Hon. Tim Holding MP
Minister for Water
Minister for Finance, WorkCover and the Transport Accident Commission
Minister for Tourism and Major Events

Application for Funding

Transport Accident Commission: HyperMED NeuroRecovery

A. Hyperbaric Oxygenation
B. Lokomat Gait Assisted Training

Summary

Previous correspondence:

1. Meeting at HyperMED 27th August 2009
2. TAC/VWA Proposal via Mr Steve Palmer Snr. Advisor Hon. Tim Holding MP 8th September 2009

1. Executive Summary

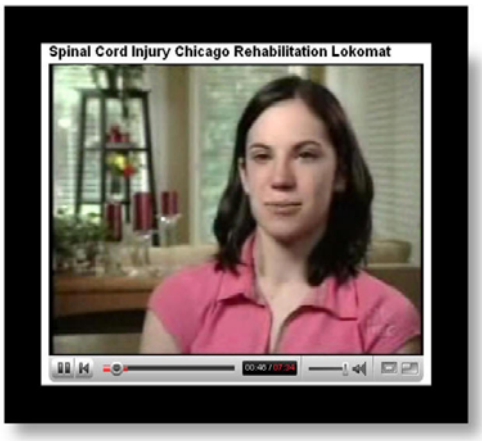
HyperMED NeuroRecovery is seeking funding for injured brain and spinal patients under existing or newly appointed TAC/VWA funding models. The Victorian NeuroTrauma Initiative current funds a number of projects on the basis of 'neuroplasticity' and 'hypoxic induced apoptosis'. HyperMED currently provides 'evidence based' therapeutic interventions with demonstrated outcomes for individuals affected by brain and spinal injury.

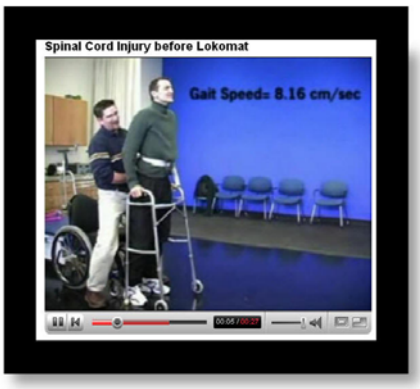
HyperMED NeuroRecovery emphasizes the principles of neuroplasticity – 'the continuing capacity to salvage back what have been damaged activating dormant and inactive neurovascular structures'. HyperMED Protocols are pivotal on 2-key clinical applications:

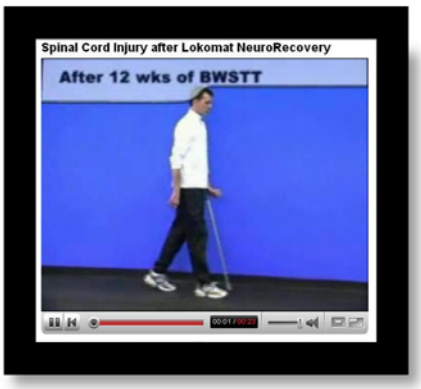
- Hyperbaric Oxygenation enriches available Oxygen into deprived (hypoxic) neurovascular structures. Hyperbaric Oxygenation mobilizes the patients own target specific circulating stem cells (CD34+) enhancing immune responses. This catalyst effect enables the body capacity to re-train, re-organize and re-learn function (5,-19,21-24,30;46pp3-20,67-103;47pp180-190,224-261,264-270)
- Robotic Assisted Rehabilitation gives tremendous opportunity for repetition and practice. Accuracy, repetition and practice drive functional changes (corticospinal) fostering new connections and improving patient conditioning even long after injury (1,2,6,7,35-44)

For the purpose of this submission we have limited equipment reference to Lokomat (Robotic Gait Assisted Training) however other robotic assisted devices are emerging with specific applications including Armeo for Upper Limb training and KinesAssist for balance and gait training.

2. Media Files – What Is Lokomat Gait Assisted Training?







3. TAC/VWA Funding Hyperbaric Oxygenation and Lokomat Gait Assisted Training?

No funding is currently available for brain or spinal patients attending HyperMED.

4. Existing Models of Care - Victorian Spinal Cord Service

In light of the fact that injured neurologic patients have a diminishing therapeutic window over time. The VSCS projects 'continuous patient improvement'; to be at the 'forefront of comprehensive spinal cord management';

'recognised for its contribution to clinical research that serves to increase the body of knowledge regarding spinal cord injury and to improve quality of life for people with a spinal cord injury'; 'promoting health and preventing complications associated with spinal cord injury'; 'supporting patients' return to full and active lives in the community' and 'building partnerships with other agencies to achieve positive outcomes for people with spinal cord injury'.

5. Current Versus Emerging Trends in Rehabilitation

Traditional goals are designed to assist the general needs of the brain and spinal patient; these goals are not focussed on facilitating functional outcomes for patients (1,2).

Professor Mary Galea is quoted: '*There is mounting evidence that a comprehensive exercise program including stimulation of the paralysed limbs can promote neural recovery and good health, and reduce secondary complications such as pressure ulcers and fractures. Innovative "activity-based therapies" have been shown to restore neurological function and are based on principles of experimental psychology, exercise physiology and neuroscience.*

In Australia considerable effort is directed towards maximizing independence through compensatory strategies using the non-paralysed limbs, especially in people with clinically complete injuries. In part this has been the result of the prevailing paradigm that only limited recovery is possible following spinal cord injury.

However, the therapy resources in Australian spinal rehabilitation units are also insufficient to provide comprehensive exercise programs beyond the initial period of rehabilitation for people with spinal cord injury. Given the published reports that such programs might have substantial health benefits, I visited leading spinal injury clinical and research centres in the USA, Canada and Europe to investigate the content, delivery, and evidence for exercise programs for people with spinal cord injury.' (1)

The Victorian Spinal Cord Service has a clear Vision however Prof Galea's (2007) report leads us to conclude that certainly more can be done to assist those living with disability.

6. Victorian NeuroTrauma Initiative

VNI is funding numerous research projects and collaborative studies. Several current projects are listed below however these areas of clinical endeavours are not new territories. Considerable published evidence already exists within each of these projects. http://www.vni.com.au/news/id/61.

- Professor Mary Galea, The University of Melbourne, $4.7 million SCIPA (Spinal Cord Injury and Physical Activity): *Intensive exercise from acute care to the community.* **Extensively published.** Considerable science has been published in this field. Intensive exercise is based on the concepts of 'neuroplasticity' which is the basis of Body Weight Support Treadmill Training for the past 15-years. HyperMED/Lokomat - Australian Experience HyperMED NeuroRecovery.pdf (2)
- *Corticospinal Regeneration - Regeneration of the Corticospinal Tract in the Injured Spinal Cord* - Chief Investigator: Professor David Howells *This project aims to explore new approaches for stimulating regeneration of the corticospinal tract through the role of inflammatory cells and growth promoting factors.* **Extensively published.** Corticospinal tracts are impacted by tissue hypoxia and the cascade of apoptosis that follows. Hyperbaric Oxygenation impacts hypoxia. Corticospinal tracts respond to functional retraining as evidenced by Functional BOLD studies. (2,5,6,7,8)
- *Functional Electrical Stimulation-assisted Hand Exercise for People with Chronic Quadriplegia* Chief Investigator: Associate Professor Mary Galea Associate Investigator: Associate Professor Douglas Brown *There is some evidence that the application of surface FES to assist grasping and release movements in quadriplegic people results in improvements in grasp strength and in daily living.* **Extensively published**. FES stimulation affecting upper limb functionality is already documented. HyperMED provides Median Nerve Stimulation (Prof Edward Cooper) improving limb function and increase neural responses in the spinal cord and brain centre National Geographic Documentary (VIDEO) - Professor Ed Cooper - Median Nerve Stimulation (48)
- *Traumatic Injury to Brain and Spinal Cord: Secondary Injury, Development and Evaluation of New Treatments* Chief Investigator: Professor Norman Saunders Associate Investigators: Associate Professor Crisitna Morganti-Kossmann, Dr Peter Crack, Associate

