# HBOT2016 New Orleans
# 10th Annual International Symposium for Hyperbaric Medicine

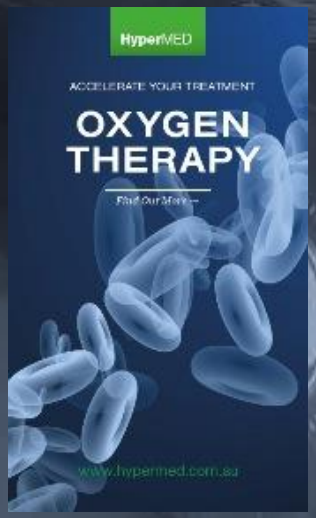
## Deploying Hyperbaric Oxygen Therapy and *Adjunctive Therapies* into the Health Care System

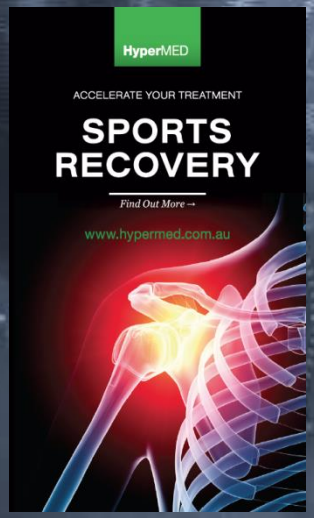
Malcolm R. Hooper
Clinical Director
HyperMED | OXYMED Australia ©

# Hyperbaric Oxygen Therapy for Disc Prolapse, Degenerative Joint Disease, Chronic Pain, Failed Surgical Syndrome

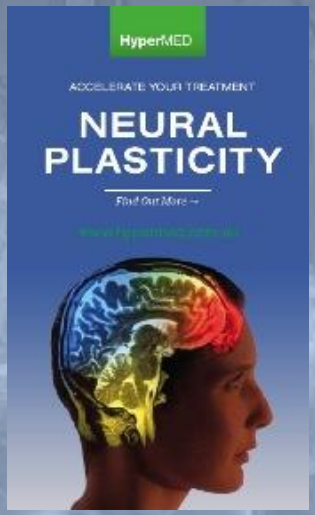
# Hyperbaric Oxygen Therapy combined with Robotic Gait Assisted Walking for Spinal Cord Injury

Malcolm R. Hooper Clinical Director - HyperMED | OXYMED Australia | OXYGEN100 – Heal The Warriors





## Clinical Director & Researcher

### HyperMED | OXYMED Australia | OXYGEN100 - Heal The Warriors | Clinical Director & Researcher

2007 – Present (9 years) | 643 Chapel Street South Yarra 3141

www.hypermed.com.au

HyperMED (Hooper) pioneered 'off-label' applications of Hyperbaric Oxygenation (HBO) in Australia in 1996. HyperMED installed the Australian first LOKOMAT (Adult and Pediatric Robotic Gait Assistance) in 2006. The combination effects of HBO & Lokomat being a 'world first'.

The 'off-label' use of HBO and the use of LOKOMAT are viewed as 'novel and unique - not supported by the greater percentage of medical doctors in Australia' (AHPRA 2013).

Across Australia there are approximately 18-HBO chambers. In China there are in excess of 5000 HBO chambers. In USA, in excess of 1200 HBO facilities provide 'off-label' applications for chronic neurologic and other complex illness disorders.

There are in excess of 500-LOKOMATS worldwide and a growing market for personal exoskeletons assisting patient mobility and functionality. In Australia there are only 2-LOKOMATS.

HyperMED pioneering efforts contributed to LOKOMAT funding in South Australia (2013). The Women and Children's Hospital (SA) is fund raising $4M to establish Australia's leading robotic (LOKOMAT) rehabilitation research clinic. The Royal Melbourne Hospital (2014) is also fund raising for a LOKOMAT.

HBO (1.5-2.4 ATA using 100% O2) is safe and effective. HBO accelerates immune responses. HBO is non-invasive. HBO increases Oxygen tension into Hypoxic tissue inhibiting opportunistic infections and cellular mutations.

HBO Up~Regulates the patient own circulating Stem Cells {8-fold (800%) increase CD34+}; enhances Mitochondrial function; proliferates anti-inflammatory Cytokines (IL4, 10, 13, INFg, etc); proliferates VEGF, BDNF & GDNF; HBO reduces Telomeres degeneration ...

HBO Down~Regulates toxic intra and extra cellular inflammatory Cytokines (IL1, 2, 6, 7, 8), Tumour Necrosis Factor Alpha (TNFα), chronic opportunistic Anaerobic (MRSA, VRE) and co-infections (Viral, Bacterial, Parasitic), Cell Sepsis ...

HBO combined with TNF blockers promotes immune modulation.


MELBOURNE

SPORTS

# Tennis Players Get an Oxygen Fix

## To aid recovery, tennis pros in Melbourne rent hyperbaric chambers

BY TOM PERROTTA

*Melbourne, Australia*

**AFTER HE WON** a four-hour, 32-minute match at the Australian Open on Sunday, Novak Djokovic, the world's best tennis player, showered, spoke to the media, and then hustled over to a quiet late-night spot that's popular among several players: A small clinic two miles from the tournament that has four hyperbaric oxygen pods for rent.

The machines look like deep-sea diving submarines with glass windows and hatches in the back. Inside, players slip on a plastic breathing mask attached to a long tube. Once the hatch seals they're off, compressor and regulator whirring and pressure building until they're basically 40-feet under water and breathing 100% oxygen through the mask (outside air contains just 21% oxygen).

Players have their own masks and tubes and don't share them (that's bad hygiene). They wear blue hospital booties over their socks and must leave behind their phones, watches or anything with a battery that could spark a fire. Outside each pod's front window is a television equipped with Netflix. American Bethanie Mattek-Sands binged on episodes of "Making a Murderer" before leaving Melbourne on Thursday after losing in mixed doubles. Djokovic spent an hour in the pod after his five-setter against Gilles Simon on Sunday, from around 10 p.m. to 11 p.m. He'll use it before matches too, as he did for an hour Tuesday afternoon before playing Kei Nishikori later that evening. Djokovic watched M. Night Shyamalan's "The Last Airbender."

"I either like comedy or, somebody calls it science fiction," he said. "I call it the world we still didn't explore."

The pods are located at HyperMED, a ground-floor clinic nestled between a hair salon and a bakery about a 10-minute drive from the Open. A few hotels popular among players are nearby. Djokovic, known as the most meticulous player on the tour, has used the pods here for several years with the hope of aiding recovery and preventing injury. Mattek-Sands started last year. This year, doubles star Mike Bryan became a pod regular. His twin brother, Bob, tried it too, though just once.

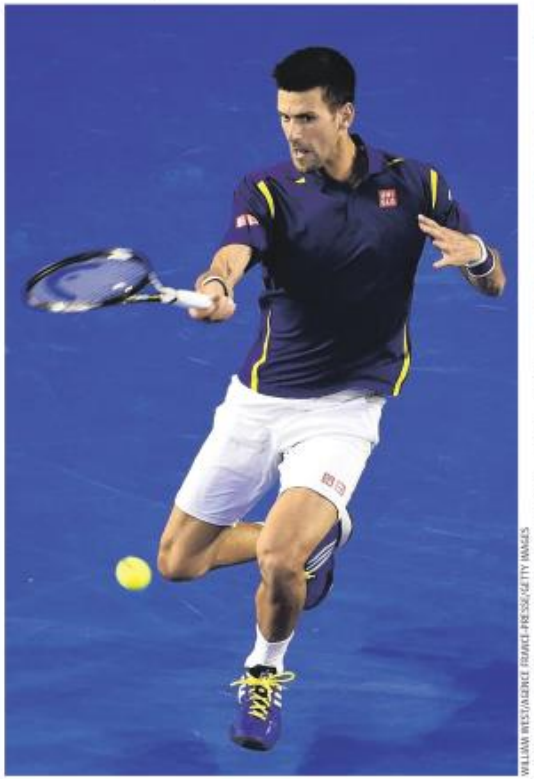
"It's great," Djokovic said. "It should get out there more, not just for athletes."

Mike Bryan said: "It just helps recovery. I felt a little better doing it."

Bryan also likes the VacuSport, a long tube with a skirt that seals a player's legs in a vacuum and flushes lactic acid. There is also a cryotherapy chamber, which cools to minus 150 degrees Fahrenheit for a few minutes. HyperMED's website has a picture of Milos Raonic, the Canadian star, standing in its chamber.

Oxygen sessions last anywhere from an hour to two hours and cost 150 Australian dollars (US$105). Mattek-Sands said the benefits are subtle but valuable. "It's not like you walk out of there feeling like Superman or anything," she said. "You sleep pretty good that night, I'll say that. You crash and you dream pretty heavy."

The facility is run by Malcolm Hooper, a former chiropractor, who sat in Djokovic's box in Rod Laver Arena Thursday evening as the world No. 1 beat Roger Federer and earned a spot in Sunday's Australian Open final, the sixth of his career. Hooper's clients include people with cerebral palsy, traumatic brain injuries and disabilities, as well as other athletes. During the Open, he opens his clinic day and night depending on players' needs. "Two, three in the morning, whatever the requirements are," he said.



WILLIAM WEST/AGENCE FRANCE-PRESSE/GETTY IMAGES

TOM PERROTTA FOR THE WALL STREET JOURNAL

Left, Novak Djokovic uses hyperbaric oxygen therapy to help with recovery. Above, a pod at the HyperMED clinic in Melbourne, Australia.

Top athletes around the world, including football, basketball and soccer stars, use hyperbaric oxygen therapy. Djokovic said he only uses hyperbaric pods in the U.S. and Australia, because access and regulations are challenging in Europe. He said there is still a stigma about oxygen therapy, that it gives athletes who use it an unfair advantage.

"It's very sensitive, especially in the European part of the world," he said. "I wish I can have this all over the place, I wish."

Mattek-Sands said she would be thrilled if the sport's major tournaments provided pods on site. "It's just kind of the new wave for the future," she said.

Hyperbaric therapy doesn't suit everyone. Andy Murray has tried it and decided it isn't for him, according to a representative. Some question its merits. A paper published last year in PeerJ, a peer-reviewed journal, found lower lung cancer incidence among people living at high elevations, which suggests oxygen could be a driver of cancer. Kamen Simeonov, an MD-PhD trainee at the University of Pennsylvania and co-author of the paper, wrote via email, "Basically, it's exposing yourself to risks with no logical reward."

Hooper, who is an affiliate member of the International Hyperbaric Medical Association, said he has seen gains in his patients, and that research suggests hyperbaric treatment can help many ailments. "Every athlete has a growing list of injuries that may benefit," he wrote in an email.

Hooper's chiropractic license was suspended for two years in 2013 after a dispute with a former cerebral palsy patient in part over the effectiveness of treatment, though the Chiropractic Board of Australia viewed Hooper's "conduct as an error of judgment rather than a defect in character," and that he was a "true believer in the treatment that was being given." (He said he hasn't practiced as a chiropractor for 20 years and no longer has a need for the license.)

Hooper also was treating Aussie Rules football players in 2013 when they separately came under investigation for the possible use of banned substances. A Court of Arbitration for Sport panel that imposed a two-year ban on 34 players earlier this month made no mention of Hooper in its findings and didn't assign him any fault. Hooper says he tells all his clients about his history. Justin Sands, the husband of Mattek-Sands, said Hooper has been open since they first met.

"He's been nothing but an upstanding, good guy," Sands said.

Sands, who played college football in the U.S., said he used hyperbaric therapy in his playing days. He says he's surprised so few tennis players use it, given the grueling demands of the game. It might even be useful, he said, for the tour's traveling husbands and wives, though for other reasons. "It's great for a hangover," he said.


BARRICADE
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MELBOURNE



REBEL



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**In USA**

- 'Nearly **80 percent of Americans** will experience low back pain at some point in their lives, and about **30 million people a year receive professional medical care for a spine problem**.
- Experts estimate that nearly **600,000 Americans opt for back operations** each year.'
- **In 2007,** the USA '**Agency for Healthcare Research and Quality**' reported **27 million adults** reported back problems with **$30.3 billion** spent on treatments to ease the pain.'
- The median salary for an **Orthopedic Surgeon $736,710.**
- '**Dr. Charles Burton, medical director for The Center for Restorative Spine Surgery** in St. Paul, Minn. "Concern is that spine surgery has gotten way beyond what is reasonable or necessary. There are **some areas of the country where the rate of spine surgery is three or four times the national average**."
- 'Burton and others recommend that patients **get a second opinion** when back surgery is recommended for the treatment of back pain without neurological symptoms, such as sciatica, especially if other treatments haven't been suggested first.'
- "We are very **successful at improving leg symptoms**," says **Dr. William Welch, vice chairman of the department of neurosurgery at the University of Pennsylvania Medical Center and chief of neurosurgery at Pennsylvania Hospital**. **"We are less successful at treating back pain."**

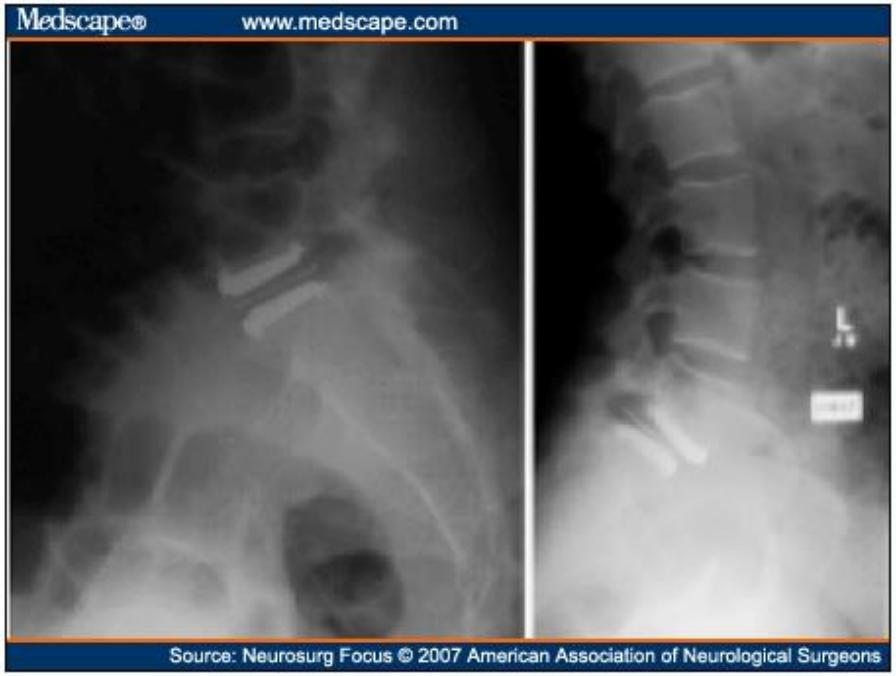
**In Australia:**

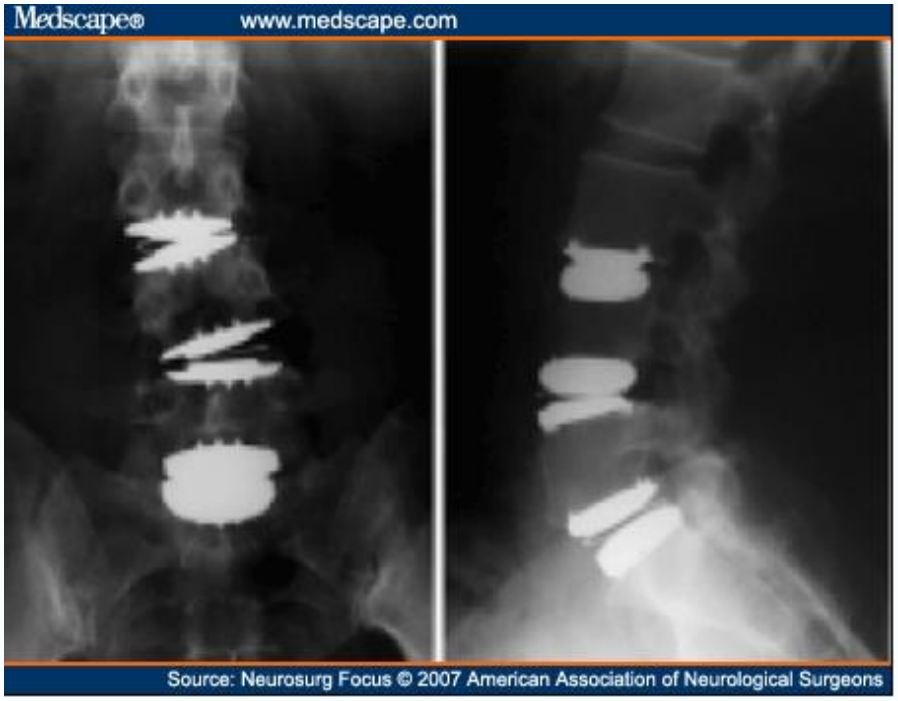
- In excess of **100,000 people are admitted for back surgery** (2015) as reported at http://www.safetyandquality.gov.au/wp-content/uploads/2015/11/SAQ201_04_Chapter3_v6_FILM_tagged_merged_3-3.pdf reports

- **'Spinal fusion surgeries for chronic low back pain are on the rise,** despite the **lack of research to back their efficacy;** experts are now calling for **tighter guidelines, including a waiting period**'. (Med Journal Aust April 2016).
- '**Dr Richard Williams, orthopaedic surgeon and spokesperson for the Royal Australasian College of Surgeons**, told *MJA InSight* that a key regulation should be that patients must **wait a period of 12 months before a spinal fusion surgery was performed**. During this time, the patient must undergo aggressive rehabilitation to try to **lose weight** and reduce their back pain.' [News Flash …. **Dr Gary Fettke Aug 2016]**
- **1995 Cochrane** review found there were **no published randomised controlled trials** which established **effectiveness of fusions** for chronic pain.'
- **2005 Cochrane** review was critical of the outcomes measured, 'limited evidence on the **long-term effects of either surgical decompression or fusion** remained a matter of concern, given the numbers and the costs of the surgical procedures being performed.'
- **'Professor Jeffrey Rosenfeld, senior neurosurgeon Alfred Hospital and director of the Monash Institute of Medical Engineering**, told *MJA InSight* that there were two main reasons for the increasing rates of spinal fusion surgeries in Australia.' The first was that patient expectations of surgery can often be high, meaning they **"lap up" the positive side of the story and don't hear the negative side'.**
- 'Rosenfeld said that for patients who do not have clear indicators for spinal fusion surgery, a **multidisciplinary approach** is preferable, which involves input from specialists, physiotherapists, chiropractors, clinicians, psychologists and other allied health professionals.' "We need to develop more structured, multidisciplinary pain management and raise the profile and reach of these services. **This will often give people better long-term pain outcomes than having multiple spinal surgeries."**

**Failed Back Surgery**

- We all know someone who has had a back operation and certainly someone who has a bad back. Invariably most back suffers continue to suffer residual problems after a back operation; and are often worse after the initial procedure.
- Patients often describe a **'honeymoon'** period after their back operation. Several months or even several years can pass with everything 'rosy' until something **'triggers'** the pain again.
- Additional MRIs invariably reveal **continuing degenerative instability** with many individuals undertaking more complex surgery.
- Surgery does not address the continuing cycle of degeneration which is often accelerated after surgery. Furthermore, various **'surgical procedures can accelerate disc degeneration'**. Department of Orthopaedic Surgery, Tokai University School of Medicine, Bohseidai, Isehara, 259-1193, Japan. [J Orthop Sci. 2005;10(1):112-8].
- Failed Back Syndrome is an increasing complication of surgery of the lumbar spine. Patients are classified as **'spinal cripples'** and are consigned to a life of long-term narcotic treatment with little chance of recovery'. Onesti ST (Neurologist. 2004 Sep;10(5):259-64)
- The issue of chronic pain associated with failed spinal surgery was reported as far back as in **1994.** Spine featured an article: **Outcome of lumbar fusion in Washington State workers' compensation** (Franklin 1994). **Washington State workers' compensation** system who received lumbar fusion between August 1, 1986 and July 31, 1987 to determine work disability status, reoperation rate, and patient satisfaction.
- Most patients reported that **back pain (67.7%) was worse and overall quality of life (55.8%) was no better or worse than before surgery.**
- **Conclusion: Outcome of lumbar fusion performed on injured workers was worse than reported in published case series.**



