 Dec;30(12):2112-31. Department of Surgery, University of Melbourne, Austin Hospital, Level 8 Lance Townsend Building, Austin Health, Studley Road, Heidelberg, Victoria, 3084 Australia. jurstine@pgrad.unimelb.edu.au
One unique feature of tumors is the presence of hypoxic regions, which occur predominantly at the tumor center. *Hypoxia has a major impact on various aspects of tumor cell function and proliferation. Hypoxic tumor cells are relatively insensitive to conventional therapy owing to cellular adaptations effected by the hypoxic microenvironment.* Recent efforts have aimed to alter the hypoxic state and to reverse these adaptations to improve treatment outcome. One way to increase tumor oxygen tensions is by hyperbaric oxygen (HBO) therapy. HBO therapy can influence the tumor microenvironment at several levels. *It can alter tumor hypoxia, a potent stimulus that drives angiogenesis.* Hyperoxia as a result of HBO also produces reactive oxygen species, which can damage tumors by inducing excessive oxidative stress. This review outlines the importance of oxygen to tumors and the mechanisms by which tumors survive under hypoxic conditions. It also presents data from both experimental and clinical studies for the effect of HBO on malignancy.

HyperMED NeuroRecovery – an Australian initiative working to help others

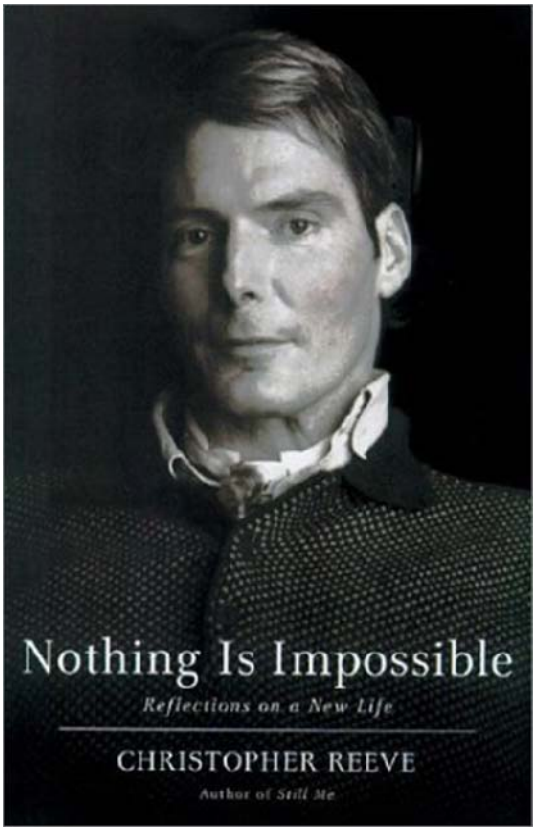
HyperMED NeuroRecovery Centre provides intensive activity based rehabilitation programs with unique protocols incorporating Lokomat (Robotic Gait Assisted Walking), Hyperbaric Oxygenation, Median Nerve Stimulation, Neuro-acupuncture, Whole Body Vibration and other assertive therapies aimed at functional improvements of the patients with different sorts of neurological diseases and post operative events. The HyperMED NeuroRecovery Centre has been the first and currently is the only centre in Australia, which has and uses the Robotically Assisted Lokomat combined with cutting edge strategies focused on outcomes; this lack of availability has meant that most patients attending HyperMED NeuroRecovery attend from interstate and many from overseas for this specific therapy combination.

HyperMED NeuroRecovery is a private therapeutic centre, which is totally funded by the patient and sponsored private sector. Patients attend in a private pay capacity; patients do not receive Government funding or funding under Third Party Insurance including Transport Accident Commission or WorkCover. Self-funded rehabilitation facilities such as HyperMED NeuroRecovery Centre, by using the Lokomat can play an important role in reducing the financial burden of neurological diseases on the government and communities' shoulders.

HyperMED NeuroRecovery provides financial subsidy for all patients attending. This economic burden has been tackled by the directors in the interest of providing modalities including Lokomat Gait Training for patients with neurologic disorders. However we need your help!

HyperMED is seeking partners and volunteers – those with corporate financial skills to assist in gaining Medicare and Third Party funding. Many patients attend from interstate and we are endeavoring to establish HyperMED centers in each and every state. Medicare funding is crucial to this objective. Establishment costs exceed AUD $1.5 million for each centre simply to provide a minimum of 2-Hyperbaric Chambers and 1-Lokomat (adult and pediatric) notwithstanding additional infrastructure expenses including staff and leasing requirements. We need practical support and every supportive idea is most welcome. In addition we seek volunteer support – there are many in the community that have appropriate skills that may elect to support HyperMED in a practical 'down to earth' manner – if you would like to discuss further your thoughts and ideas – please do not hesitate to contact Dr Mal Hooper direct or email info@hypermed.com.au

An empathetic smile can go a long way however individuals with disability need treatment regimes that make a difference NOW! Can you help?



Nothing is Impossible!

"What I do is based on powers we all have inside us; the ability to endure; the ability to love, to carry on, to make the best of what we have – and you don't have to be a 'Superman' to do it." Christopher Reeve.

The Christopher Reeves Foundation is wholly committed to finding cures and treatments for spinal cord injuries as well as improving the quality of life for people living with disabilities. The Foundation features Lokomat Gait Assisted Walking programs; for more information regarding Grants and Research projects visit www.christopherreeve.org

Spinal cord injury and stroke related injury are typically sudden and unexpected. Neurodegenerative disorders are more progressive with all groups resulting in significant and progressive loss of neurological function and increasing disability.

Neurological disorders are devastating and costly in human and social terms. Medical improvements have greatly increased survival rates however individuals are living longer but with disability with little hope of improvement – until NOW!

HyperMED NeuroRecovery can assist …

'Why wait in hope of a miracle when healing has already begun – release the gift of Life that God has given us all'
Dr Mal Hooper

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