Professor David Howells, Professor Peter McIntyre, Professor Seong-Seng Tan, Dr Peter Batchelor, Associate Professor Kate Dziegielewska, Dr Jennifer Callaway - *Damage to the brain and spinal cord is categorised as primary (immediate consequences) and secondary (processes that occur after initial impact). The secondary processes involve an activation of complex cascades leading to death of nerve cells and other brain cells as well as clinical complications such as brain swelling, raised intracranial pressure and ischaemic damage to the affected regions. The purpose of this study is to develop a better understanding of the mechanisms that lead to secondary damage following traumatic brain and spinal cord injury. This project also aims to identify targets for therapeutic intervention in order to limit the extent of damage and functional loss.* **Extensively published.** Hyperbaric Oxygenation in Cerebral Injury (5,-19,21-24,30;46pp3-20,67-103;47pp180-190,224-261,264-270)

- *Pilot Project: Enhancing Endogenous Neurogenesis as a Potential Therapy Following Traumatic Brain Injury. The precise characterisation of neurogenesis induced after TBI identifies a window of opportunity for the administration of compounds which could enhance the survival of these new cells and increase the number of cells differentiating into neurons, potentially contributing to augment neurogenesis and improved functional outcome.* **Extensively published.** – Clinical Research: Cerebrolysin
- *Role of Post-Traumatic Hypoxia in the Exacerbation of Cerebral Inflammation Elicited by Brain Injury* Project Summary**:** *There is clinical evidence showing that 45% of patients with severe Traumatic Brain Injury (TBI) are subjected to respiratory distress leading to reduced oxygen delivery to the brain or hypoxia. Although brain hypoxia is thought to aggravate tissue damage caused by trauma, its impact on secondary pathological pathways has not been thoroughly investigated. Based on previous evidence showing that hypoxia itself induces brain inflammation, we hypothesize that the combination of TBI and post-traumatic hypoxia will exacerbate the production of inflammatory mediators in the injured brain, thus aggravating tissue and neurological damage. This hypothesis will be tested in a model of diffuse traumatic axonal injury (TAI) in which rats will be subjected to trauma with or without post-traumatic hypoxia. Clinical relevance of the results obtained in the animal models will be characterised on patients with severe TBI. Candidate injury marker proteins with potential prognostic and diagnostic value from animal data will also be validated in the human samples to determine clinical suitability.* **Extensively published.** Hyperbaric Oxygenation impacts the cascade effect of hypoxic induced apoptosis. (5,-19,21-24,30;46pp3-20,67-103;47pp180-190,224-261,264-270)

7. Impact Of Brain and Spinal Cord Injury

Traumatic Brain Injury (TBI) and Spinal Cord Injury (SCI) have a significant impact on quality of life, life expectancy and economic burden, with considerable costs associated with primary care and loss of income. Patients are typically injured at a young age and are disabled for the remainder of their lives leading to very high costs. The lifetime cost of newly acquired brain and spinal cord injury occurring in 2008 was $10.5 billion in Australia (Victorian NeuroTrauma Initiative June 2009).

The extent of disability after injury varies greatly, depending on the severity and location of the injury and which nerve fibers are damaged. The resulting neurological deficit can be temporary or permanent, complete or incomplete; one of the primary goals for people with neurologic disability is to improve locomotor function. This capacity to regain functionality including the ability to walk is based on the principles of neuroplasticity notwithstanding the therapeutic window diminishes over time.

Neuroplasticity is the term describing the body's ability to salvage back what has been damaged. This is a relatively new concept in Australian rehabilitation which is typically focussed on living and coping with disability (1,2). However simply managing disability is also associated with continuing economic burden. Many suffer a range of secondary complications associated with injury including cardiovascular problems, type II diabetes, muscle wasting, osteoporosis, immune deficiencies, and other life-threatening problems (2,3,4).

8. Neurologic Patients Attending HyperMED

Most neurologic patients presenting at HyperMED are greater than 6-12 months post injury. Most have become stagnant in their rehabilitative outcomes. Many suffer additional conditions and disorders that have emerged since injury. All patients undertake an extensive clinical assessment including additional MRIs and blood profiles when commencing at HyperMED.

- The objective at HyperMED is to slow the secondary cascade effects associated with complex injury whilst promoting functional changes (neuroplasticity).

More recently another C4/5 quadriplegic patient classified as incomplete with severe spasticity attended HyperMED after being discharged from in-patient spinal rehabilitation. The emphasis of his in-patient spinal rehabilitation was to control his spasms using Baclofen. Prior to commencing at HyperMED he states that his spasticity is better managed however did not experience or observe any significant changes to his level of disability or overall functionality. The following is his statement in response to his solicitor's inquiry regarding benefits he has observed since commencing at HyperMED. TAC will not fund any aspect of him attending HyperMED.

- *Improved movements both hands and fingers*
- *Improved movement in both feet*
- *Voluntary control and lifting both legs*
- *Stronger voluntary motor control generally*
- *Use hip extension to assist with initiating swing*
- *Improved balance*
- *Improved posture, head holding, reduction of emerging kyphosis*
- *Improved ability to transfer body weight*
- *Removal of spasms after training*
- *Improved range of motion*
- *Reduction and control of dysreflexia and hypotension*
- *Improved blood circulation, reduced leg swelling*
- *Improved responsiveness to sensory input*

These changes are significant and cannot be ignored. An extensive list of Patients attending HyperMED Protocols is also available at www.hypermed.com.au (48). We anticipate this patient and others attending HyperMED will continue to gain functionality whilst also improving overall conditioning, cardiovascular and circulatory function.

9. Magnetic Resonance Imaging

Most neurologic patients are initially investigated using the 1.5T (Tesla) MRI at the time of injury. Most are discharged from hospital and rehabilitation units without being reassessed with an additional MRI to determine functional changes and or post surgical stabilisation.

Every individual responds differently to injury – functional changes may be positive or negative. Even in the absence of notable deterioration many neurologic patients demonstrate further destructive change evident on additional MRI post injury. Neurologic patients with progressive neurovascular degeneration have increased risk associated with post injury complications (4,5,7,23).

All neurological patients benefit from a higher magnitude MRI investigation including 3.5T BOLD MRI to determine integrity of underlying neurovascular structures post injury (5,6,7,37,39,47pp188-190). Functional BOLD MRI provides greater clinical insight than simple 1.5T MRI. Functional BOLD MRI provides an accurate 'bench mark' which can assist the requirement for therapy and potential for functional outcomes.