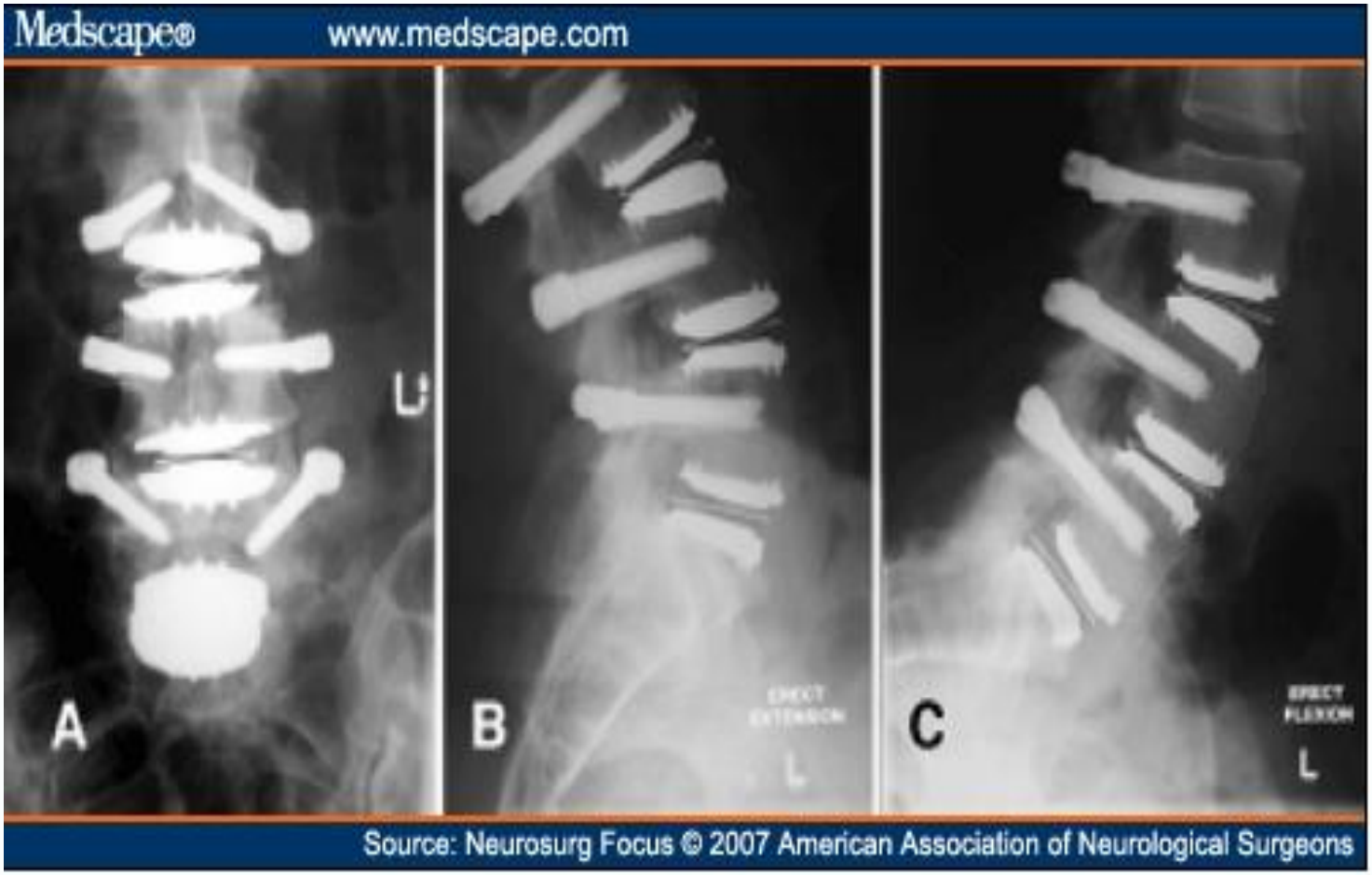

**Posterior Dynamic Stabilization Devices in the Coming Age of Lumbar Disc Replacement**
Matthew Scott-Young, M.B.B.S., F.R.A.C.S., F.A.Orth.A. Neurosurg Focus. 2007;22(1) © 2007 American Association of Neurological Surgeons.

The author has a **'declared interest'** Disclosure: **Dr. Scott-Young is a shareholder in Implant Inc., which owns the TOPS device.**

This series of X-Rays are of the same patient with a single level L5/S1 intervention ultimately requiring multi-level stabilisation.

Fig1 Top Left: Lateral view of L5/S1 obtained immediately postoperatively, displaying optimum positioning and placement of the prosthesis. Fig 1 Right: **Routine postoperative evaluation at 12 months** - patient is asymptomatic (no pain or disability) however demonstrating instability of L5/S1 with anteriorlisthesis slippage subluxation and disc narrowing.

Fig 2: Continuing L5/S1 instability - patient receives multi level disc prosthesis.



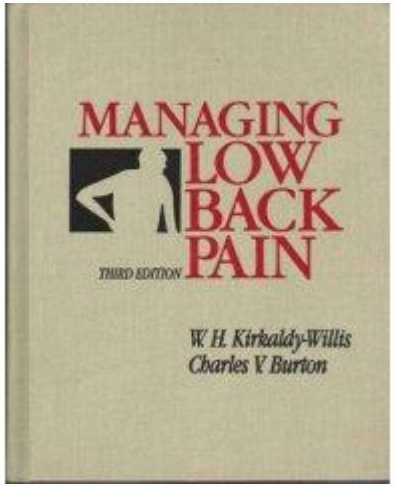

Patient receives Dynamic Stabilization A: Coronal plane. B: Sagittal view of lumbar spine in extension with Dynesys system and C: Lumbar spine in flexion with Dynesys system.

**Comment**

- Back surgery may be inevitable but should be as the absolute LAST RESORT.
- **Surgery does not address the continuing cycle of degeneration which is often accelerated after surgery.** [J Orthop Sci. 2005;10(1):112-8.]

**Managing Low Back Pain** (**1986; 3rd Edition 1999**); William H. Kirkaldy-Willis, MA, MD, LLD (Hon), FRCS (E and C), FACS, FICC (Hon), Emeritus Professor and Head, Department of Orthopaedic Surgery, University of Saskatchewan College of Medicine; Canada.

- KW details the **ischemic model of back pain describing the 'degenerative cascade'** associated with degenerative disc disease.
- 'Structures within the spine have a very poor and often inadequate blood supply. There is minimal blood supply to the disc, and blood is what brings healing nutrients and Oxygen to damaged structures in the body. This means that the spinal disc lacks any significant reparative powers. Unlike muscles, which have good blood supply, once a spinal disc is injured it cannot repair itself.'



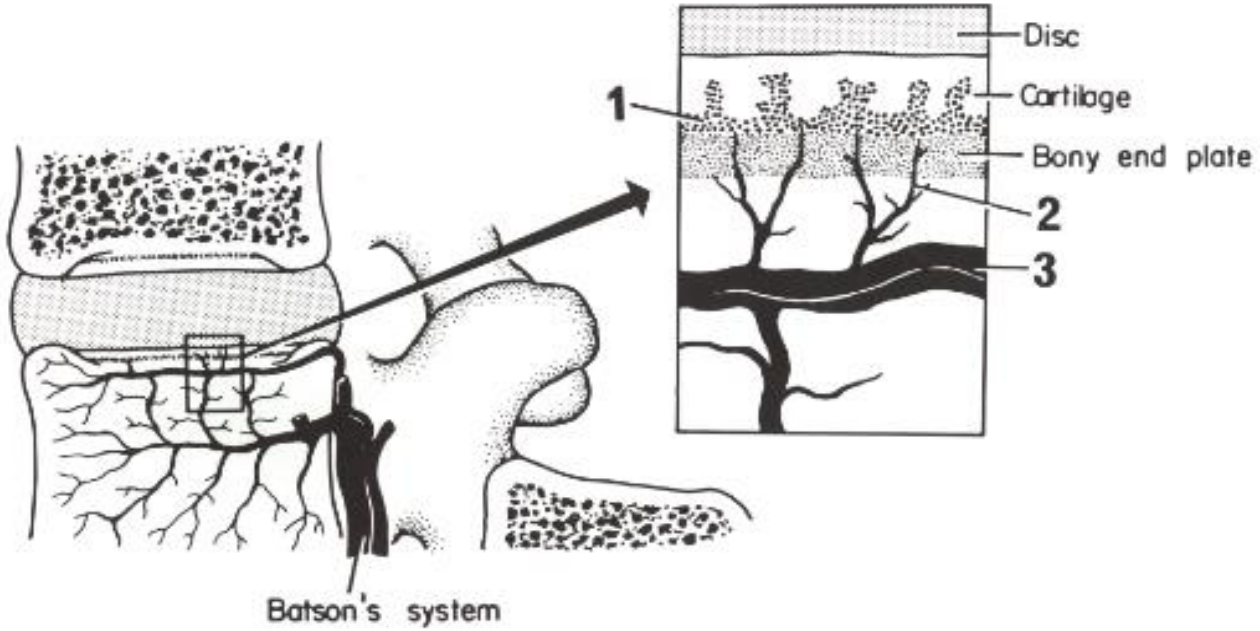




**Fig. 2-14** Vascular arrangement at the vertebral endplate according to Crock and Yoshizawa.[10,11] 1. capillary bed in direct contact with the endplate cartilage; 2. postcapillary venous network; 3. subarticular horizontal collecting system. [From Dupuis and Kirkaldy-Willis,[22] with permission.]

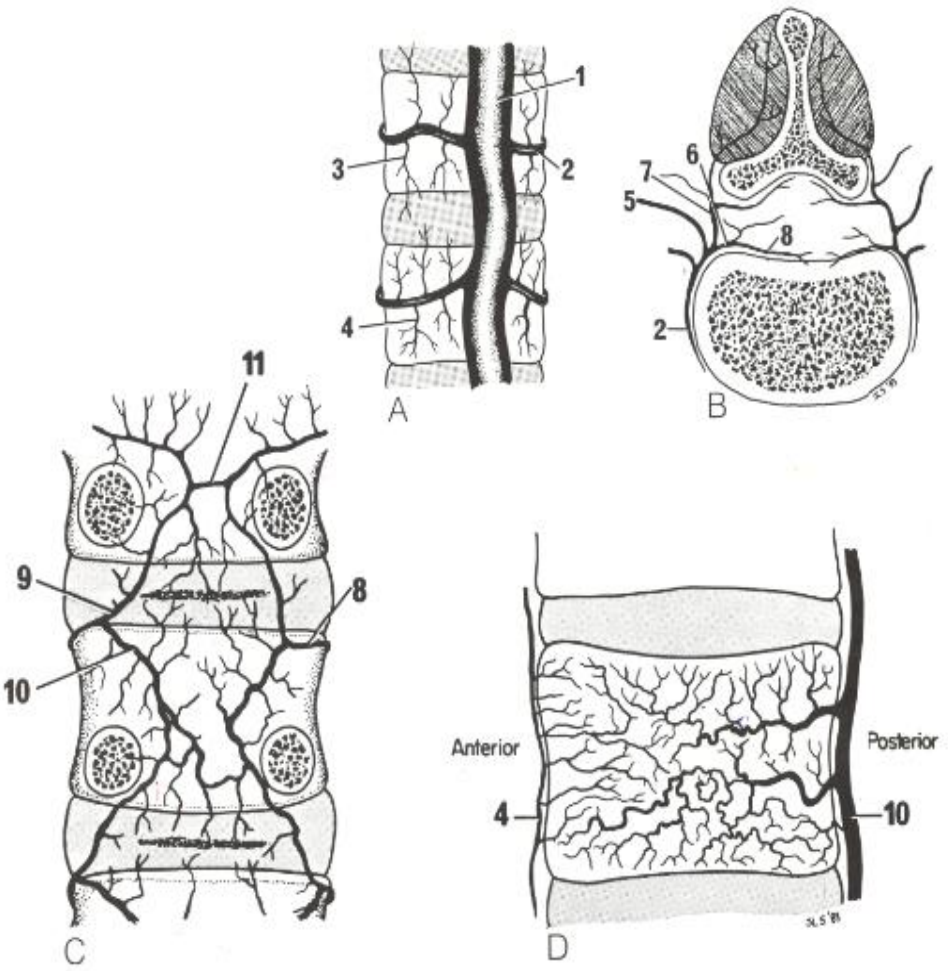
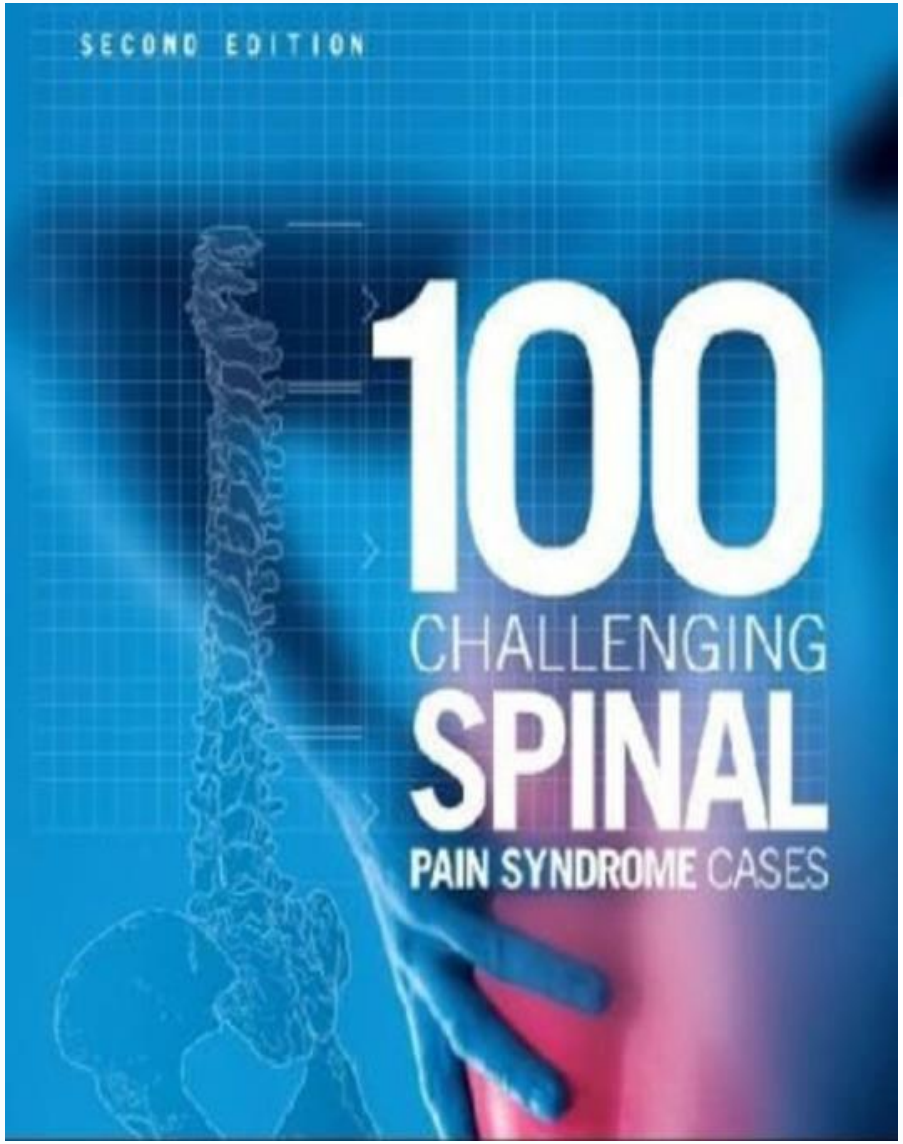




**Fig. 2-13** Vascular supply to the spine. Spine viewed **(A)** from the front and **(B)** from above (axial cut): 1. aorta; 2. segmental artery; 3. long ascending and descending branches; 4. short ascending and descending branches; 5. anterior branch of segmental artery; 6. spinal branch of segmental artery; 7. posterior branch of segmental artery; 8. anterior division of spinal branch. Spine viewed **(C)** from the back with posterior elements removed and **(D)** from the side (midbody sagittal cut): 9. ascending limb of anterior spinal branch; 10. descending limb of anterior spinal branch; 11. transverse anastomosis between left and right systems. (From Dupuis and Kirkaldy-Willis,[22] with permission.)

**Historical**

- **Bassett and Hermann (1961)** HBOT adjunctive therapy for the management of fractures. Multi-potential precursors of fibroblastic origin from bone exposed to increased Oxygen tensions and compressive forces.
- **Bentley and Schlapp** 'Experiments on the blood supply of nerves' Journal Physiology, (London) **1943**; 102:62-71, 'HBOT proven benefits in reversing the effects of ischemia'.
- **Boyd** **'Textbook of Pathology'** (8th Ed. **1987** pg. 69), **'irritation of nerve roots with attending muscle spasm along the segmental distribution of the nerve root can create ischemic changes' can leading to chronic pain and physical impairment.**
- **Davidkin** (**1977**) HBOT management of 134 orthopedic injury cases - reported 72.2% improvement over conservative measures. HBOT combats hypoxia, local and generalized.
- **Dekleva (1981)** HBOT important auxiliary therapeutic measure in traumatology.
- **Eltorai** 'HBOT in the management of pressure sores in patients with injuries to the spinal cord' Journal Dermatological Surgical Oncology (7:9 Sept **1981**; 737-739).
- **Hood** 'Diseases of the central nervous system' BMJ **1975**; 3:398-400, 'ischemia has a depressant effect on nerve conduction, especially in the more sensitive afferent fibers'.
- **Jackson 'The Cervical Syndrome'** (4th Ed. **1999** pg. 148**), 'major cause of musculoskeletal pain originates from ischemia, and compares the pain experienced in angina'.**
- **Jain/Teller (1995)** Approx 20% of the body's consumption of Oxygen occurs within 3-5% of the body mass – the brain and spinal cord structures. These structures are extremely sensitive to Oxygen deficiency - dramatic results are produced from either deficiency or the benefits of HBO.

- **Kirkaldy-Willis (1986)** Ischemic model of Degeneration.
- **Lewis** 'Pain in muscular ischemia', Archives Internal Medicine **1932**; 49(5): 713-27, 'many conditions of the central nervous system stem from vascular ischemia'.
- **Magladery** et al 'Electrophysiological studies of nerve and reflex activity in normal man' Bulletin John Hopkins Hospital **1950**; 86:291-312, 'ischemic changes in nerve root microcirculation often leads to intraneural edema'.
- **Nylander (1985)** Circulatory Shock, 40:9-13. 'reduction of edema and facilitative aerobic metabolism in ischemic muscle structure as a result of HBOT'.
- **Nylander (1988)** 'HBOT dramatically reduced the phosphorylase activity, a sensitive marker for muscle cell damage'.
- **Rydevik** 'Pathophysiology of nerve root compression' Spine **1984**; 9 (1): 7-15, 'recovery of nerve and other tissue depends on eliminating ischemia in the affected tissue'.
- **Sirsjo (1989)** 'HBOT enhances the recovery of blood flow and functional capillary density in pressure induced post-ischemic muscle tissue'.
- **Strauss (1983)** 'HBOT reduces muscle damage significantly in experimentally produced compartment syndromes. **Strauss (1987) '**resolution of neuropathies, arrest of tissue necrosis and absence of secondary infections using HBOT'.
- **Tsybulyak (1973)** 'hypoxic states in cases of trauma as an indication for HBOT.
- **Yeo** - 'Medical Journal of Australia' July 30, **1977** pg.145-147. Hyperbaric Oxygenation on the experimental spinal cord injury'
- **Zhao (1991)** HBOT adjunct to peripheral nerve repair. 89.2% of 54 patients, with 65 nerve injuries repaired using HBOT supplementary treatment. HBOT also documented as improving ischemic limb pain.

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# SOME ILLUSTRATIONS SHOWING EXAMPLES OF POSSIBLE CAUSES OF NON-SPECIFIC SPINAL PAIN SYNDROMES OF MECHANICAL ORIGIN

## Lumbar spine

### *Intervertebral disc broad-based posterior protrusion (Fig. vii.1A and B)*

Clinical relevance

This may cause low back pain and radicular symptoms due to:

1. Pressure upon the pain sensitive anterior surface of the dural tube (Summers et al 2005).
2. Pressure upon the recurrent meningeal nerve between the protrusion and the dural tube.
3. Pressure upon blood vessels causing ischaemia (Giles 1973, Sunderland 1975) and vascular damage (Hoyland et al 1989, Jayson 1997) between the protrusion and the dural tube.
4. Pressure upon a nerve root (Mixter & Barr 1934, Crock 1976, Summers et al 2005).

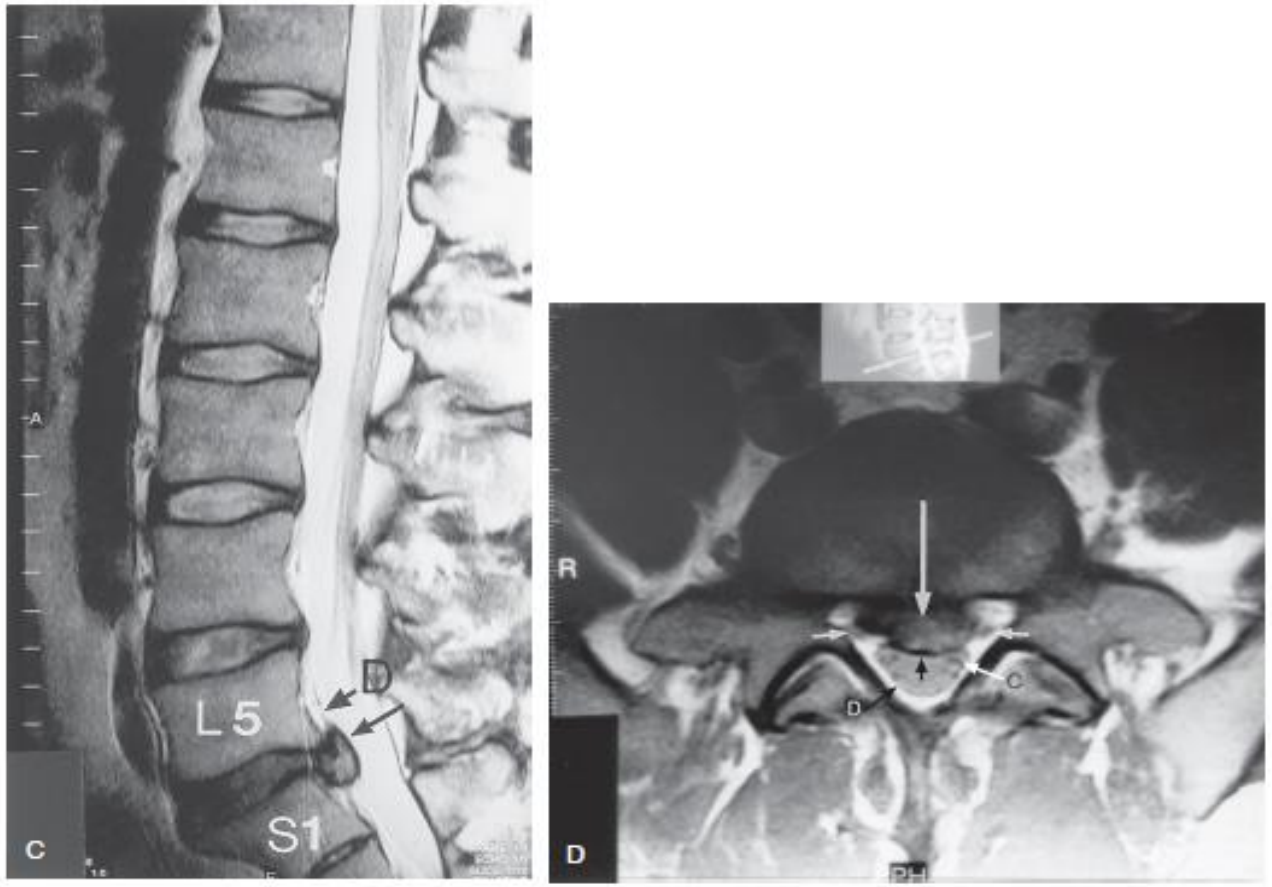



**Figure 2.2 Cont'd** (C) Lumbosacral spine MRI sagittal T2-weighted image showing the S1 = first sacral segment. The posterior disc protrusion at the L5–S1 level is shown by the black arrow; it can be seen compressing the anterior part of the dural tube (D). Note that the disc is becoming 'black' between L5 and S1 which indicates that it is undergoing dehydration (desiccation) as a result of injury. The L4–5 disc shows some early desiccation with essentially normal disc hydration at the levels above. (D) Lumbosacral MRI axial T2-weighted image at the L5–S1 level. The long arrow shows the degree of disc protrusion and the effect that it is having on the pain sensitive anterior surface of the dural tube (D) (small black arrow) and, to some extent, on the S1 nerve roots (small white arrows). C = cauda equina nerve roots; R = right side of patient.

**KEY POINT**

Retrolisthesis at L5–S1 is indicative of L5–S1 intervertebral disc prolapse (Giles et al 2006).

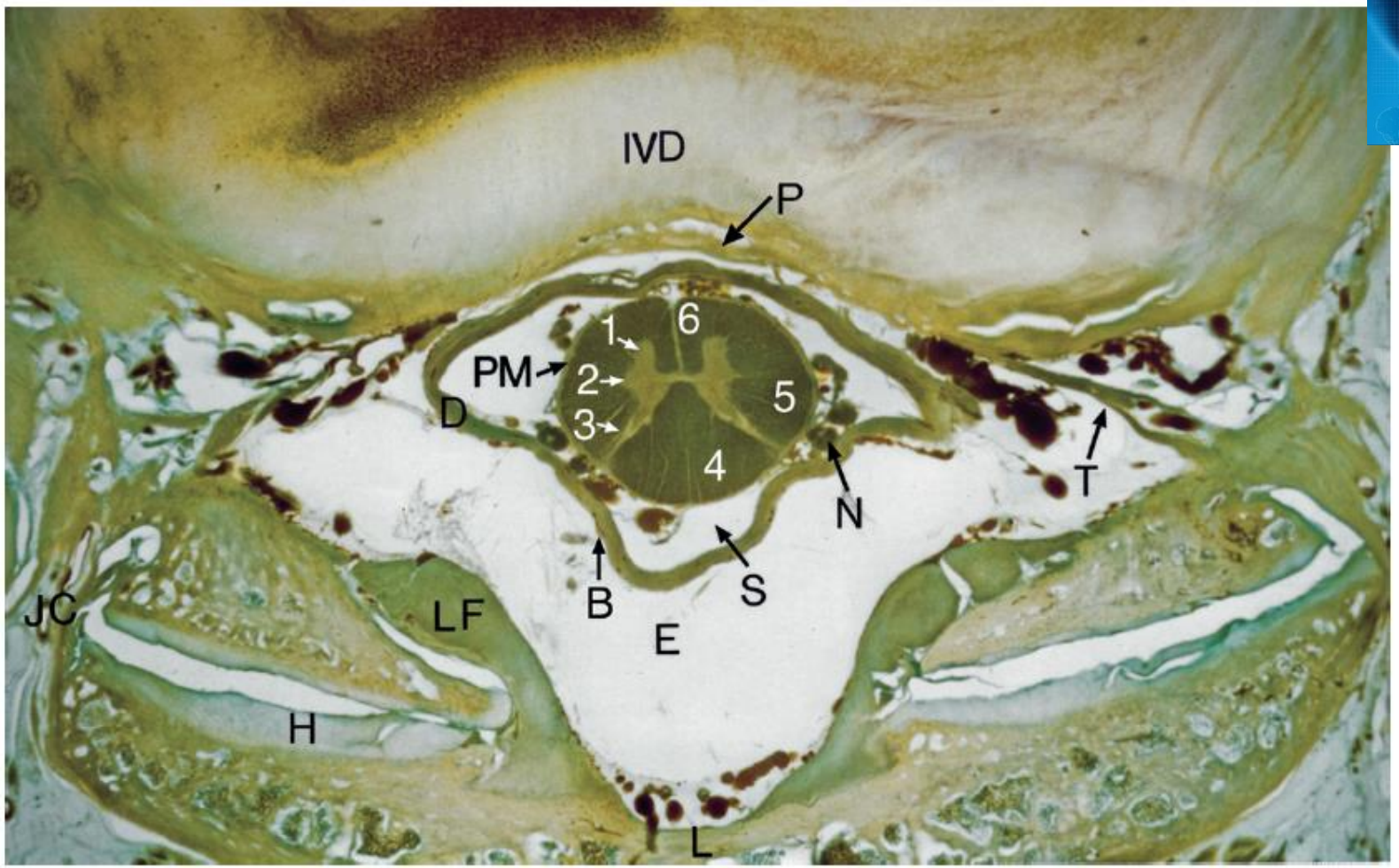



**Figure 94.3** A 200-micron thick horizontal (axial) histological section through the thoracic spine of a 40-year-old male cadaver representing the approximate area in the rectangle in Fig. 94.2 A. This shows the anatomy of the spinal canal and related structures at this level but without osteophytes. B = blood vessels within the dural membrane; D = dural tube; E = extradural (epidural) space; H = hyaline articular cartilage on the inferior articular process facet of the vertebra above; IVD = intervertebral disc; JC = zygapophysial (facet) joint capsule; L = lamina junction; LF = ligamentum flavum; N = dorsal (posterior) nerve root; P = posterior longitudinal ligament; PM = pia mater; S = subarachnoid space; T = transforaminal ligament crossing the intervertebral foramen; 1 = anterior grey column; 2 = lateral grey column; 3 = posterior grey column; 4 = posterior funiculus; 5 = lateral funiculus; 6 = anterior funiculus. (Ehrlich's haematoxylin and light green counterstain.)

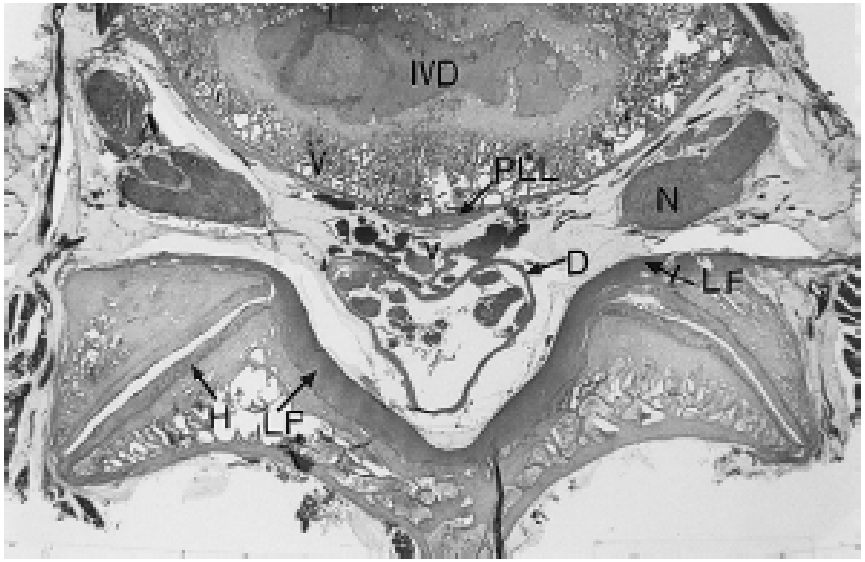
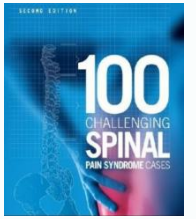



**Figure 21.3** A 200-micron thick horizontal histopathological section through the lower lumbar spine of a 46-year-old male that serves to illustrate the principle involved in the above case. Note the intervertebral disc material (IVD), the posterior of the vertebral body (V) and the nerve root ganglion (N) within the intervertebral foramen. The space between the neural structures (N) and the posterior part of the vertebral body and disc and, for that matter, the anteromedial portion of the ligamentum flavum (LF tailed arrow) can be seen. Therefore, with contrast medium in the nerve root sleeve (sheath) it should be possible to see a space between the neural structures and the adjacent structures, due to contrast material being introduced, if the structures under investigation are adjacent to each other and not apart from each other. The dural tube (D) is shown containing some of the cauda equina nerve roots. Small blood vessels (v) are seen between the posterior longitudinal ligament (PLL) and the dural tube. The hyaline articular cartilage (H) on the articular facet surfaces can be seen. (Ehrlich's haematoxylin and light green counterstain).




### *Blood vessels associated with intervertebral disc posterior protrusion or bulge (Figs. vii.13 and 14)*

Clinical relevance

Pressure upon blood vessels due to intervertebral disc posterior protrusion or disc bulge may cause pain due to venous stasis and ischaemia (Giles 1973, Sunderland 1975, Hoyland et al 1989, Jayson 1997).

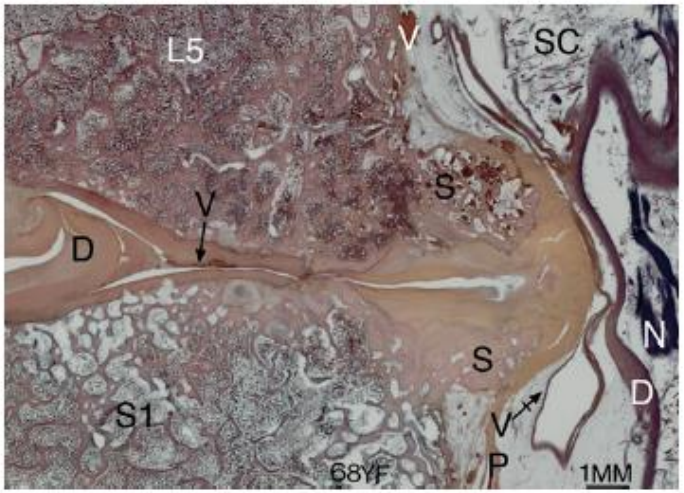



**Figure vii.13** A 200-micron thick sagittal histopathology section from a 68-year old female cadaver showing a lumbosacral posterior midline intervertebral disc protrusion with large bilateral osteophytic spurs (S) projecting into the spinal canal (SC) and causing stenosis of the canal and traction and occlusion of the adjacent vascular structures (V tailed arrow). D = intervertebral disc; L5 = fifth lumbar vertebral body; N = neural structure within the dural tube; P = posterior longitudinal ligament; S1 = first sacral body; V (arrow) = small blood vessels within the degenerative intervertebral disc. (Ehrlich's haematoxylin and light green counterstain). (From Taylor J R, Giles L G F 1997 Lumbar intervertebral discs. In: Giles L G F and Singer K P (eds) Clinical anatomy and management of low back pain, Edinburgh, Butterworth-Heinemann, p 49-71.)

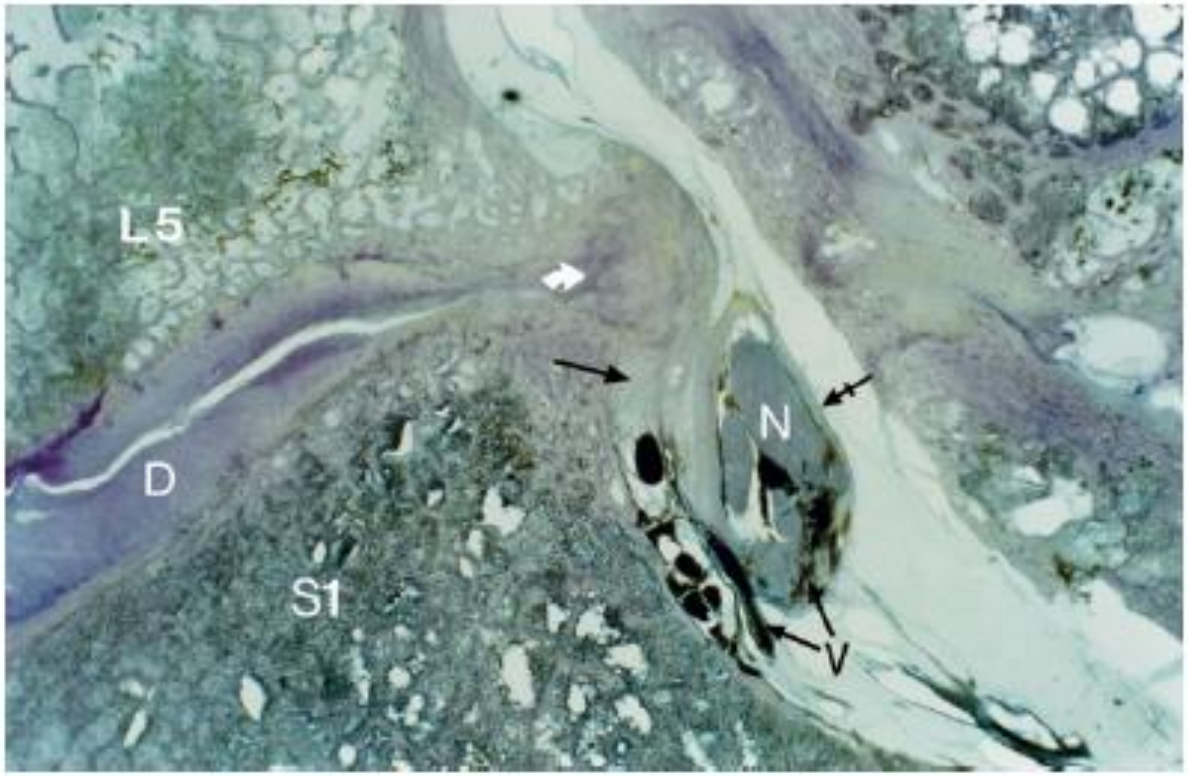
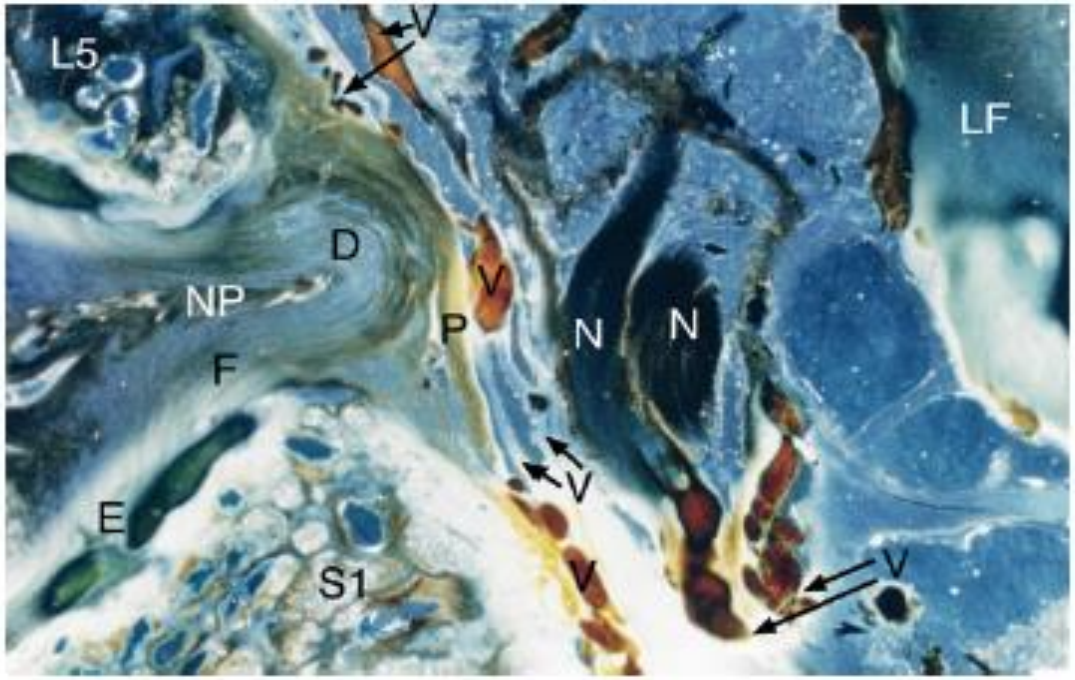



**Figure vii.6** A 200-micron thick histopathology section, cut in the parasagittal plane through the lumbosacral intervertebral disc of a 59-year-old cadaver, showing a disc protrusion (small curved white arrow) with perineural adhesions (arrow) between the protrusion and the adjacent dural sleeve (tailed arrow) containing neural structures (N). D = intervertebral disc; L5 = fifth lumbar vertebral body; S1 = first sacral segment. Note the extensive vascularity (V) posterior to the sacrum and within and around the neural structures. (Ehrlich's haematoxylin and light green counterstain.)