10. What Happens Following Spinal Cord Injury?

- Spinal Injury may result in either complete or incomplete injury. Many patients informed they are 'complete' presume their cord is severed. The term complete 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. Many spinal patients classified as 'complete' may still re-gain functional responses even years after their injury.
- 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. Christopher Reeve's recovery commenced five to seven years after his injury. 'Reeve believed his improved function was the result of vigorous physical activity to re-train function and awaken dormant nerve pathways.' (American Association of Neurological Surgeons, Craig Hospital, Christopher and Dana Reeve Foundation, The National Institute of Neurological Disorders and Stroke)

- Surgical strategies at the time of injury are primarily orthopaedic focused with emphasis on reduction and stabilization of bony dislocation. All spinal patients require additional MRI within the following months to determine the integrity of the surgical procedure. Many spinal patients suffer additional complication due to progressive scar formation, bony fragments and lack of plate and screw integrity. These additional factors not only inhibit recovery but often contribute to additional cord and immune complications
- Laceration, extensive bruising, and massive swelling results in cord hypoxia. Cord hypoxia triggers a cascade of destructive cellular responses. Hypoxic damage causes destructive Apoptotic cells from the immune system to migrate to the injury site causing further damage to some neurons and death to others that survived the initial trauma. Immediate strategies must be implemented to minimize this cascade of programmed cellular destruction. Hyperbaric Oxygenation impacts tissue hypoxia minimizing the cascade effects of progressive damage
- Within weeks of the initial spinal 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). Early HBOT intervention potentially has the greatest impact to the destructive spread of cord hypoxia
- Continuing hypoxic induced apoptosis results in progressive hemorrhagic myelomalacia - spread of myelomalacia progresses above and below the injured site due to progressive intramedullary hemorrhage of the spinal cord. This can potentially lead to further loss of neurologic function and cord atrophy (wasting and thinning of the cord) severely inhibiting the capacity to regenerate and recover function. Comparison MRI post surgical stabilization is critical within the early months to evaluate this destructive process – functional changes an injured spinal patient may be getting does not rule out the potential cascade of secondary complications. Functional BOLD (Blood Oxygen Level Dependency) MRI measures progressive hypoxic damage and apoptosis spread. Functional BOLD MRI also measures the impact of Hyperbaric Oxygenation intervention and Lokomat functional outcomes (5,6,7,13,14,18)
- Experiments conducted on spinalized cats demonstrate that spinal circuitry (reflex generators) below the level of injury remains active (even years after injury) and functional neuronal properties can respond to peripheral input from *below* the level of injury. Treadmill cats can be trained to walk (2)
- Lack of appropriate and 'accurate' stimulation induces functional incapacity called the ‘learning non-use’. HyperMED Australia : Do Wheel Chairs Inhibit Recovery?
- Motor cortex centers in the brain also show signs of functional loss due to spinal cord injury. Functional BOLD MRI demonstrate that the motor cortex and cerebellum parts of the brain 're-allocate functional capacity lost through spinal cord injury'. These changes are frequently associated with Mental Health issues that further contributes to disability (2)
- 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 at spinal and higher brain centers. Functional BOLD MRI measures the capacity to retrain function in both the brain and spinal cord neural pathways. The injured spinal cord has capacity to 'wake-up' - salvage back tissue damage, re-activate and re-train dormant neural pathways improving functionality

11. Hyperbaric Oxygenation for Neurologic Injury

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

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 (5,-19,21-24,30;46pp3-20,67-103;47pp180-190,224-261,264-270).

International trends confirm the widespread application of Hyperbaric Oxygenation to impact functional changes due to hypoxic induced neurovascular degeneration (46,47,48)

Additional references

- PubMed *Hyperbaric Oxygen Therapy and Hypoxia* identifies 761-articles

12. What Exactly Does Hyperbaric Oxygenation Do For Neurologic Insult?

HBOT acts as a 'catalyst' promoting functional immune responses by correcting deep seated hypoxia in damaged tissue structures. HBOT results in increased blood flow by fostering the formation of 'new capillary dynamics' (neovascularization) into damaged regions of the body. HBOT accelerates neuroplasticity - activating damaged and dormant nerve cells. HBOT diminishes the cascade of apoptosis (programmed cellular degeneration). HBOT activates dormant and inactive nerve cells hastening recovery (11-15,46pp87-103).

American Journal Physiology - Heart and Circulatory Physiology 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 approximately 40-hours HBOT - circulating CD34+ cells increases eight fold (800%) (30,46pp101-102).

- 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 clinical endeavours

Additional references

- PubMed *Hyperbaric Oxygen Therapy and Stem Cells* identifies 57-articles
- PubMed *Hyperbaric Oxygen Therapy and Neural Stem Cells* identifies 7-articles
- PubMed *Hyperbaric Oxygen Therapy and Neuro-Trophic factors* identifies 17-articles

13. What Australian Hospitals Feature Lokomat Gait Assisted Training?

No Australian hospitals feature Lokomat (45).

In December 2006 HyperMED NeuroRecovery 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.

Over 31-countries feature Lokomat Gait Training with in excess of 250-Lokomats world wide. In the USA in excess of 50-Lokomats exist in larger neurorehabilitation hospitals including Chicago Rehabilitation, Spaulding Rehabilitation, Shepherd Hospital, Miami Hospital, Kernig Hospital, Sister Kenny Rehabilitation Hospital, West Gables Hospital, Moss Rehab Hospital, Cardinal Hill Rehabilitation (45,48).

14. HyperMED Lokomat (Robotic Gait Assisted Walking) Gait Assisted Training

Patients receiving Lokomat Gait Assisted Training are scheduled daily; initially 1-hour session and then as the patient builds protocols increase up to 2-hours each day attending. An initial base line of between 40-60 hours Lokomat training is typical of most patients attending with disability. Functional changes are often evident within the first 20-hours of Lokomat training.

Lokomat Gait Assisted Training is not passive involvement. The Lokomat is constantly adjusted to best assist the functional responses of the patient. Patients commence with passive assistance however as the patient compliancy builds the Lokomat settings and various programs are tailored to the patient's performance and capabilities. Some patients have high level spasticity and others a complete loss of tone. Each patient's presentation is different - Lokomat provides excellent opportunity to 'best-fit' the patient's specific capabilities and capacity to re-train function. And this is replicable on every separate training session!

In addition the support harness treadmill system is utilized independent of the Lokomat to promote functional changes. Functional changes being driven by 'man and machine' are then put to the test with the patient then able to implement strategies being focused on during each Lokomat session.

This combination effect is both unique and significant towards each neurologic patient developing a sense of supportive assistance whilst focusing on improving functional independence.

Walking requires a 'fluid like connection between spinal reflex generators and higher brain centres'. The combined approach is invaluable to promote functional changes - neuroplasticity (the ability to salvage back what has been damaged).

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 (2).

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.

15. What Are The Limits Of Lokomat Gait Training?

Patients with brain and 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 (2).

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 accommodating individuals with a range of disability.

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.

16. Background Information – Body Weight Support Treadmill Gait Training

For the past 15-years bodyweight supported treadmill training (BWSTT) has become a prominent gait rehabilitation method in leading rehabilitation centers throughout the world (1,2). 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.

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 sit, stand and walk' (2).

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.

17. Basis of Locomotor Training

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 (2).

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! (2)

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' (2).

Activity based rehabilitation (1) 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 (2).

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 (2).

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 (2).

18. Lokomat Gait Training - 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 functioning nervous system. When the brain and spinal cord suffer 'hypoxic injury' the normal functioning skills become replaced by abnormal signals 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 (2).

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 (2).

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. 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 (2).

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 spinal patient, supporting family and therapist. Acquired deformity results in a cascade effect of adaptation and dysfunction notwithstanding psychological effects.