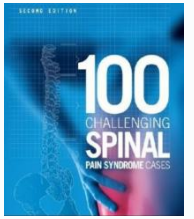




**Figure vii.14** A 200-micron thick sagittal histopatholgy darkfield section from a middle-aged cadaver showing a lumbosacral posterior midline intervertebral disc (D) bulging into the spinal canal and elevating the posterior longitudinal ligament (P). The annular fibres (F) attached to the cartilaginous endplate (E) arch around the posteriorly migrated nucleus pulposus (NP). The bulging disc with the posterior longitudinal ligament press upon the adjacent blood vessels. L5 = fifth lumbar vertebral body; LF = ligamentum flavum; N = neural structures within the spinal canal; S1 = first sacral body; V = blood vessels posterior to the disc bulge and associated with the neural structures. (Ehrlich's haematoxylin and light green counterstain.)

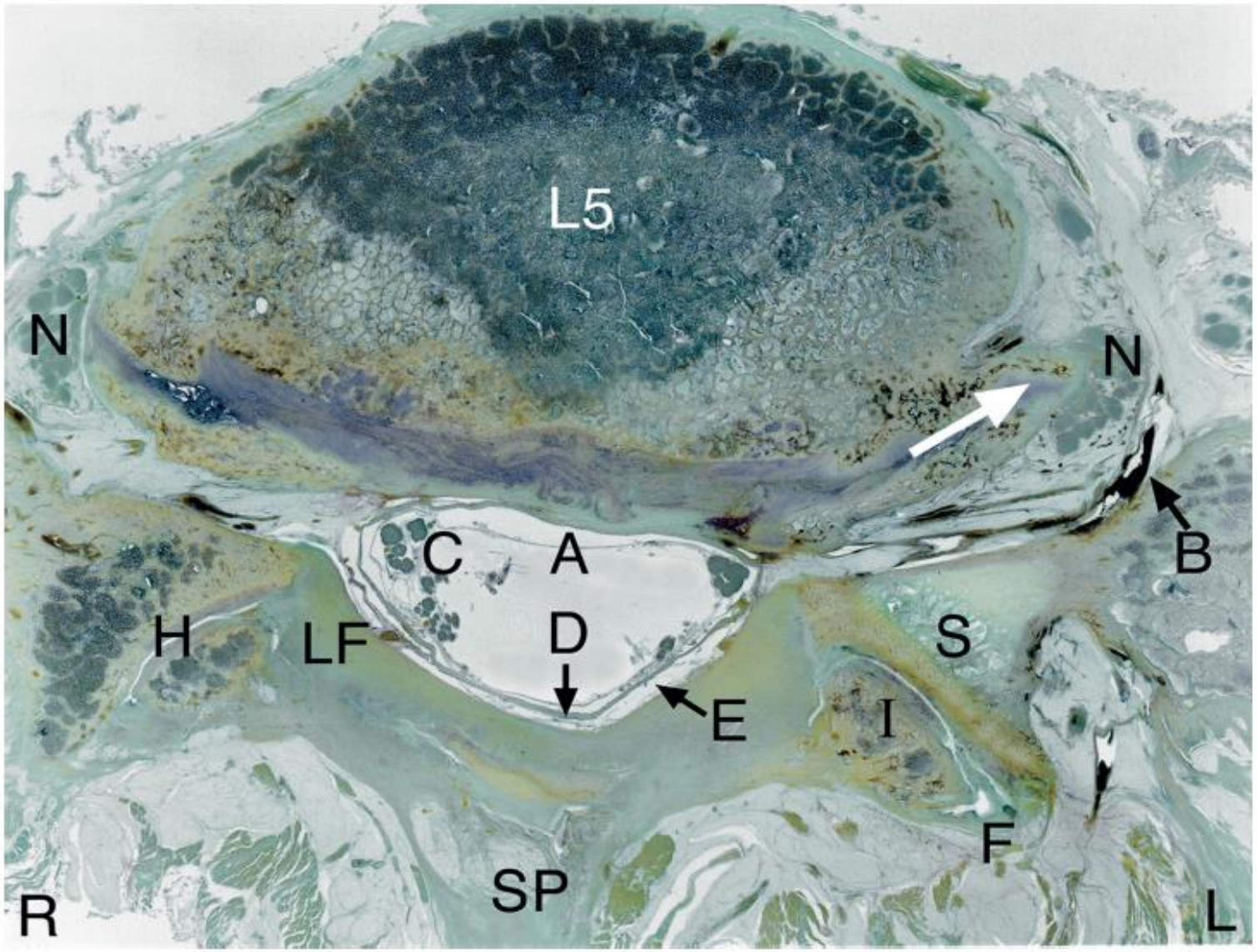
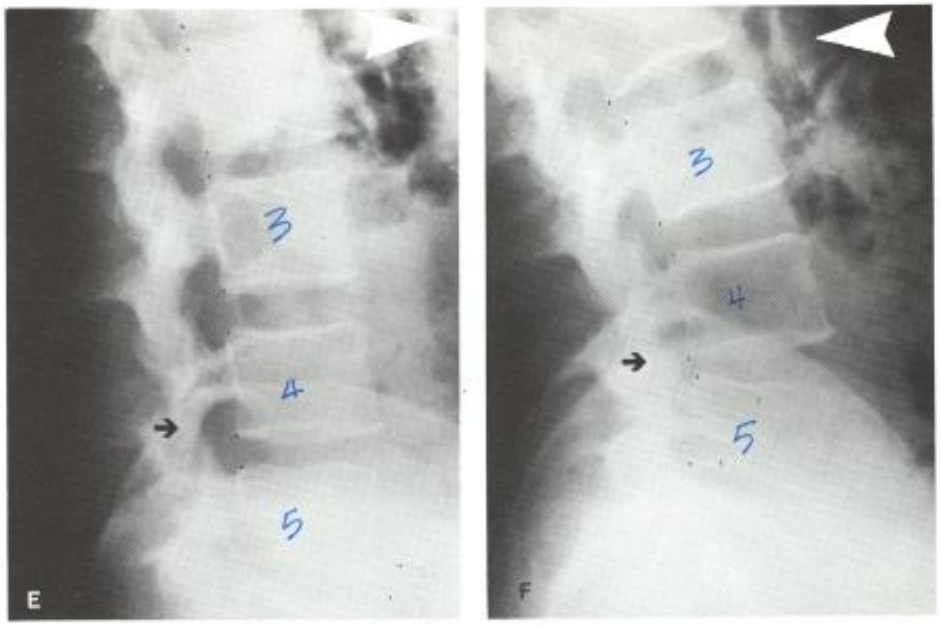
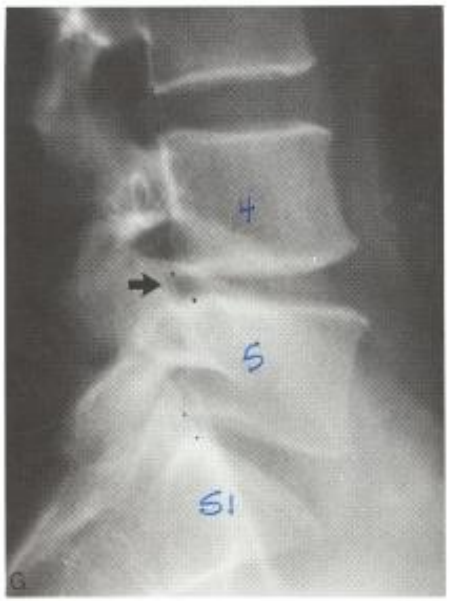



**Figure 37.6** An axial histopathology section from the L5–S1 level of a 60-year-old postmortem specimen. On the right side (R), there is no osteophyte of any significance and the spinal nerve (N) passes freely beside the L5 vertebral body. However, on the left side (L), there is an osteophyte (arrow) abutting the adjacent spinal nerve that is being deformed by the osteophyte. A = arachnoid membrane; B = blood vessel; C = cauda equina nerve roots within the lumbar dural tube; D = dural membrane; E = epidural fat in the epidural space; F = fibrous capsule posteriorly for the zygapophysial joint; H = hyaline articular cartilage on the zygapophysial joint facet surfaces; I = inferior articular process of the L5 vertebra; LF = ligamentum flavum; L5 = body of the L5 vertebra; S = superior articular process of the sacrum; SP = spinous process.









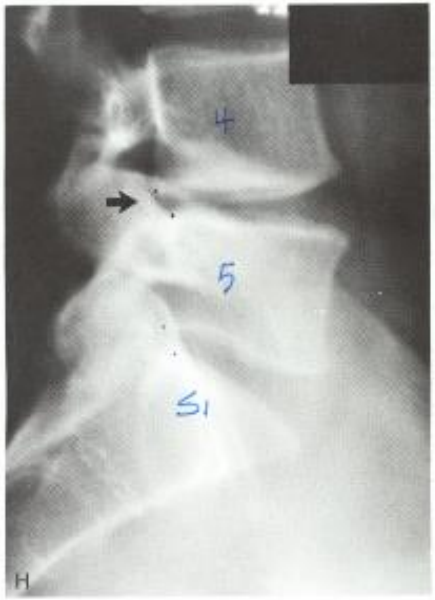





**Fig. 8-5** *(Continued)* **(E)** Lateral view in flexion. Posterior aspects of the vertebral bodies (arrow) are aligned normally. **(F)** The same patient as in (E). In extension the body of L4 is displaced posteriorly on that of L5 (arrow). Retrospondylolisthesis is indicative of instability of minor degree. **(G)** Lateral view in flexion. The vertebral body of L4 is displaced posteriorly on that of L5 (arrow). **(H)** The same patient as in (G). In extension the body of L4 is further displaced posteriorly on that of L5. The anterior aspect of the L4 – 5 disc has opened. Marked retrospondylolisthesis indicates gross instability. *(Figure continues.)*

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# Do vertebral endplate signal changes (modic changes) hurt? A systematic review

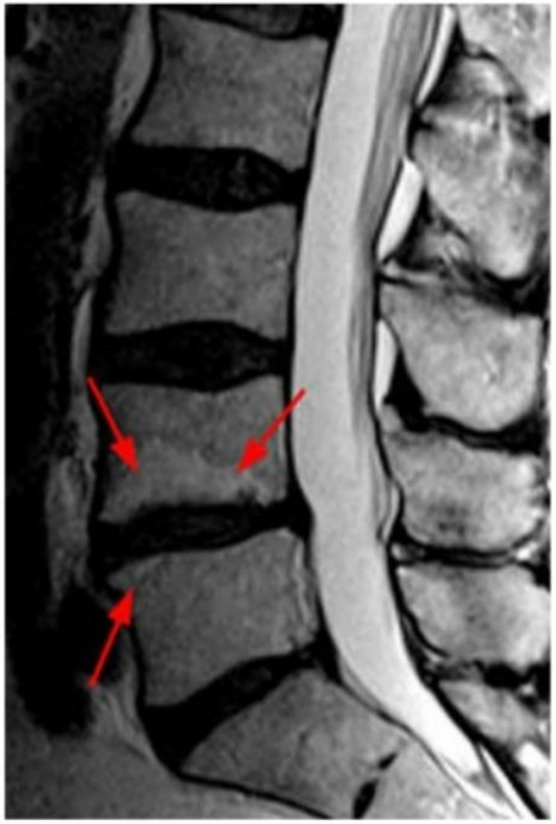
**Poster No.:** C-2418

**Congress:** ECR 2010

| Prevalence of pain (median) | | |
|---|---|---|
| **All discs (n=4457)** | **Discs with Modic changes (n=447)** | **Discs without Modic changes (n=4010)** |
| **47%** | **89%** | **42%** |

**Figure 4:** The median prevalence of pain on discography in 4457 discs from eight studies using provocative discography as outcome.

Ref: Modic et al Radiology, 1988



Popularly termed as
'EP changes'.
However,
These changes are
in the vertebral marrow
and subchondral bone
and **not the EP**.

## 'Degenerative Marrow Changes'

(Signal intensity changes)

- adjacent to the endplates of degenerated discs are a common observation on MR images
- First noted on MRI by de Roos et al in 1987
- Modic et al. (1988) described classification (3 types of changes)

## Modic changes and LBP

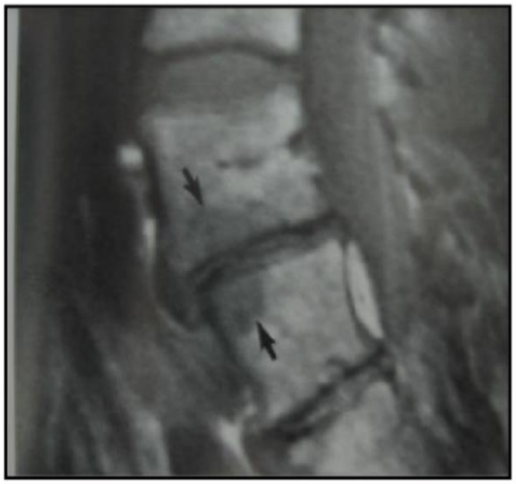
- DDD on its own a fairly quiet disorder,
- DDD with Modic changes much more frequently associated with clinical symptoms.
- MI is the most strongly associated with LBP compared to type 2 & 3

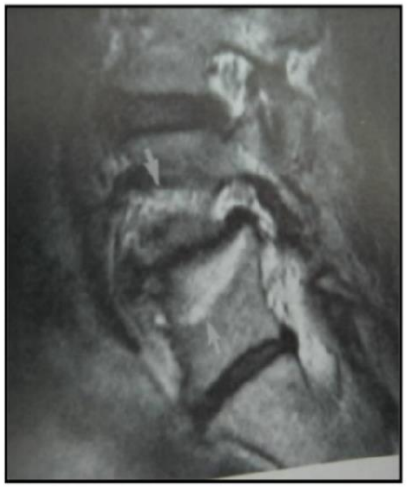
## Modic 1

- **Fibrovascular tissue replacement** of normal bone marrow.
- **Inflammatory, painful (89%) & ongoing DJD.**
- **Hypo**T1w & **Hyper**T2w MRI.

### Modic Type I (Edema)

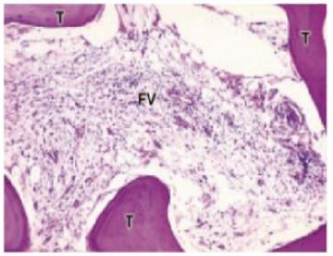
**Described as** disruption and fissuring of the endplate with regions of degeneration, regeneration, and vascular granulation tissue.
**Correspond to** the inflammatory stage of DDD
**Indicate** an ongoing active degenerative process



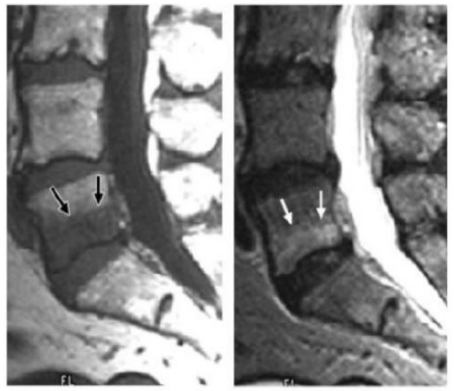


### Type I changes

- identified in
  - 4% of scanned patients
  - 19% of lumbar DDD
  - 8% after discectomy
  - 40%–50% of chymopapain-treated disks, ( a model of acute disk degeneration).
- Enhancement is seen with contrast that at times extends to involve the disc itself (related to the vascularized fibrous tissue within the adjacent marrow)




Histologic slide
Fibrovascular tissue *(FV)* has replaced normal marrow elements between thickened bone trabeculae *(T)*.

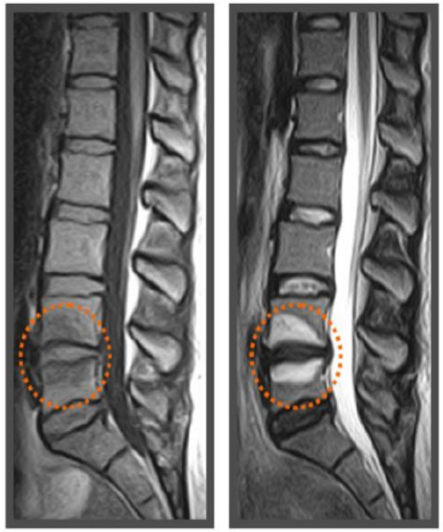


## Modic 1

- **Fibrovascular tissue replacement** of normal bone marrow.
- **Inflammatory, painful (89%) & ongoing DJD.**
- **Hypo**T1w & **Hyper**T2w MRI.

### Modic changes – type 1

- Histology
  - Fibrovascular tissue
  - Fissures in the endplate
- MRI
  - Hypointense on T1w
  - Hyperintense on T2w



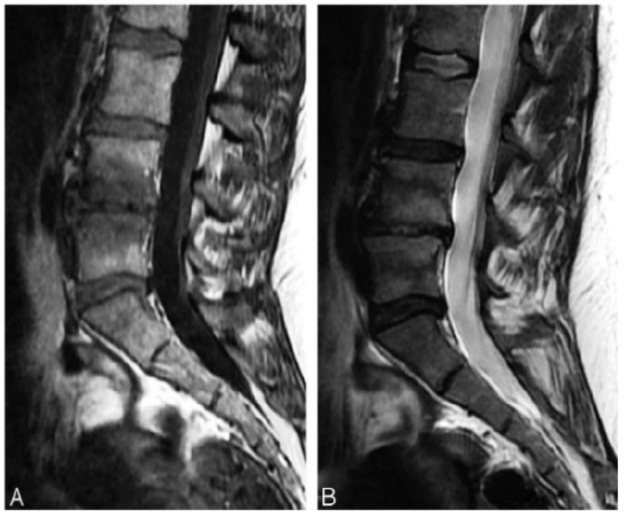
T1w T2w

Reference: Modic et al, Radiology, 1988

### Modic type 1 deg. changes (MI)

Hypointense on T1WI (A)

Hyperintense on T2WI (B)

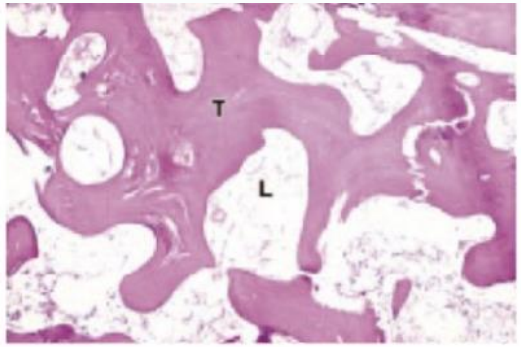


**Modic 2**

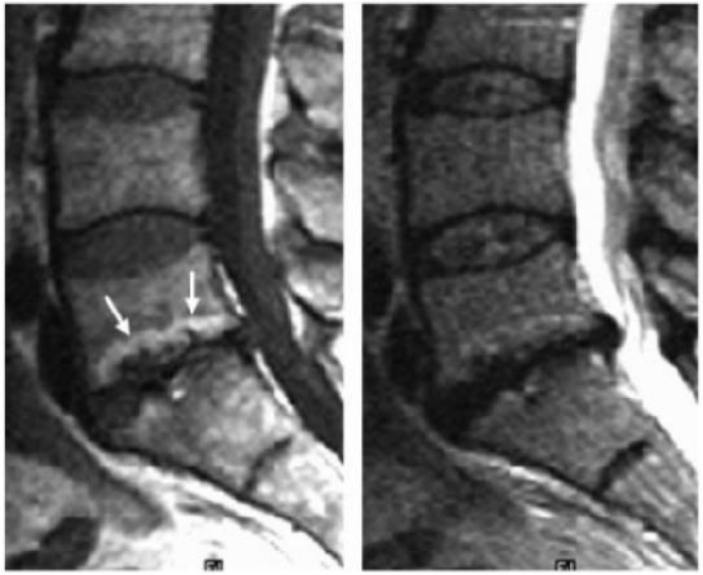
- **Fibrovascular/Lipid tissue** replacement of normal marrow.
- **Inflammatory, painful & ongoing DJD.**
- **Possible Discitis.**
- **Hyper**T1w & **Hyper**T2w MRI.

# Type II changes

- Identified in
  - 16% of scanned patients
  - 59% of lumbar DDD
- Discs with type II changes also show evidence of endplate disruption




Increased lipid content of the marrow space *(L)*. Note also thickened woven bone trabeculae *(T)*.



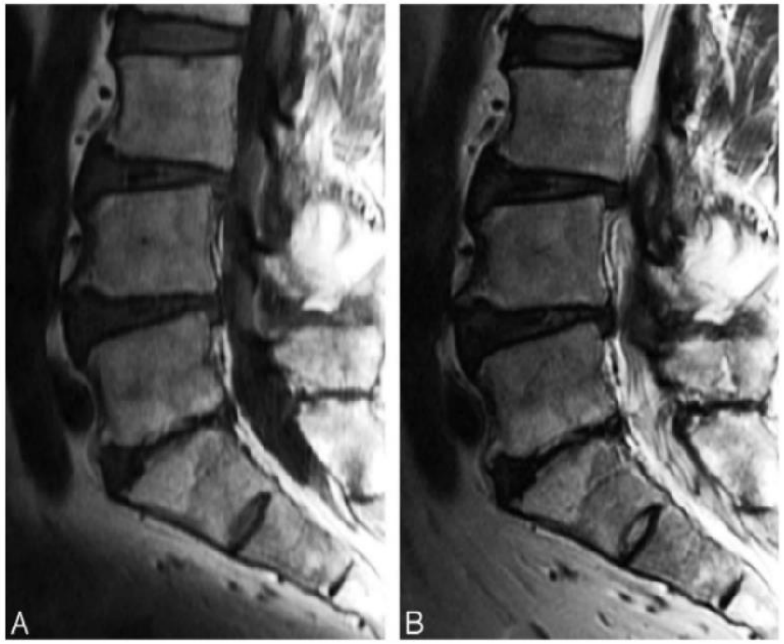
## Modic 2

- **Fibrovascular/Lipid tissue replacement** of normal marrow.
- **Inflammatory, painful & ongoing DJD.**
- **Possible Discitis.**
- **Hyper**T1w & **Hyper**T2w MRI.

### Modic type 2 degenerative changes (MII)

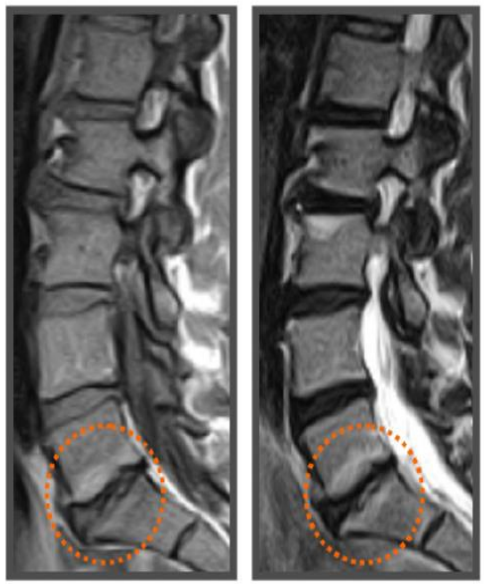
hyperintense on T1WI (A)

isointense or slightly hyperintense on T2WI (B




### Modic changes – type 2

- Histology
  - Fatty tissue
  - Fissures of the endplate
- MRI
  - Hyperintense on T1w
  - Hyperintense on T2w



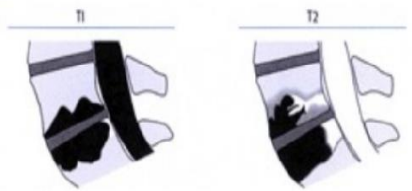

Reference: Modic et al, Radiology, 1988

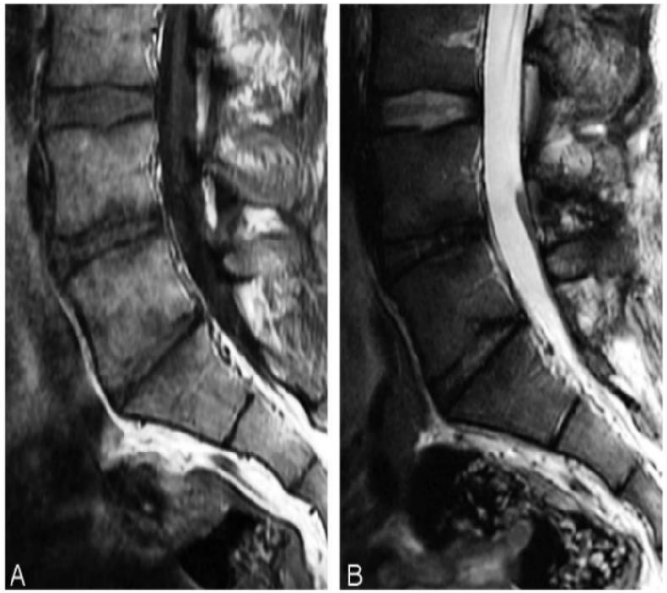
## Modic 3

- **Absence of normal bone marrow.**
- **Advanced DJD, canal & foraminal stenosis.**
- **Hypo**T1w & **Hypo**T2w MRI.

## Modic type 3 degenerative changes (MIII)

Hypointense on both T1WI (A) and T2WI (B)

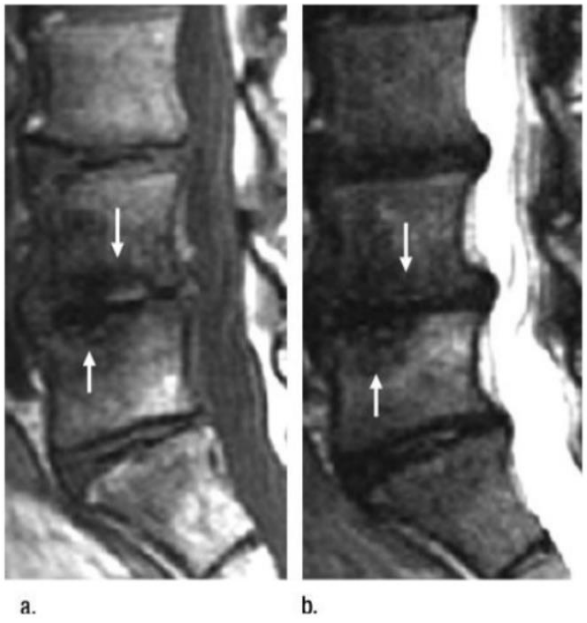



## Type III changes

(Lack of signal)

- Correlate with extensive bony sclerosis on plain radiographs.
- Reflects the relative absence of marrow in areas of advanced sclerosis
- Considering the histology;
  - dense woven bone within the vertebral body




# Modic changes
# Differential Diagnosis

**Intervertebral disk space infections**
**(Spondylodiscitis)**

Typically mimicking type 1 Modic changes

Contrast enhancement may occur in both conditions

The disc T2WI signal intensity is typically increased in discitis

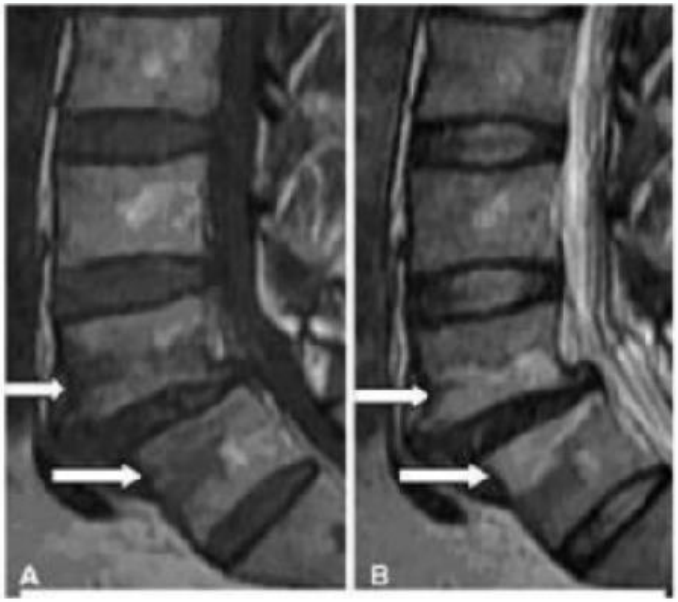
but often appears normal or hypointense on T2WI in DDD,

Also, the vertebral endplates are eroded or destroyed in disc space infection but usually preserved in DDD

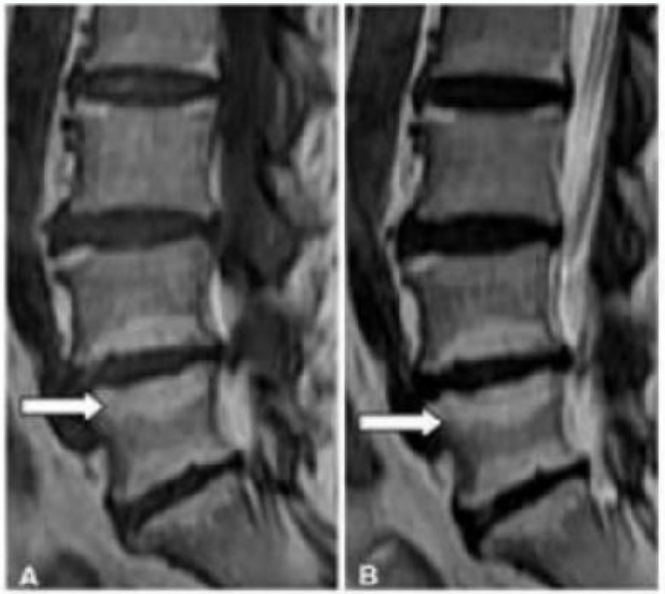
Finally, the presence of paraspinal or epidural inflammation and/or collection should orient the diagnosis toward an infectious process.

The clinical presentation

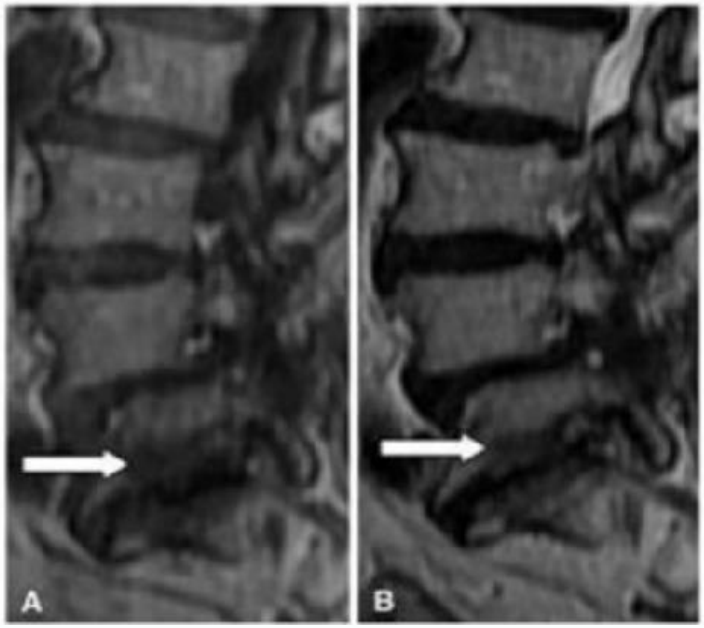
The laboratory tests such as ESR and CRP (very reliable indicator of infection) being raised in up to 100% of patients




MC type I (arrows): hypointense on T1WI (A) and hyperintense on T2WI (B)




MC type II (arrows): hyperintense on T1WI (A) and isointense or hyperintense on T2WI (B)




MC type III (arrows): hypointense on T1WI (A) and hypointense on T2WI (B)

# What is Intervertebral Disc Degeneration, and What Causes It?

**Michael A. Adams, PhD; Peter J. Roughley, PhD**

Spine. 2006;31(18):2151-2161. ©2006 Lippincott Williams & Wilkins
Posted 09/19/2006

- 'In adult discs, blood vessels are normally restricted to the outmost layers of the annulus. Metabolite transport is by diffusion. **Low oxygen tension in the center of a disc leads to anaerobic metabolism, resulting in a high concentration of lactic acid and low pH.**

- *In vitro* experiments show that a **chronic lack of oxygen** causes nucleus cells to become quiescent, whereas a chronic lack of glucose can kill them. **Deficiencies in metabolite transport (hypoxia) appear to limit both the density and metabolic activity of disc cells.** As a result, discs have only a limited ability to recover from any metabolic or mechanical injury.

- Endplate permeability and disc metabolite transport decrease during growth and aging, and yet increase in the presence of disc degeneration and following endplate damage. This is an essential difference between aging and degeneration.

ANTIMICROBICS AND INFECTIOUS DISEASES NEWSLETTER

Editor-in-Chief
**Charles W. Stratton, MD**
*Vanderbilt University*
*School of Medicine*
*Nashville, Tennessee*

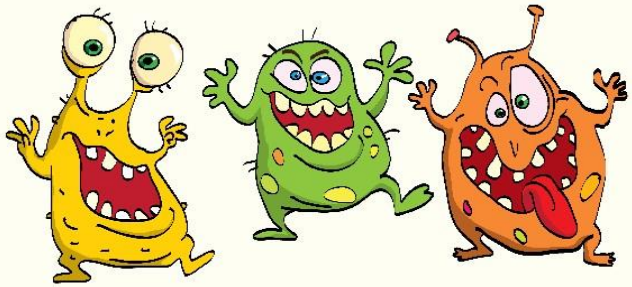
*Full editorial board appears on back cover*

Volume 18, Number 7
July 2000

## Association of *Chlamydia pneumoniae* with Chronic Human Diseases

- Blood investigations may include **Mycoplasma profile, Chlamydia profile, Rickettsia profile, Herpes strains, Cytomegalovirus, Epstein Barr Virus, Borrelia, Bartonella** …

- **Chlamydia pneumonia** and other chronic **anaerobic based infections** are associated with arthritis and chronic pain syndromes. **Opportunistic Infections act as a *triggering agent* driving chronic pain cycles and progressive degeneration.**



## Does antibiotic or anti-viral medication reduce back pain?

https://ama.com.au/ausmed/antibiotics-could-cure-40-cent-chronic-back-pain

Eur Spine J. 2013 Apr;22(4):697-707. doi: 10.1007/s00586-013-2675-y. Epub 2013 Feb 13.

# Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized clinical controlled trial of efficacy.

Albert HB[1], Sorensen JS, Christensen BS, Manniche C.

**Author information**

[1]Research Department, Spine Centre of Southern Denmark, Institute of Regional Health Services Research, Lillebaelt Hospital, University of Southern Denmark, Middelfart, Denmark. hanne.birgit.albert@slb.regionsyddanmark.dk

**Abstract**

**PURPOSE:** Modic type 1 changes/bone edema in the vertebrae are present in 6 % of the general population and 35-40 % of the low back pain population. It is strongly associated with low back pain. The aim was to test the efficacy of antibiotic treatment in patients with chronic low back pain (>6 months) and Modic type 1 changes (bone edema).

**METHODS:** The study was a double-blind RCT with 162 patients whose only known illness was chronic LBP of greater than 6 months duration occurring after a previous disc herniation and who also had bone edema demonstrated as Modic type 1 changes in the vertebrae adjacent to the previous herniation. Patients were randomized to either 100 days of antibiotic treatment (Bioclavid) or placebo and were blindly evaluated at baseline, end of treatment and at 1-year follow-up.

**OUTCOME MEASURES:** Primary outcome, disease-specific disability, lumbar pain. Secondary outcome leg pain, number of hours with pain last 4 weeks, global perceived health, EQ-5D thermometer, days with sick leave, bothersomeness, constant pain, magnetic resonance image (MRI).

**RESULTS:** 144 of the 162 original patients were evaluated at 1-year follow-up. The two groups were similar at baseline. The antibiotic group improved highly statistically significantly on all outcome measures and improvement continued from 100 days follow-up until 1-year follow-up. At baseline, 100 days follow-up, 1-year follow-up the disease-specific disability-RMDQ changed: antibiotic 15, 11, 5.7; placebo 15, 14, 14. Leg pain: antibiotics 5.3, 3.0, 1.4; placebo 4.0, 4.3, 4.3. Lumbar pain: antibiotics 6.7, 5.0, 3.7; placebo 6.3, 6.3, 6.3. For the outcome measures, where a clinically important effect size was defined, improvements exceeded the thresholds, and a trend towards a dose-response relationship with double dose antibiotics being more efficacious.

**CONCLUSIONS:** The antibiotic protocol in this study was significantly more effective for this group of patients (CLBP associated with Modic I) than placebo in all the primary and secondary outcomes.

**Minocycline modulates cytokine and gene expression profiles in the brain after whole-body exposure to radiation.**

Loma Linda University, Loma Linda, (2014), CA 92354, U.S.A.

**Abstract**

An effective countermeasure against radiation damage to normal tissues is urgently needed. The major goal of the present study was to determine if minocycline could modify the immunomodulatory effects of radiation on the brain. C57BL/6 mice were treated with minocycline intraperitoneally for 5 days beginning immediately before total-body exposure to 0, 1, 2 and 3 Gray (Gy) (60)Co γ-rays. Brains were collected on days 4 and 32 post-irradiation for cytokine and gene analyses.

- **Minocycline treatment significantly increased the levels of interleukin (IL)-10, IL-15 and vascular endothelial growth factor (VEGF)** in the brain on day 4 in one or more irradiated groups compared to radiation-alone ($p<0.05$).
- **IL-10 is anti-inflammatory,**
- **IL-15 can prevent apoptosis and**
- **VEGF is neuroprotective.**

Overall, the data warrant further testing of minocycline as a ***potential neuroprotectant*** against radiation-induced damage.