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 spinal patients can increase strength as well as result in higher gait velocity. Similar to strength training, treadmill training with partial body weight support, as discussed can improve walking speed and endurance of spinal patients who have partial walking ability. 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 spinal patients (2).

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.

19. 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 (2).

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 (2).

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 (2).

20. Conclusion

The Victorian NeuroTrauma Initiative current funds a number of projects on the basis of 'neuroplasticity' and 'hypoxic induced apoptosis'.

HyperMED currently provides evidence based therapeutic interventions with demonstrated outcomes for individuals affected by brain and spinal injury.

- *Intensive exercise from acute care to the community*. **Extensively published.** Intensive exercise is based on the concepts of 'neuroplasticity' which is the basis of Body Weight Support Treadmill Training for the past 15-years.
- *Corticospinal Regeneration - Regeneration of the Corticospinal Tract in the Injured Spinal Cord*. **Extensively published.** Corticospinal tracts are impacted by tissue hypoxia and the cascade of apoptosis that follows. Hyperbaric Oxygenation impacts hypoxia. Corticospinal tracts respond to functional retraining as evidenced by Functional BOLD studies.
- *Functional Electrical Stimulation-assisted Hand Exercise for People with Chronic Quadriplegia*. **Extensively published.** HyperMED provides Median Nerve Stimulation (Prof Edward Cooper) improving limb function and increase neural responses in the spinal cord and brain centre National Geographic Documentary (VIDEO) - Professor Ed Cooper - Median Nerve Stimulation
- *Traumatic Injury to Brain and Spinal Cord: Secondary Injury, Development and Evaluation of New Treatments Damage to the brain and spinal cord is categorised as primary (immediate consequences) and secondary (processes that occur after initial impact). The secondary processes involve an activation of complex cascades leading to death of nerve cells and other brain cells as well as clinical complications such as brain swelling, raised intracranial pressure and ischaemic damage to the affected regions. The purpose of this study is to develop a better understanding of the mechanisms that lead to secondary damage following traumatic brain and spinal cord injury. This project also aims to identify targets for therapeutic intervention in order to limit the extent of damage and functional loss.* **Extensively published**. Hyperbaric Oxygenation impacts the cascade effect of hypoxic induced apoptosis.
- *Role of Post-Traumatic Hypoxia in the Exacerbation of Cerebral Inflammation Elicited by Brain Injury There is clinical evidence showing that 45% of patients with severe Traumatic Brain Injury (TBI) are subjected to respiratory distress leading to reduced oxygen delivery to the brain or hypoxia. Although brain hypoxia is thought to aggravate tissue damage caused by trauma, its impact on secondary pathological pathways has not been thoroughly investigated. Based on previous evidence showing that hypoxia itself induces brain inflammation, we hypothesize that the combination of TBI and post-traumatic hypoxia will exacerbate the production of inflammatory mediators in the injured brain, thus aggravating tissue and neurological damage. This hypothesis will be tested in a model of diffuse traumatic axonal injury (TAI) in which rats will be subjected to trauma with or without post-traumatic hypoxia. Clinical relevance of the results obtained in the animal models will be characterised on patients with severe TBI. Candidate injury marker proteins with potential prognostic and diagnostic value from animal data will also be validated in the human samples to determine clinical suitability.* **Extensively published.** Hyperbaric Oxygenation impacts the cascade effect of hypoxic induced apoptosis.

Hyperbaric Oxygenation 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! (2)

21. Additional Publications

Websites including www.searchmedica.com and www.ncbi.nlm.nih.gov/pubmed/ a service of the U.S. National Library of Medicine and the National Institutes of Health provide a valuable resource regarding studies and trials associated with the use of Lokomat (Gait Assisted Training), Hyperbaric Oxygenation and other supportive modalities including Whole Vibration Training.

Search Medica - Lokomat Gait Training

Functional and Physiological Responses to Lokomat Therapy (Pilot Study) - Full Text View - ClinicalTrials.gov
... Functional and Physiological Responses to **Lokomat** Therapy (Pilot Study) **...** such as those who have **spinal cord injury** stroke traumatic brain injury **...** occur as a result of receiving **Lokomat** therapy. The investigators will **...** Supported treadmill ambulation training after **spinal cord injury**: a pilot study. **...** http://www.clinicaltrials.gov/ct2/show/study/NCT00883142

Cardiovascular Fitness for Robotically Assisted Treadmill Training in Persons With Chronic Incomplete Spinal Cord Injury
... This proposal investigates the hypothesis that progressive aerobic exercise with **Lokomat** is feasible in people with motor incomplete **spinal cord injury** and three months of training will improve cardiovascular fitness **...** premature cardiovascular disease the investigation of robotic-assisted interventions in **spinal cord injury** (SCI) such as the **Lokomat** may have important health benefits in both cardiovascular fitness as well as functional mobility. **...** http://www.clinicaltrials.gov/ct2/show/study/NCT00385918

Enhancing Walking in People With Incomplete Spinal Cord Injury: a Pilot Study - Full Text View - ClinicalTrials.gov
... Enhancing Walking in People With Incomplete **Spinal Cord Injury**: a Pilot Study **...** robotic gait trainer (the **Lokomat**) on functional ambulation **...** Enhancing Walking in People With Incomplete **Spinal Cord Injury** by Improving Swing Phase **...** (BWSTT) with the **Lokomat** which differ only in the **...** http://www.clinicaltrials.gov/ct2/show/NCT00610974

Changes in spinal reflex and locomotor activity after a complete spinal cord injury: a common mechanism? -- Dietz et al. 132
... leg muscle electromyography activity evoked by mechanically assisted locomotion (**Lokomat**) in biceps femoris rectus femoris tibialis anterior and gastrocenmius medialis. **...** http://brain.oxfordjournals.org/cgi/content/short/132/8/2196?rss=1

Spinal decompression sickness presenting as partial Brown-Sequard syndrome and treated with robotic-assisted body-weight support
... rehabilitation outcome of incomplete **spinal cord injury**. Its usefulness has **...** training was administrated using the **Lokomat**. Primary outcomes were American **...** Test and Walking Index for **Spinal Cord Injury**. RESULTS: **...** After 3 months of rehabilitation including 18 **Lokomat** sessions American Spinal Cord Association **...**

Cardiovascular Fitness for Robotically Assisted Treadmill Training in Persons With Chronic Incomplete Spinal Cord Injury
... Treadmill Training in Persons With Chronic Incomplete **Spinal Cord Injury ... Spinal Cord Injuries** More general conditions related to this trial **...** Interventions listed in this trial **Lokomat** Training Home stretching protocol **...** http://www.clinicaltrials.gov/ct2/show/related/NCT00385918

Locomotor Training in Persons With Multiple Sclerosis - Full Text View - ClinicalTrials.gov
... walking in patients with stroke **spinal cord injury** and cerebral palsy. **...** accomplished via a robotic device the **Lokomat** which will move the patient's **...** Device: **Lokomat** locomotor training using body weight support on a treadmill **...** http://www.clinicaltrials.gov/ct2/show/study/NCT00607126

Virtual gait training for children with cerebral palsy using the Lokomat gait orthosis.
... Virtual gait training for children with cerebral palsy using the **Lokomat** gait orthosis. 204-9 The **Lokomat** gait orthosis was developed in the **Spinal Cord Injury** Center at the University Hospital Balgrist Zurich and provides automatic gait training for patients **...** Each patient undergoes a task-oriented **Lokomat** rehabilitation training program via a **...**

Full Article | Biomechanics
... tested the effectiveness of the **Lokomat** an FDA-approved robotic gait **...** symmetrical stepping assistance using the **Lokomat**. With body-weight supports **...** Subjects with incomplete **spinal cord injury** revealed greater metabolic costs **...** http://www.biomech.com/full_article/?ArticleID=1101&month=09&year=2008

Locomotor Training in Persons With Multiple Sclerosis - Tabular View - ClinicalTrials.gov
... walking in patients with stroke **spinal cord injury** and cerebral palsy. **...** accomplished via a robotic device the **Lokomat** which will move the patient's **...** Device: **Lokomat** Procedure: resistive training Study Arms / Comparison Groups **...** http://www.clinicaltrials.gov/ct2/show/record/NCT00607126

Swing Phase Resistance Enhances Flexor Muscle Activity During Treadmill Locomotion in Incomplete Spinal Cord Injury -- Lam et al
... Muscle Activity During Treadmill Locomotion in Incomplete **Spinal Cord Injury ...** ambulatory patients with incomplete **spinal cord injury** (SCI). **...** velocity-dependent resistance applied by the **Lokomat** robotic gait orthosis. **...** http://nnr.sagepub.com/cgi/content/abstract/22/5/438?rss=1

Method of estimating the degree of active participation during stepping in a driven gait orthosis based on actuator force prof
... gait orthosis (DGO) **Lokomat** an estimation of the patient's **... Spinal Cord Injury** Center Balgrist University Hospital Zurich Switzerland. **...**

Reviews of effectiveness of training after spinal cord or traumatic brain injury -- Ivers 14 (3): 209 -- Injury Prevention
... Spinal cord injury (SCI) and traumatic brain injury **...** the robotic-assisted device "**Lokomat**" as one of the **...** Locomotor training for walking after **spinal cord injury**. **...** http://injuryprevention.bmj.com/cgi/content/full/14/3/209

The Evolution of Walking-Related Outcomes Over the First 12 Weeks of Rehabilitation for Incomplete Traumatic Spinal Cord Injury:
... Rehabilitation for Incomplete Traumatic **Spinal Cord Injury**: The Multicenter Randomized **...** Background. The **Spinal Cord Injury** Locomotor Trial (SCILT) **...** Trial Evaluating the Effectiveness of the **Lokomat** in Subacute Stroke **...** http://nnr.sagepub.com/cgi/content/abstract/21/1/25

Limb alignment and kinematics inside a Lokomat robotic orthosis.
... In particular the **Lokomat** robotic orthosis (Hocoma AG **...** facilities treating patients with **spinal cord injury** stroke and other neurological **...** trajectories between walking in the **Lokomat** and walking on a treadmill **...**

Quantum Sufficit - July 1, 2004 - American Family Physician
... need to carefully review the discounts and features of the various cards. A robot named **Lokomat** is helping patients with **spinal cord injuries** learn to walk again according to a press release from the University of Texas Southwestern Medical Center at Dallas. **...** body to step. After using **Lokomat** for a month a 50 **...** http://www.aafp.org/afp/20040715/quantum.html

Neurorehabilitation and Neural Repair
... Therapy in Motor-Incomplete **Spinal Cord Injury** ” Neurorehabil Neural Repair **...** function in individuals with **spinal cord injury** (SCI). **...** activation for voluntary plantarflexion following **Lokomat** training may not be what **...** status and gait speed following **Lokomat** body weight–supported training. **...** http://nnr.sagepub.com/cgi/reprint/20/1/233.pdf?ck=nck

Prospective, Blinded, Randomized Crossover Study of Gait Rehabilitation in Stroke Patients Using the Lokomat Gait Orthosis -- Ma
... electromechanical-driven gait orthosis (**Lokomat**) for treadmill training. **...** (A = 3 weeks of **Lokomat** training B = 3 weeks **...** Muscle Activity During Treadmill Locomotion in Incomplete **Spinal Cord Injury ...** http://nnr.sagepub.com/cgi/content/abstract/1545968307300697v1?ck=nck

Standardized voluntary force measurement in a lower extremity rehabilitation robot.
... gait orthosis (DGO) **Lokomat**. To evaluate the capabilities **... Spinal Cord Injury** Center Balgrist University Hospital Zurich Switzerland. **...**

Weight-supported treadmill vs over-ground training for walking after acute incomplete SCI -- Dobkin et al. 66 (4): 484 -- Neurol
... Scott MD and the **Spinal Cord Injury** Locomotor Trial (SCILT) **...** in patients with incomplete **spinal cord injury** (SCI) **...** Trial Evaluating the Effectiveness of the **Lokomat** in Subacute Stroke **...** http://www.neurology.org/cgi/content/abstract/neurology;66/4/484

Locomotor activity in spinal cord-injured persons -- Dietz and Harkema 96 (5): 1954 -- Journal of Applied Physiology
... Dietz Balgrist Univ. Hospital **Spinal Cord Injury** Center Forchstr. **...** Gait Rehabilitation in Stroke Patients Using the **Lokomat** Gait Orthosis **...** Treadmill training after **spinal cord injury**: Good but not better **...** http://jap.physiology.org/cgi/content/abstract/96/5/1954?ck=nck

Treadmill Training With Partial Body Weight Support and an Electromechanical Gait Trainer for Restoration of Gait in Subacute St
... Trial Evaluating the Effectiveness of the **Lokomat** in Subacute Stroke **...** Gait Rehabilitation in Stroke Patients Using the **Lokomat** Gait Orthosis **...** Therapist-Assisted Treadmill Walking in Individuals With Incomplete **Spinal Cord Injury ...** http://stroke.ahajournals.org/cgi/content/short/01.STR.0000035734.61539.F6v1?ck=nck

Locomotor activity in spinal man: significance of afferent input from joint and load receptors -- Dietz et al. 125 (12): 2626 --

... Plasticity of Spinal Centers in **Spinal Cord Injury** Patients: New Concepts **...** Gait Rehabilitation in Stroke Patients Using the **Lokomat** Gait Orthosis **...** Degradation of neuronal function following a **spinal cord injury**: mechanisms and countermeasures **...** http://brain.oxfordjournals.org/cgi/content/abstract/125/12/2626?ck=nck

Metabolic and cardiac responses to robotic-assisted locomotion in motor-complete tetraplegia: a case report.
... ASIA B C3-C4 **spinal cord injury**--walked on a **...** walking with stepping assistance from a **Lokomat**-driven gait orthosis.