## Epidural Haematoma

**The density of the supposed disc fragment is different to that of the large L5/S1 protrusion posterior to the L5/S1 IVD.**
**DDx – Epidural Haematoma.**

**Look at the films!**

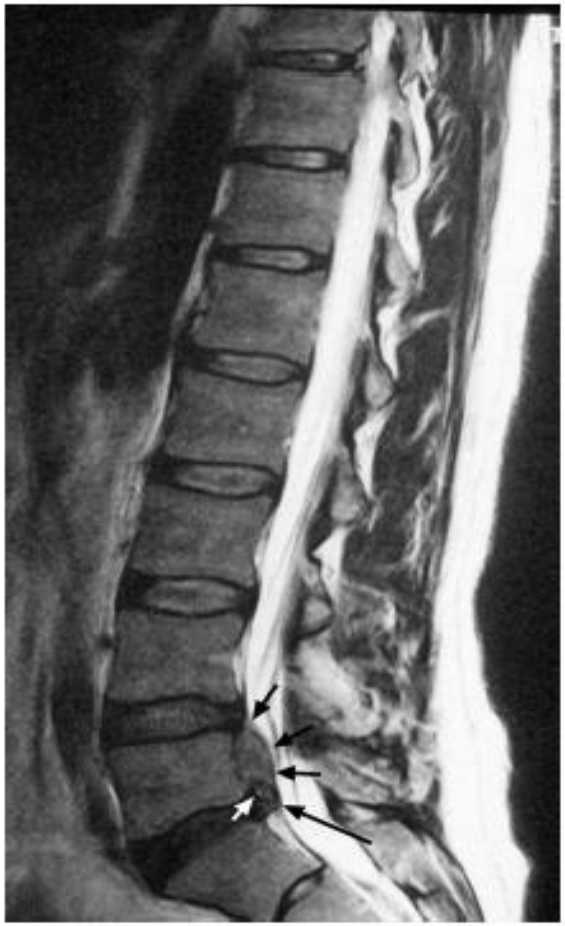
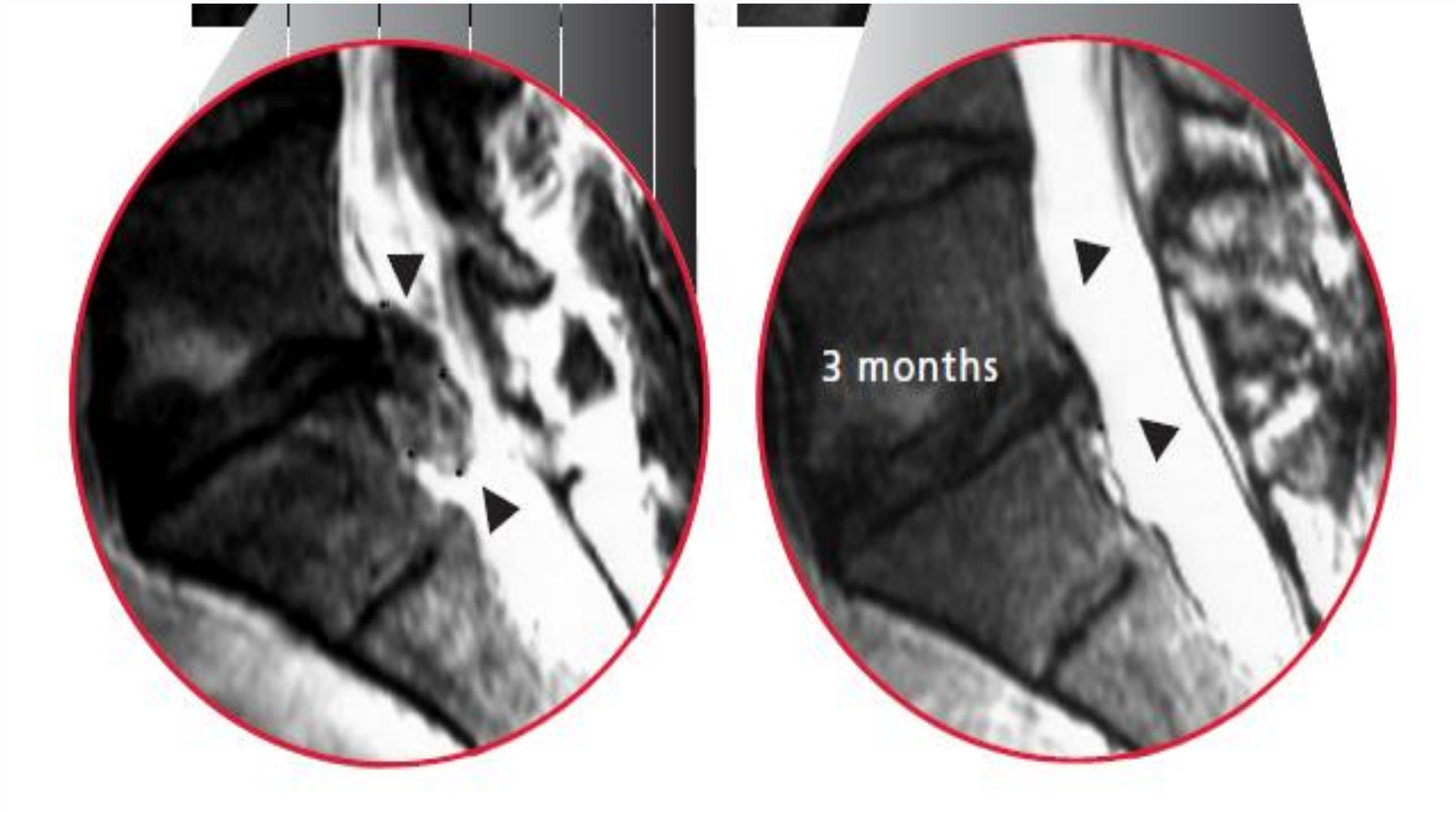


Figure 24.3 Lumbar spine MRI parasagittal T2-weighted image. Note what was reported as a large sequestrated disc fragment extending superiorly behind the L5 body (short black arrows), above the large protrusion (long black arrow) at the L5–S1 level, that has a tear/high intensity zone in it (white arrow). (See Fig. 24.4 for a series of axial views.) However, the density of the supposed sequestrated disc fragment is quite different to that of the large protrusion posterior to the L5–S1 intervertebral disc, so a differential diagnosis of epidural haematoma should be considered for the material extending superiorly behind the L5 body.

**State and Federal Submissions**
**– Victorian WorkCover Authority 1997 (Hooper)**

**Adverse Manipulation – Mr CD, L5/S1 Disc Sequestration, Haematoma.**

- **HBO 3-months**
- **Smoothing response** (Harch/Fogerty 2016)

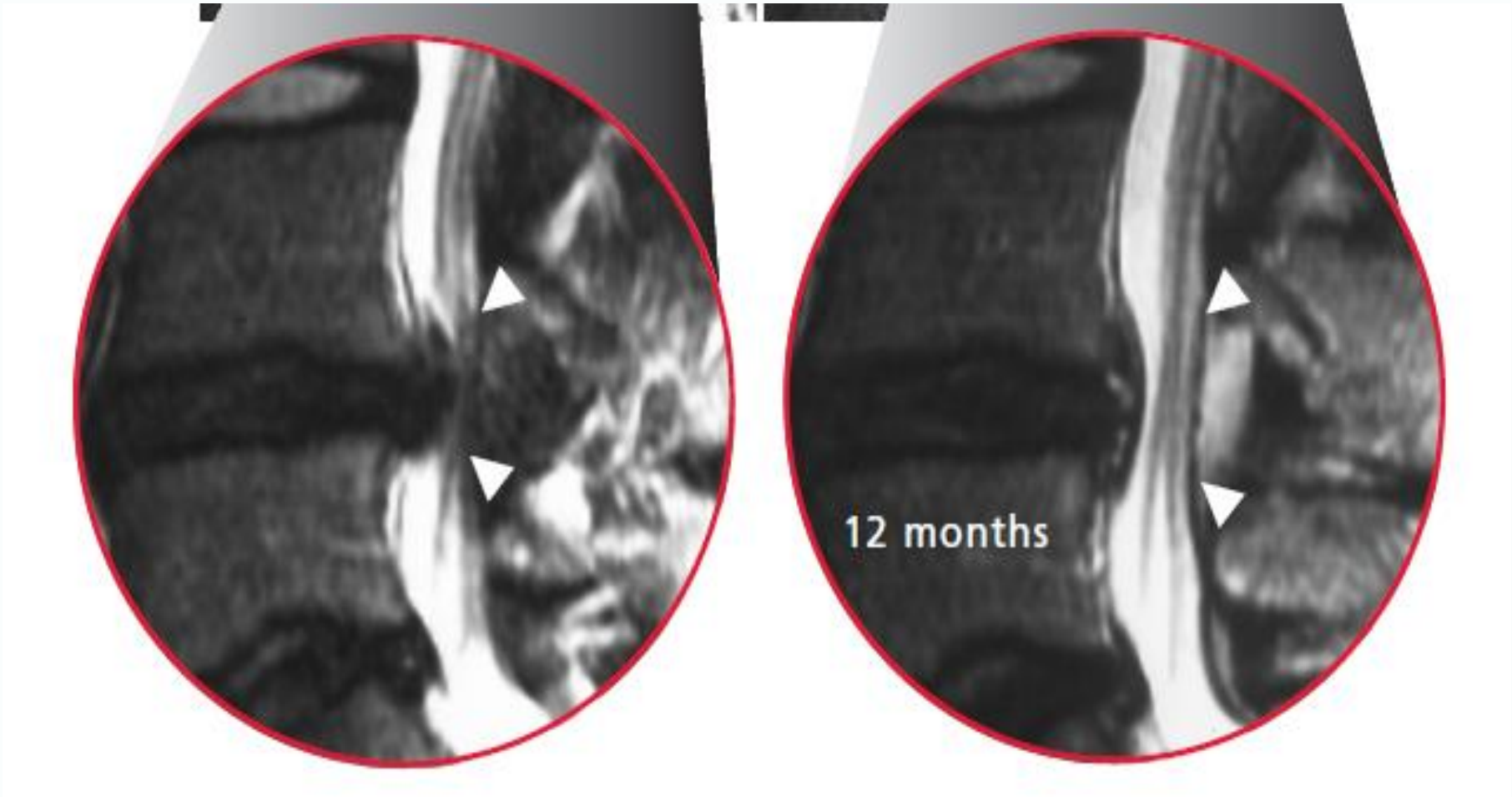


**Adverse Manipulation – Mr JB, L5/S1 Disc Sequestration, Haematoma**

- **HBO 3-months**
- **Smoothing response**

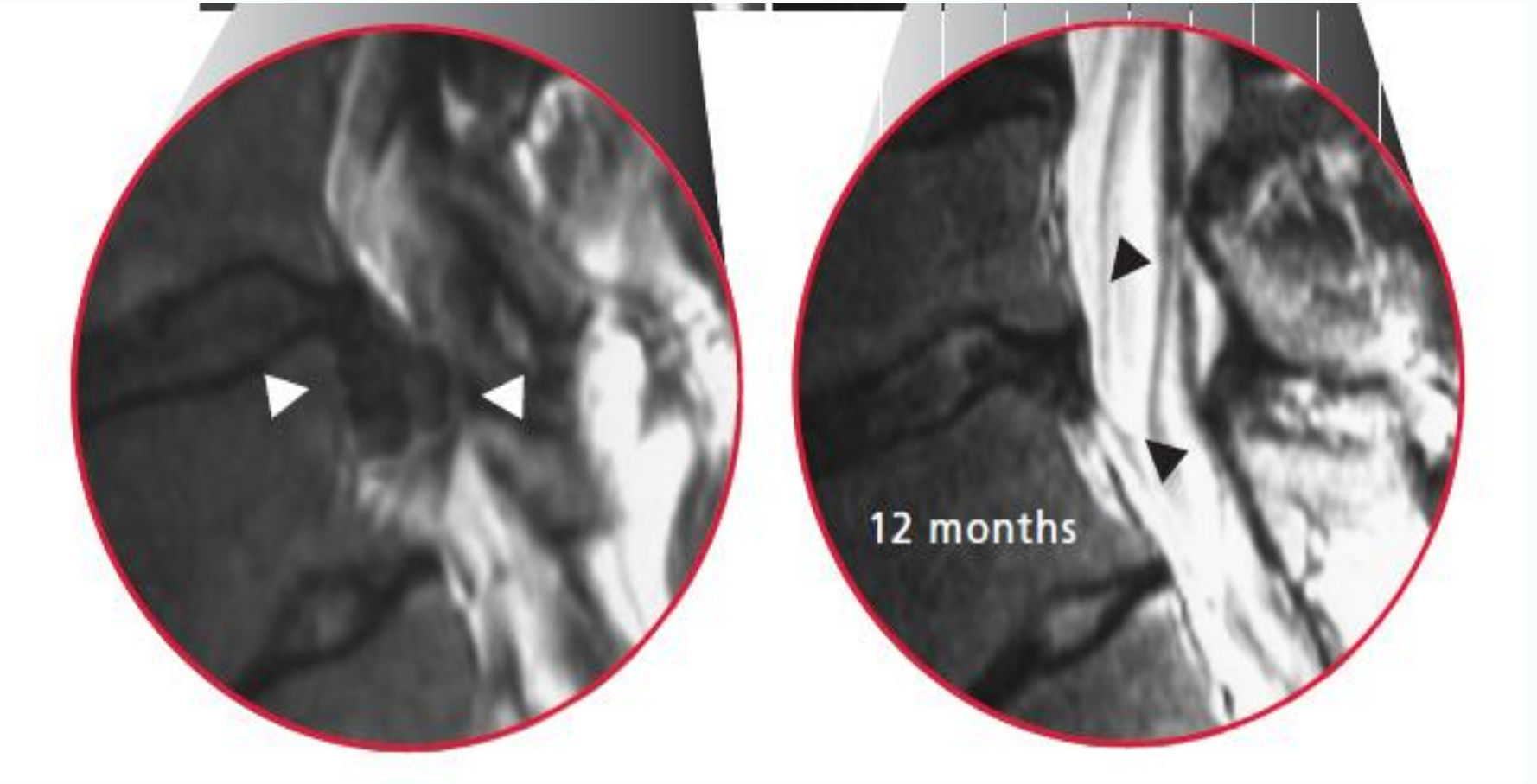
**15m Fall – Mr JF, L4/5 Canal Stenosis**

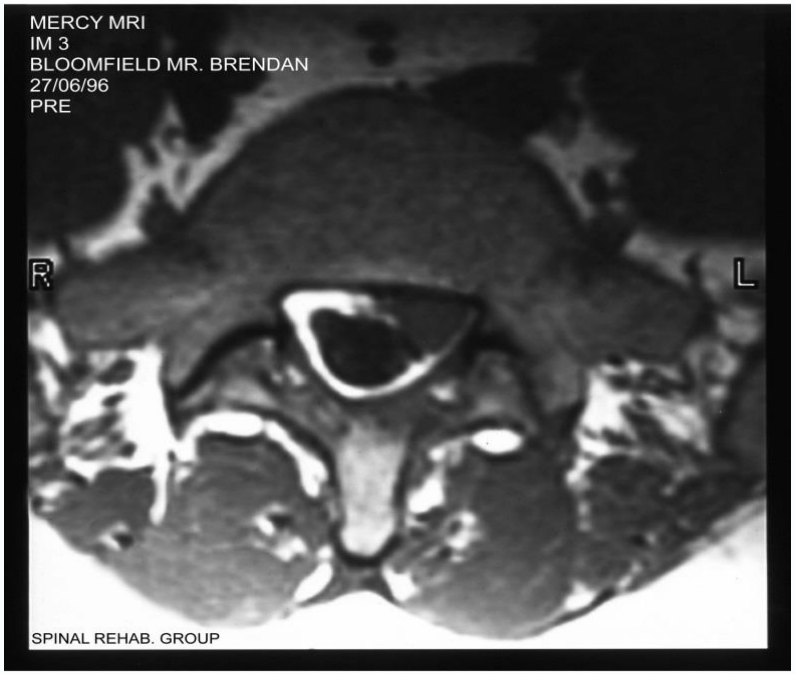
- **HBO 12-months**
- **Smoothing response**

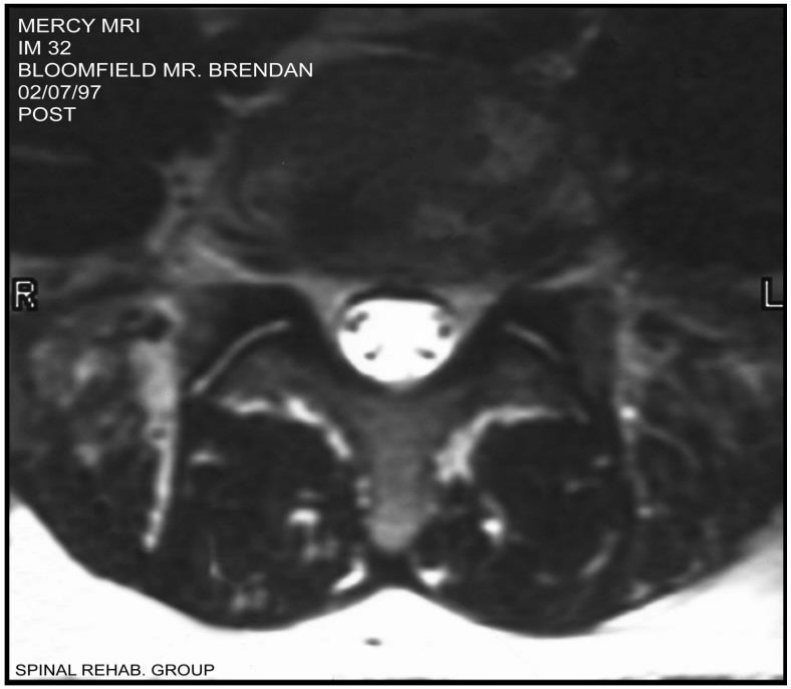


**Adverse Manipulation – Mr BB, L5/S1 Disc Sequestration**

- **HBO 12-months**
- **Smoothing response**

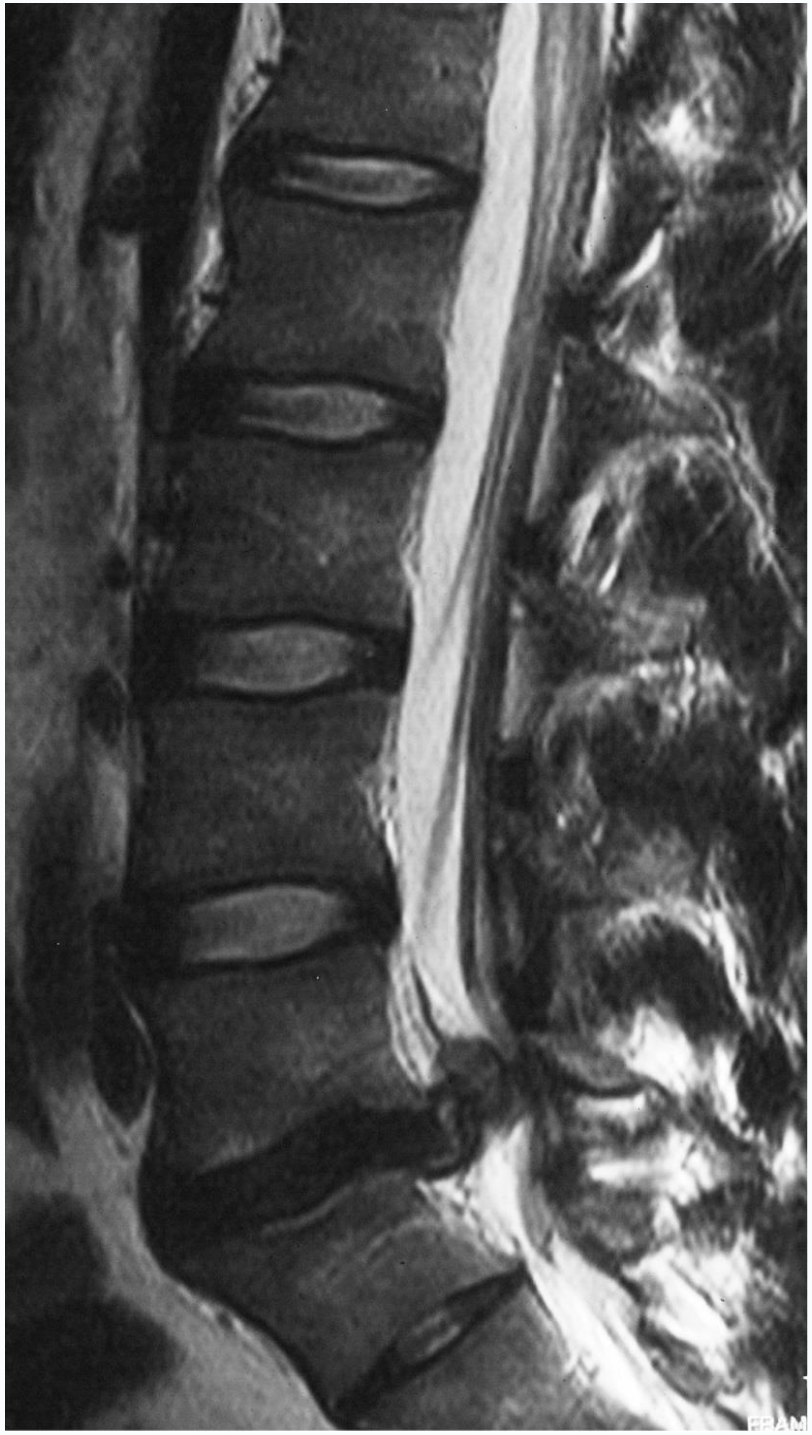


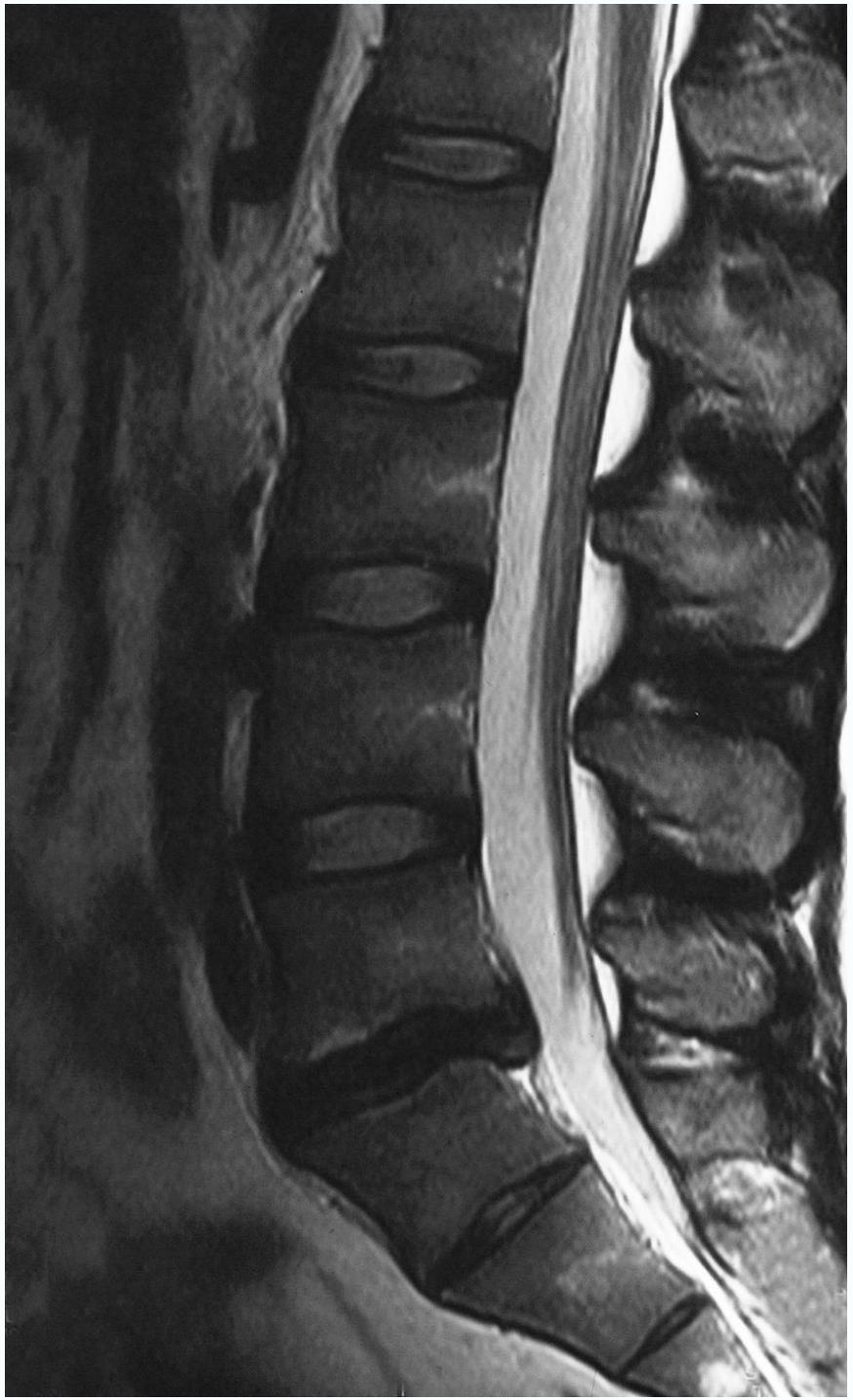



**Adverse Manipulation – Mr BB, L5/S1 Disc Sequestration**

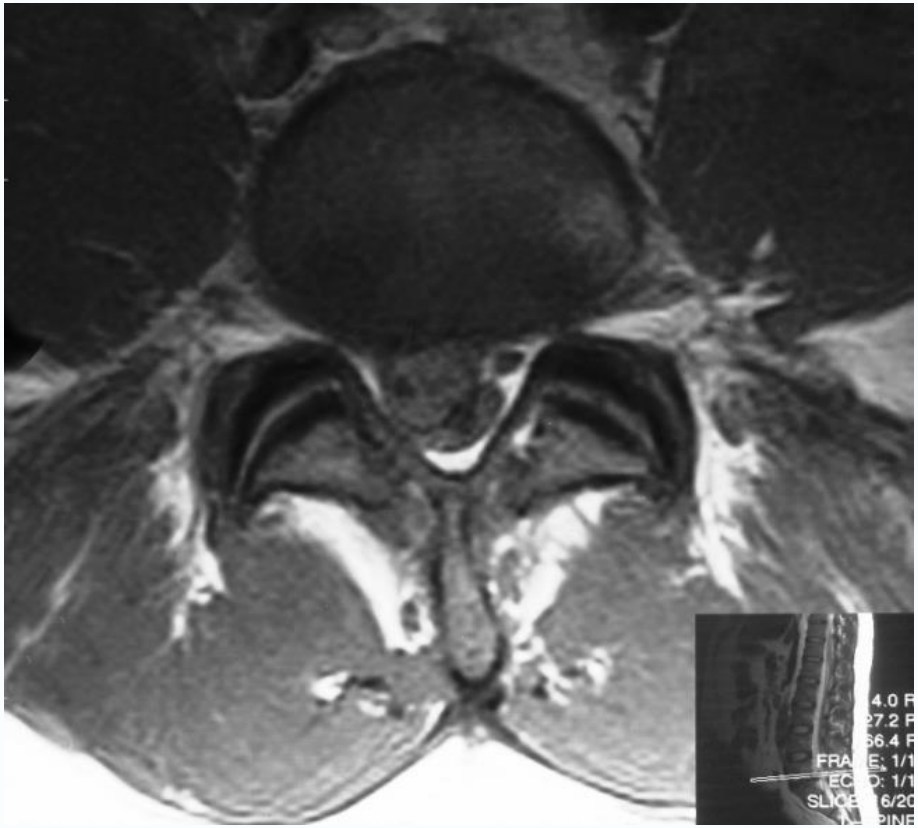
- **HBO 12-months**

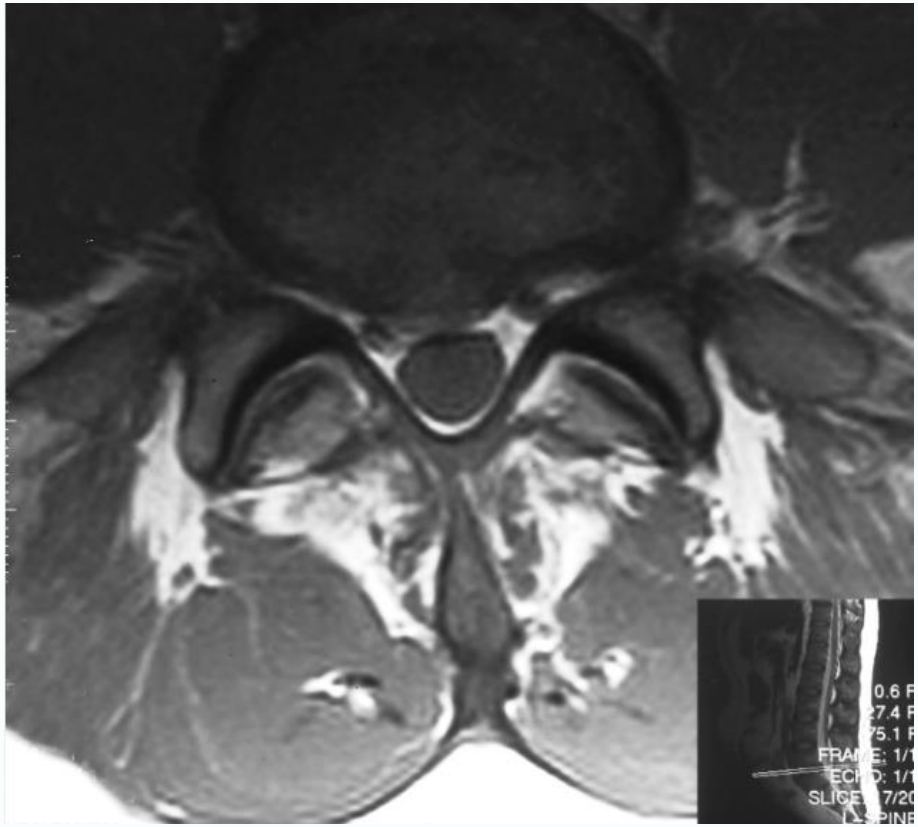




**Adverse Manipulation – Mr JB2, L5/S1 Disc Sequestration**

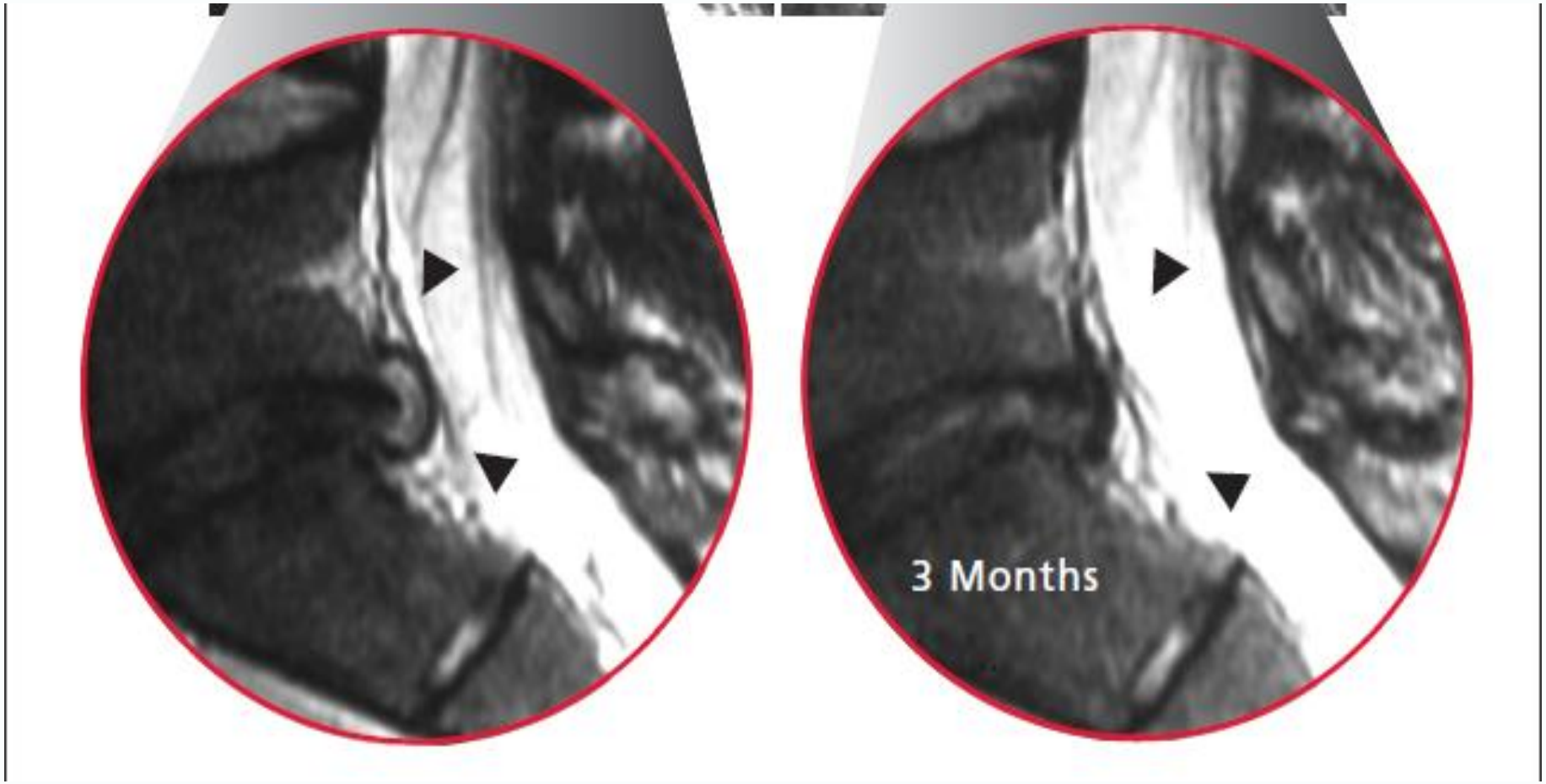
- **HBO 3-months**
- **Smoothing response**





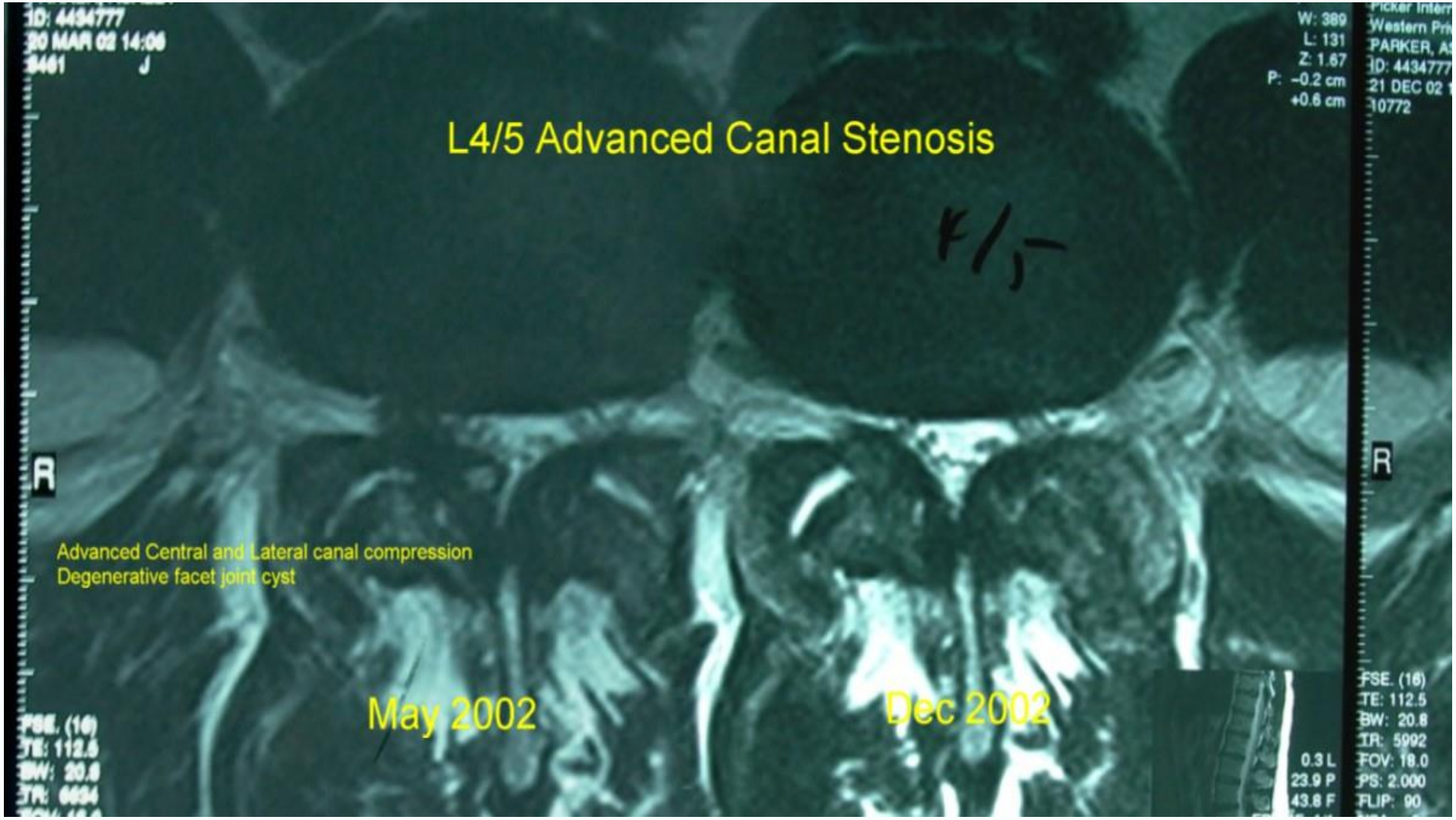
**Adverse Manipulation – Mr HN, L5/S1 Disc Prolapse**

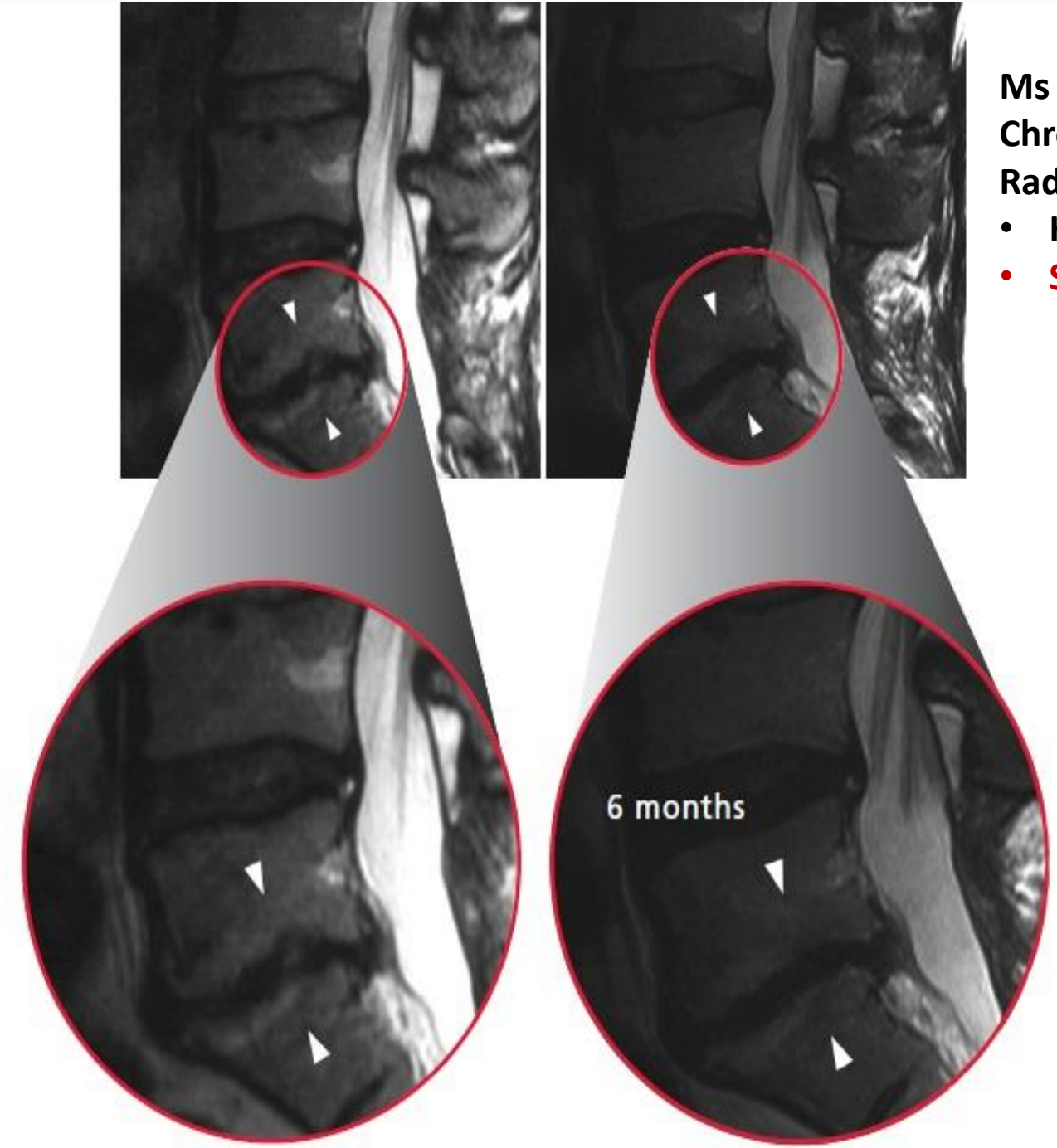
- **HBO 3-months**
- **Note increased T2 signal post HBO**
- **Smoothing response**