Locomotor activity in spinal man: significance of afferent input from joint and load receptors -- Dietz et al. 125 (12): 2626 --
... muscle; SCI = **spinal cord injury**; TA = tibialis **...** orthosis (DGO) '**Lokomat**' (Hocoma AG Zurich) **...** A) six complete **spinal cord injury** (SCI) **...** http://brain.oxfordjournals.org/cgi/content/full/125/12/2626?ck=nck

A New Approach to Retrain Gait in Stroke Patients Through Body Weight Support and Treadmill Stimulation -- Visintin et al. 29 (6
... Trial Evaluating the Effectiveness of the **Lokomat** in Subacute Stroke **...** Validity of the Walking Scale for **Spinal Cord Injury** and Other Domains **...** Gait Rehabilitation in Stroke Patients Using the **Lokomat** Gait Orthosis **...** Functional Recovery After Experimental **Spinal Cord Injury**: Implications of Basic **...** http://stroke.ahajournals.org/cgi/content/short/29/6/1122?rss=1&ssource=mfc

Energy cost and muscular activity required for propulsion during walking -- Gottschall and Kram 94 (5): 1766 -- Journal of Appli
... Trial Evaluating the Effectiveness of the **Lokomat** in Subacute Stroke **...** Therapist-Assisted Treadmill Walking in Individuals With Incomplete **Spinal Cord Injury ...** http://jap.physiology.org/cgi/content/abstract/94/5/1766

Load-Regulating Mechanisms in Gait and Posture: Comparative Aspects -- Duysens et al. 80 (1): 83 -- Physiological Reviews
... Activity After Treadmill Training in Subjects With Incomplete **Spinal Cord Injury ...** Gait Rehabilitation in Stroke Patients Using the **Lokomat** Gait Orthosis **...** http://physrev.physiology.org/cgi/content/abstract/80/1/83?ck=nck

Treadmill Training With Partial Body Weight Support Compared With Physiotherapy in Nonambulatory Hemiparetic Patients -- Hesse e
... Trial Evaluating the Effectiveness of the **Lokomat** in Subacute Stroke **...** Gait Rehabilitation in Stroke Patients Using the **Lokomat** Gait Orthosis **...** Locomotor Training After Human **Spinal Cord Injury**: A Series of Case Studies **...** Review : Walking After **Spinal Cord Injury**: Control and Recovery **...** http://stroke.ahajournals.org/cgi/content/short/26/6/976

Search Medica - Hyperbaric Oxygenation – Neurologic Injury

Hyperbaric oxygen (HBO) therapy for acute traumatic cervical spinal cord injury.
... oxygen (HBO) therapy for acute traumatic cervical **spinal cord injury**. 538-40 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**. **...**

Prediction of neurologic outcome in patients with spinal cord injury by using hyperbaric oxygen therapy.
... 385-9 The effectiveness of **hyperbaric** oxygen therapy (HBO) in predicting neurological recovery in patients with **spinal cord injury** was evaluated. HBO has been used to treat **spinal cord injury** but HBO does not appear to greatly alter the neurological outcome. **...**

Hyperbaric oxygen in the treatment of patients with cerebral stroke, brain trauma, and neurologic disease.
... 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. **...**

MRI findings and clinical outcome in 45 divers with spinal cord decompression sickness.
... cord decompression sickness. 1112-6 BACKGROUND: Decompression sickness (DCS) affecting the **spinal cord** is the most dangerous form of diving-related **injury** with potential sequelae. This study was conducted to evaluate the relationship **...** DCS that were referred to our **hyperbaric** facility with clinical evidence of spinal **...**

The clinical application of hyperbaric oxygen therapy in spinal cord injury: a preliminary report.
... clinical trials with **hyperbaric** oxygen therapy of acute **spinal cord injury**. A series of treatment protocols have thus been designed for treatment of acute **spinal cord injury** utilizing **hyperbaric** oxygen. The study has been in progress for the last two years and involved more than 50 patients; **...**

The use of hyperbaric oxygen to modify the effects of recent contusion injury to the spinal cord.
... occurring at the level of the **spinal cord** lesion. **Hyperbaric** oxygen (HBO) **...** 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. **...**

Preliminary report on ten patients with spinal cord injuries treated with hyperbaric oxygen.
... Preliminary report on ten patients with **spinal cord injuries** treated with **hyperbaric** oxygen. 572-3 A preliminary report is presented on 10 patients with **spinal cord injuries** who were treated with **hyperbaric** oxygen. The results suggest that by supporting injured **spinal cord** tissue with oxygen under pressure improvement in nerve function may occur. **...**

Cervical Spine Acute Bony Injuries: Treatment & Medication - eMedicine Sports Medicine
... Decrease inflammation by suppressing the migration of polymorphonuclear leukocytes and reversing increased capillary permeability. Indicated for known or suspected **spinal cord injury**. To be administered within 8 h of **injury**. Dosing Interactions Contraindications Precautions Adult **...** Undersea and **Hyperbaric** Medical Society and Wilderness Medical Society Disclosure: Nothing to disclose. **...** http://emedicine.medscape.com/article/94234-treatment

Acute Nerve Injury: Treatment - eMedicine Neurosurgery
... matrix and MRI for evaluation of intrinsic **spinal cord** parenchymal changes and potential neural **...** Antivirals and steroids help to decrease endoneurial edema an etiology of nerve **injury**.17 **Hyperbaric** oxygen (HBO) is an approved adjunctive treatment **...** http://emedicine.medscape.com/article/249621-treatment

Acute Postoperative Paraplegia Complicating with Emergency Graft Replacement of the Ascending Aorta for the Type A Dissection
... drained for three days. **Hyperbaric** oxygenation therapy was started four **...** Prevention and detection of **spinal cord injury** during thoracic and thoracoabdominal **...** Narayana PA Kudrle WA Liu SJ Charnov JH Butler BD Harris JH Jr. Magnetic resonance imaging of **hyperbaric** oxygen treatment rats with **spinal cord injury**: preliminary studies. Magn Reson Imaging 1991; 9: 423-8. **...** http://www.nv-med.com/atcs/pdf/2003_9_5/330.pdf

Hyperbaric oxygen and acute spinal cord injuries in humans.
... 573-5 Clinical assessment of a regime of **hyperbaric** oxygen within 12 hours of acute spinal **injury** in humans suggests that further study **...**

Hyperbaric oxygen therapy: implications for spinal cord injury patients with intrathecal baclofen infusion pumps. Case report.
... injury patients with intrathecal baclofen infusion pumps. Case report. 281-4 A patient with a cervical **spinal cord injury** receiving intrathecal baclofen for spasticity control underwent a 7 week course of **hyperbaric** oxygen therapy to induce healing of an ischial decubitus ulcer. **...**

Osteomyelitis in the spinal cord injured: a review and a preliminary report on the use of hyperbaric oxygen therapy.
... liable to develop osteomyelitis mostly by extension from pressure ulcers. In 2055 records reviewed in the Long Beach **Spinal Cord Injury** Service of the Veterans Administration Medical Center the incidence was found to be 4.3 per cent. **...** osteomyelitis were treated in a monoplace **hyperbaric** oxygen (HBO) **...**

Hyperbaric oxygen in the management of pressure sores in patients with injuries to the spinal cord.
... Print 0148-0812 Print 7 9 1981 Sep The Journal of dermatologic surgery and oncology **...**

22. Selected References

1. Prof Mary Galea www.churchilltrust.com.au/res/File/Fellow_Reports/Galea%20Mary%202007.pdf

2. HyperMED/Lokomat - Australian Experience HyperMED NeuroRecovery.pdf

3. 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** Neuroscience Unit, Laval University Medical Center (CHUL-CHUQ), Quebec City, Quebec, Canada. 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.

4. 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.

5. 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** Department of Neuroscience, Karolinska Institutet, 17177, Stockholm, Sweden. Toshiki.Endo@ki.se 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.

6. **Changes in supraspinal activation patterns following robotic locomotor therapy in motor-incomplete spinal cord injury** Neurorehabil Neural Repair. 2005 Dec;19(4):313-24 University of Texas Southwestern Medical Center, Department of Physical Therapy, Dallas, TX 75390-8876, 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.*

7. **Reorganization of sensory processing below the level of spinal cord injury as revealed by fMRI** Exp Neurol. 2008 Jan;209(1):155-60. Epub 2007 Sep Department of Neuroscience, Karolinska Institutet, 17177, Stockholm, Sweden. Toshiki.Endo@ki.se 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.*

8. **Effects of hyperbaric oxygen therapy on long-tract neuronal conduction in the acute phase of spinal cord injury.** J Neurosurg. 1981 Oct;55(4):501-10. 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.*

9. **Hyperbaric oxygen therapy protects against mitochondrial dysfunction and delays onset of motor neuron disease in Wobbler mice** Neuroscience. 2003;120(1):113-20. 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.*

10. **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** Spine. 2007 Aug 15;32(18):1955-62. 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.*

11. **Hyperbaric oxygen in the treatment of patients with cerebral stroke, brain and spinal cord trauma and neurologic disease.** Adv Ther. 2005 Nov-Dec;22(6):659-78.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.

12. **Magnetic resonance imaging of hyperbaric oxygen treated rats with spinal cord injury: preliminary studies.** Magn Reson Imaging. 1991;9(3):423-8. 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.*

13. **Hyperbaric oxygen induces endogenous neural stem cells to proliferate and differentiate in hypoxic-ischemic brain damage in neonatal rats.** Undersea Hyperb Med. 2008 Mar-Apr;35(2):113-29. 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.*

14. **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. 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.

15. **Hyperbaric oxygenation in fluid microembolism.** Neurol Res. 2007 Mar;29(2):156-61. *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.

16. **Successful treatment of cervical spinal epidural abscess by combined hyperbaric oxygenation.** Mt Sinai J Med. 2005 Nov;72(6):381-4. 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.*

17. **Preconditioning with hyperbaric oxygen induces tolerance against oxidative injury via increased expression of heme oxygenase-1 in primary cultured spinal cord neurons.** Life Sci. 2007 Feb 27;80(12):1087-93. Epub 2006 Dec 5. 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.*

18. **The role of multiple hyperbaric oxygenation in expanding therapeutic windows after acute spinal cord injury in rats.** J Neurosurg. 2003 Sep;99(2 Suppl):198-205. 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.*

19. **Human Amniotic Fluid Mesenchymal Stem Cells in Combination with Hyperbaric Oxygen Augment Peripheral Nerve Regeneration** Neurochem Res. 2009 Jan 17. 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.*

20. **Stem cell infusion and Hyperbaric Oxygenation improves Pancreatic function in Diabetes** Source: Cell Transplantation Center of Excellence for Aging and Brain Repair **(Vol. 17 No.12)** A study to determine if patients with type 2 diabetes can benefit from a combination of autologous (patient self-donated) stem cell infusions (ASC) and hyperbaric (above the normal air pressure of) oxygen treatment (HBO) before and after ASC has found "significant benefits" in terms of "improvements in glycemic control" along with "reduced insulin requirements." The combination therapy could decrease type 2 diabetes morbidity and mortality, said the authors. ‘Autologous stem cell therapies are an emerging with promising results and low side effects profiles,’ said Esteban Estrada, MD, of Stem Cell Argentina. ‘In addition, hyperbaric oxygen therapy, used primarily in the treatment of carbon monoxide poisoning, air embolism suffered by divers, and as an enhancement to wound healing, has been shown to increase stem cell mobilization and the release of endothelial progenitor cells via a nitric oxide-dependent mechanism.’ The clinical trial evaluated the ASC-HBO combination treatment in 25 patients with type 2 diabetes. According to the researchers, it is well known that with type 2 diabetes, there is an ongoing inflammation of the pancreas. Their hypothesis suggested that *mobilizing stem cells would cause the growth of blood vessels (angiogenesis) and release factors that would result in the local differentiation of progenitor cells with a resulting anti-inflammatory effect.* Diabetes has been shown to impair progenitor cell mobilization, a problem that local stem cell infusion could remedy. The effect of the *hyperbaric oxygen therapy would be to increase stem cell mobilization* in such a way as ‘to target more than one crucial reparative step’ to counteract the chronic injury that attack the endothelial progenitor cells and the islet cells. ‘Overall, our results show that a close follow-up with intensive diabetic management alone could not be the only cause of the positive, progressive and consistent outcomes we obtained in this trial over one year of follow-up,’ said Dr. Estrada. ‘A decade ago, research had explored stem cell transplantation and hyperbaric oxygen therapy as stand-alone treatments. This Stem cell infusion and Hyperbaric Oxygenation improves Pancreatic function in Diabetes study highlights the potential benefits of using an unusual combination therapy to treat diabetes’ said Dr. Cesar V Borlongan, Professor University of South Florida College of Medicine.

21. **Prophylactic hyperbaric oxygen treatment and rat spinal cord re-irradiation.** Cancer Lett. 2003 Feb 28;191(1):59-65. 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.

22. **Hyperbaric oxygen (HBO) therapy for acute traumatic cervical spinal cord injury.** Spinal Cord. 2000 Sep;38(9):538-40. 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.*

23. **Experimental acute dorsal compression of cat spinal cord: correlation of magnetic resonance signal intensity with spinal cord evoked potentials and morphology.** Spine. 1996 Jan 15;21(2):166-73. 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.

24. **The use of hyperbaric oxygen to modify the effects of recent contusion injury to the spinal cord.** Yeo JD. Cent Nerv Syst Trauma. 1984 Winter;1(2):161-5. 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.*

25. **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.

26. **The neuroprotector effect of a new taurine derivative on a model of compression spinal cord trauma in rats** Eksp Klin Farmakol. 2005 Nov-Dec;68(6):45-8. 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.

27. **Spinal taurine levels are increased 7 and 30 days following methylprednisolone treatment of spinal cord injury in rats** Brain Res. 2001 Mar 2;893(1-2):292-300 Department of Cell Biology, University of Oklahoma Health Sciences Center, Post Office Box 26901, Biomedical Sciences Building Room 553, Oklahoma City, OK 73190, USA. richard-benton@ouhsc.edu *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.

28. **Stem cells and neurological diseases** Cell Prolif. 2008 Feb;41 Suppl 1:94-114 Department of Neurology, Medical College of Georgia, Augusta, GA 30912, USA. dhess@mail.mcg.edu 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. 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. 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.

29. **Human umbilical cord blood-derived CD34+ cells may attenuate spinal cord injury by stimulating vascular endothelial and neurotrophic factors** Shock. 2008 Jan;29(1):49-55 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.*

30. **Stem cell mobilization by hyperbaric oxygen** Am J Physiol Heart Circ Physiol. 2006 Apr;290(4):H1378-86. Institute for Environmental Medicine, University of Pennsylvania, Philadelphia, PA 19104-6068, USA.

sthom@mail.med.upenn.edu 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. The number of colony-forming cells (CFCs) increased from 16 +/- 2 to 26 +/- 3 CFCs/100,000 monocytes plated. Elevations in CFCs were entirely due to the CD34(+) subpopulation, but increased cell growth only occurred in samples obtained immediately posttreatment. A high proportion of progeny cells express receptors for vascular endothelial growth factor-2 and for stromal-derived growth factor. 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.*

31. **Human umbilical cord mesenchymal stem cells and the treatment of spinal cord injury** Chin Med J (Engl). 2009 Jan 20;122(2):225-31 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, as a peculiar source of stem cells, hUCMSCs may play an important role in the treatment of spinal cord injury.

32. **Generation of Functional Neural Artificial Tissue from Human Umbilical Cord Blood Stem Cells** Tissue Eng Part A. 2009 Jan 27. 1 Department of Neurorepair, Medical Research Institute , Polish Academy of Sciences, Warsaw, Poland ., 2 Department of Neuropeptide, Medical Research Institute , Polish Academy of Sciences, 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 , Polish Academy of Sciences, 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).* The main purpose of this study was to generate HUCB-derived neural artificial tissue and investigate their functional properties. Neural organoids formed on human-originated biodegradable scaffolds within 3 weeks and resembled niche structure where immature stem cells (Oct4+ and Sox2+) and proliferating neuroblasts (Nestin+, GFAP+, and Ki67+) were present. Such aggregates were placed on multi-electrode chips and differentiated toward mature neurons (TUJ1+ and MAP2+). These three-dimensional aggregates in contrast to two-dimensional cultures formed functional circuits and generated spontaneous field/action potentials. Our results indicate that three-dimensional environment facilitates maturation of HUCB-derived NSC what should be considered regarding regenerative medicine application.

33. **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.

34. **Dietary restriction started after spinal cord injury improves functional recovery** Exp Neurol. 2008 Sep;213(1):28-35 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.*

35. **Training improves the electrophysiological properties of lumbar neurons and locomotion after thoracic spinal cord injury in rats** Neurosci Res. 2008 Nov;62(3):147-54 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.*

36. **BDNF-exercise interactions in the recovery of symmetrical stepping after a cervical hemisection in rats** Neuroscience. 2008 Sep 9;155(4):1070-8 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.*

37. **Reorganization of sensory processing below the level of spinal cord injury as revealed by fMRI** Exp Neurol. 2008 Jan;209(1):155-60. Epub 2007 Sep 26. Department of Neuroscience, Karolinska Institutet, 17177, Stockholm, Sweden. Toshiki.Endo@ki.se 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.

38. **Can the spinal cord learn and remember?** ScientificWorldJournal. 2008 Aug 1;8:757-61 Neuroscience Unit, Laval University Medical Center (CHUL - CHUQ), Quebec City,Quebec, Canada. Pierre.Guertin@crchul.ulaval.ca 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*.

39. **Cortical sensory map rearrangement after spinal cord injury: fMRI responses** Brain. 2007 Nov;130(Pt 11):2951-61. Epub 2007 Oct 3 Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden. toshiki.endo@ki.se 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.

40. **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** Exp Neurol. 2008 Feb;209(2):407-16. Epub 2007 Jul 6 Department of Psychology, Vanderbilt University, Nashville, TN 37203, USA. jon.h.kaas@vanderbilt.edu *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.

41. **Spinal Abstracts Sept 2008 - Specific locomotor (LOKOMAT) versus unspecific weight training and their effects on gait function and corticospinal conductivity after chronic incomplete spinal cord injury** R. Labruyère, V. Dietz, H.J.A. van Hedel Spinal Cord Injury Center, Balgrist University Hospital, CH-8008 Zurich, Switzerland Bodyweight supported treadmill training improves locomotion in patients with a chronic incomplete spinal cord injury (iSCI). This improvement occurs in parallel to an increase in corticospinal conductivity of lower leg muscles (Thomas and Gorassini 2005). The aim of the present study is to investigate whether a specific locomotor training (Lokomat - automated locomotor training with a driven gait orthosis) is accompanied by larger changes in corticospinal conductivity of the lower limb compared to unspecific training (conventional lower extremity strength training) in such subjects. Methods: 30 ASIA C and D subjects are randomly assigned to one of the training groups. All of them receive 32 training sessions of each 45-minutes within 8 weeks. Directly before and after the intervention and at 6 months after finishing the intervention, corticospinal conductivity will be assessed by the use of transcranial magnetic stimulation. *Corticospinal conductivity improves more after specific compared to unspecific locomotor therapy.*

42. **Plasticity in the injured spinal cord: can we use it to advantage to reestablish effective bladder voiding and continence?** Prog Brain Res. 2006;152:147-62 Department of Pharmacology, Faculty of Medicine, Dalhousie University, 5850 College St., Halifax, NS B3H 1X5, Canada. nzinck@dal.ca 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.*

43. **Transplants and neurotrophic factors increase regeneration and recovery of function after spinal cord injury** Prog Brain Res. 2002 Department of Neuroscience, Georgetown University Medical Center, Washington, DC 20007, USA. bregmanb@georgetown.edu 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.

44. **Comprehensive evaluation of spinal cord function accompanying Lokomat rehabilitation in patients with incomplete spinal cord injury** Galen **S**, Catton C, Hunt KJ1, Allan DB2, Conway BA Bioengineering Unit, University of Strathclyde, Glasgow, G4 0NW, UK 1Centre for Rehabilitation Engineering, University of Glasgow, Glasgow, G12 8QQ, UK 2Queen Elizabeth National Spinal Injuries Unit, Southern General Hospital, Glasgow, G51 4TF, UK. In this study, patients are recruited to a gait rehabilitation programme based on the use of a computer controlled robot (Lokomat) and any subsequent changes in status during the rehabilitation programme are charted through the application of a comprehensive battery of functional and physiological assessments. The goal of this testing procedure is to identify tests of sensory and motor function that are sensitive to the changes that occur in response to rehabilitation/ natural recovery in incomplete spinal cord injured patients. **Lokomat Training & Assessment** The Lokomat rehabilitation programme we have adopted requires patients to attend for 1 hour of daily (Monday – Friday) Lokomat walking over a 6 week period. In addition, sensory and motor function is assessed longitudinally prior to the onset of Lokomat training, at the mid-point of training and following the cessation of training. For all recruits the level of body weight support and the treadmill speed is adjusted over the 6 week training period in relation to the rate of change in an individual's walking capability. Assessment protocols include a battery of standard clinical measures such as the Standard Neurological Classification of Spinal Cord Injury (ASIA), a range of functional tests of walking capability and a variety of quantitative measures of sensory and motor function. **Patient Recruitment & Compliance** At the time of writing 14 patients have completed the study, and a further 2 are currently undertaking Lokomat training. Compliance to the training regime (30 sessions) for the 14 subjects who have completed the study was high and averaged 94% with the majority of subjects missing fewer than 3 sessions over the 6 week training period. The reasons for missing a session were all unrelated to the use of the Lokomat. Subjects recruited to the study were allocated to an acute (<6 months post injury) or chronic (>6 months post injury) group and were ASIA C or D. Within the acute group 4 subjects were non-ambulatory prior to Lokomat training while all chronic patients showed some level of locomotor capability. **Training Outcomes** Preliminary group analysis of overground walking judged from gait analysis parameters together with WSCII demonstrate that both acute and chronic subjects show significant improvements in overground walking capability over the period of Lokomat training. Importantly, the degree of improvement appears greater within the acute group. Furthermore, the rate of gait improvements in the acute group is greatest within the first 3 weeks of training with patients who show the fastest improvements being those who can sustain the fastest daily reductions in percentage body weight support. These observations in themselves have implications for the design and usage of rehabilitation programmes based on devices like the Lokomat but also serve to improving gait performance in incomplete spinal cord injured patients and an appropriate platform to base investigations on adaptive changes in spinal cord function. **Sensory and Motor Assessments** Alterations have been observed in ASIA sensory and motor scores and in quantitative sensory testing of touch, vibration and electrical perceptual threshold in spinal segments above and below lesion sites. Of particular interest with respect to sensitivity in detecting changing function are the results of Somatosensory Evoked Potentials, Vibration thresholds and Motor Evoked Potentials testing in erector spinae muscles.

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