**Mr AP, Advanced Central L4/5 Canal Stenosis, Bilateral Foraminal Stenosis, Osteophytic Spur Right Foramina, Advanced Facet Joint Arthropathy, Right Medial Synovial Cyst.**

- **HBO 7-months**
- **Smoothing response**



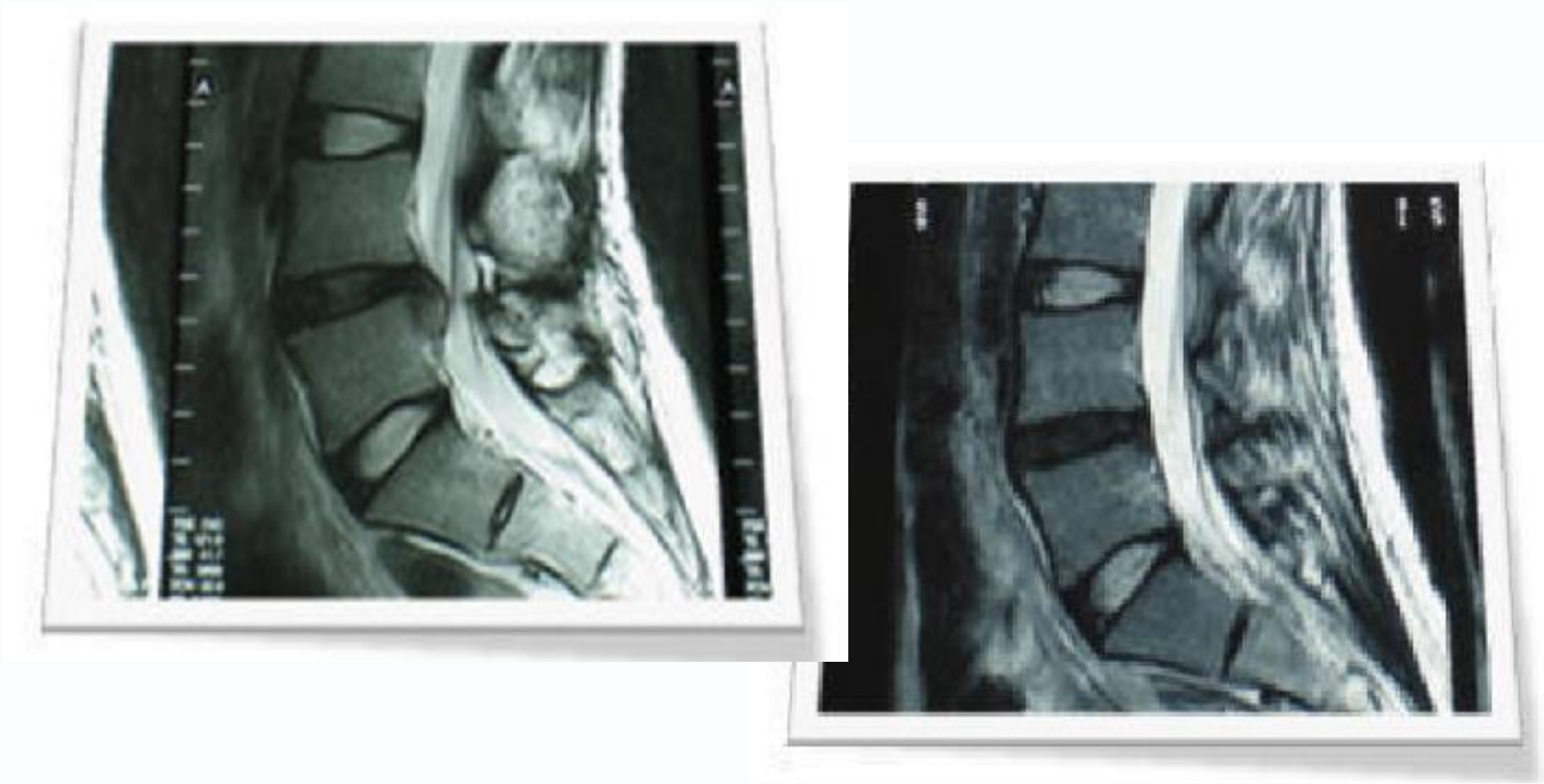



**Ms CS, Discectomy L5/S1 – Chronic Post Operative Discitis, Radicular Neuropathy (CRP)**

- **HBO 6-months**
- **Smoothing response**

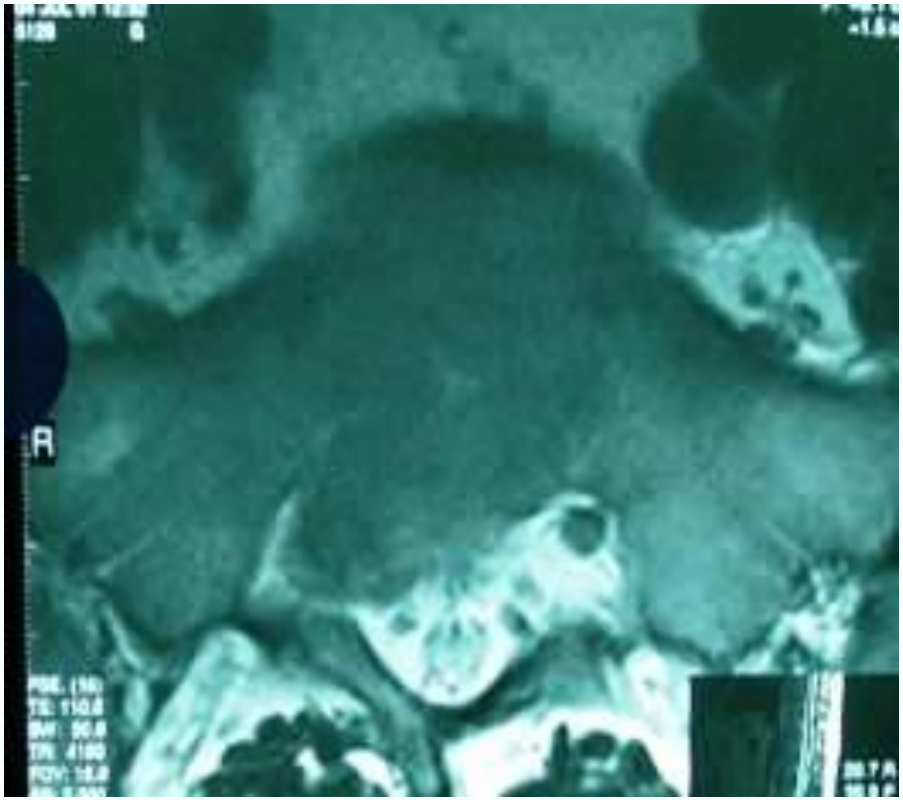
**Ms KH, Chronic Back and Leg Pain - Partial Discectomy & Laminectomy L4/5 – Recurrent L4/5 Disc Herniation**

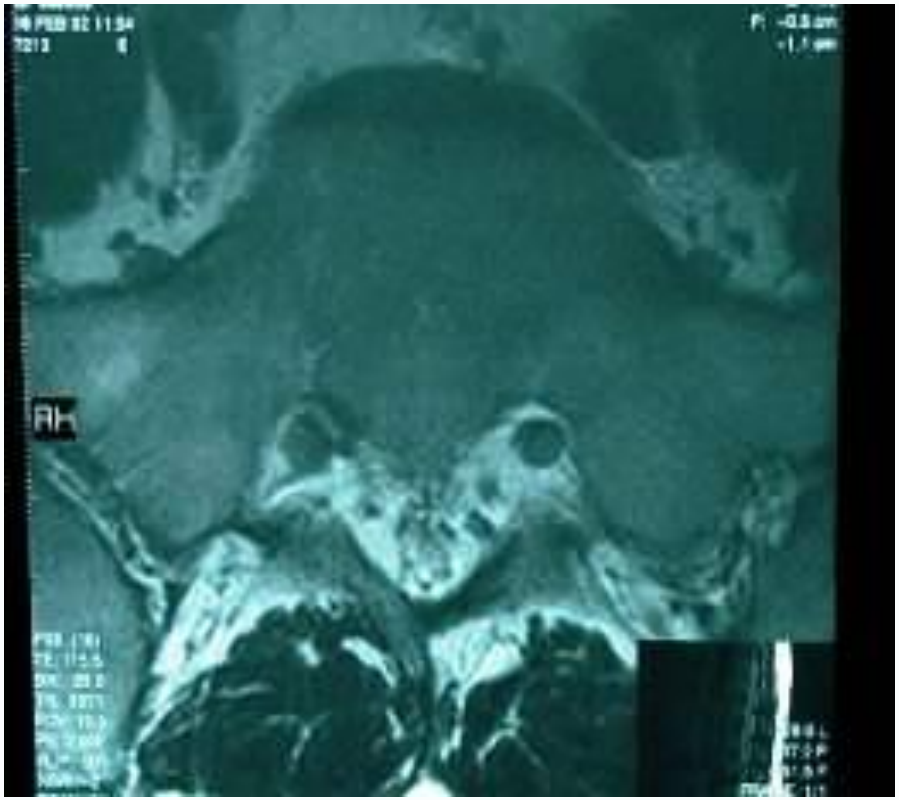
- **HBO 10-months**



**Adverse Manipulation – Mr AH, L5/S1 Disc Prolapse**

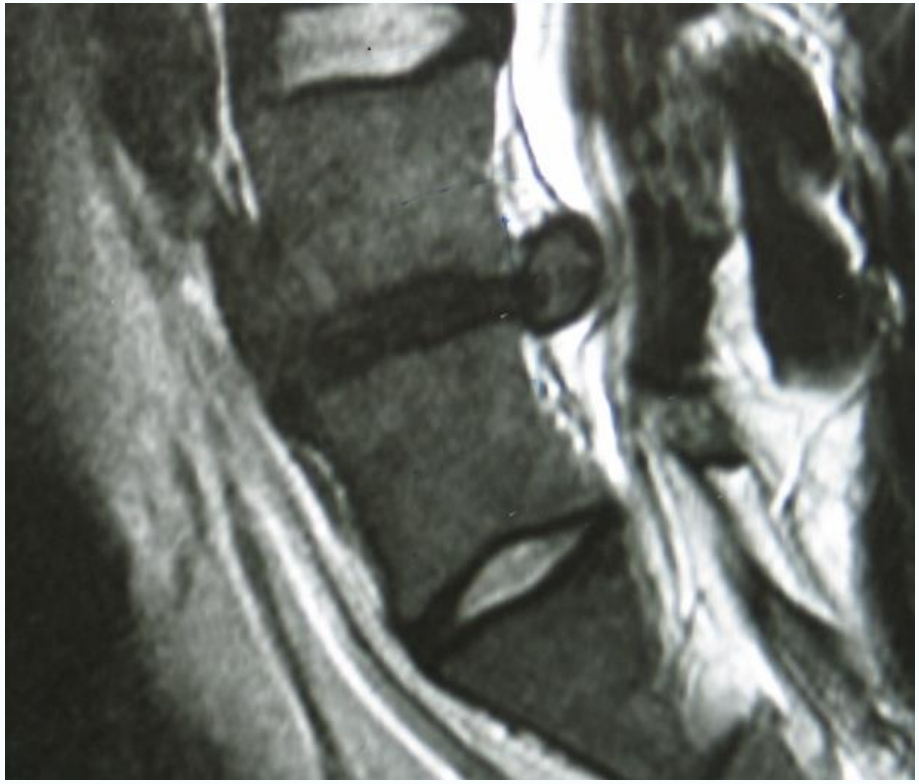
- **HBO 8-months**
- **Smoothing response**

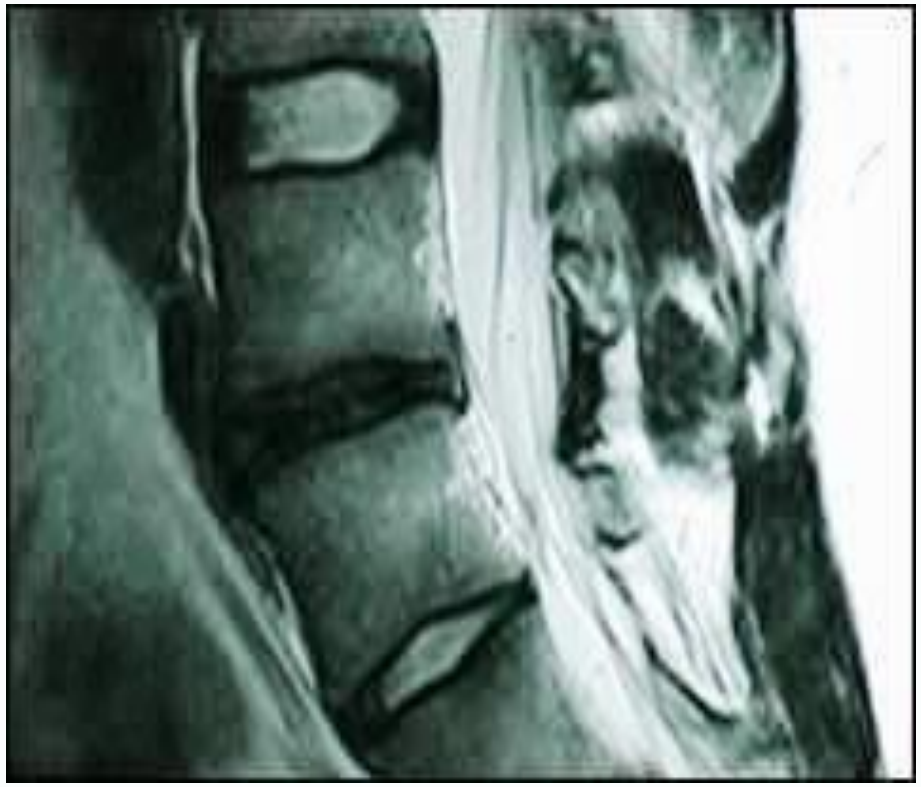


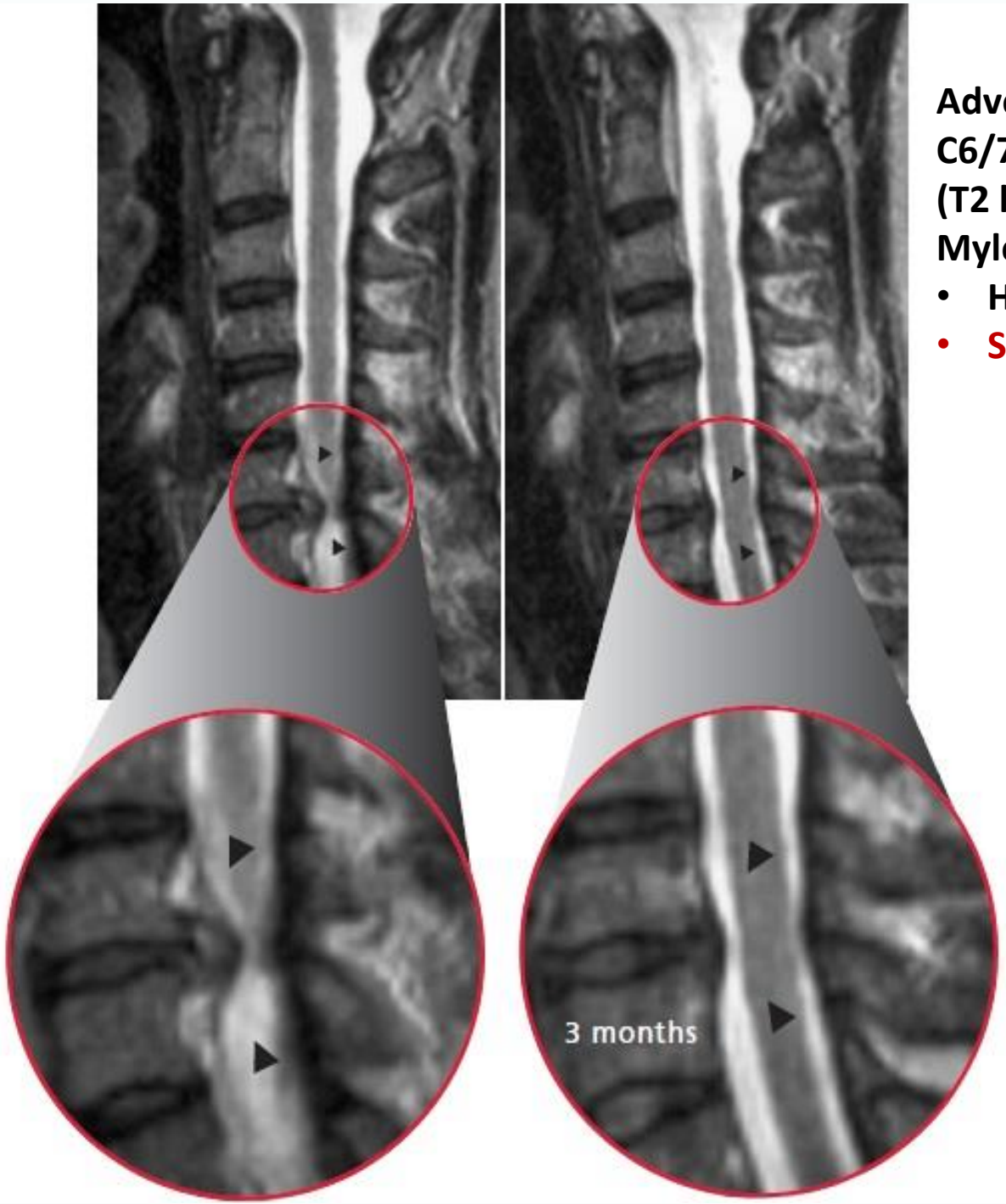


**Adverse Manipulation – Mr SM, L4/5 Disc Prolapse**

- **HBO 2 weeks**








**Adverse Manipulation – Ms GA, C6/7 Disc Prolapse, Cord Edema (T2 hyperintensity), Compressive Myleomalacia C6-T1.**

- **HBO 3-months**
- **Smoothing response**

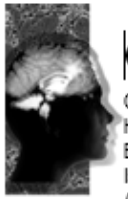
**Cytokines**

- Cytokines are signalling proteins and glycoproteins that **'orchestrate immune responses'.** Cytokines are also involved in **cell growth and differentiation, cell death, angiogenesis, normal development and neuromodulations.** They can be defined as either **pro-inflammatory or anti-inflammatory.**

- Cytokine imbalances are known to be involved in multiple **autoimmune disorders, chronic pain syndromes, trauma, chronic infections, metabolic disorders as well as neuropsychiatric disorders.** Elevated pro-inflammatory markers are linked with progressive neurodegenerative disease.

**Chronic Symptoms Associated With Cytokine Related Illness**
**(Dr Sam Shor Tick Borne Disease Conference 2014, Sydney, Australia)**

- Fatigue, Weakness, Aches, Muscle Cramps, Unusual Pain, Ice Pick Pain, Headache, Light Sensitivity, Red Eyes, Blurred Vision, Tearing, Sinus Problems, Cough, Shortness of Breath, Abdominal Pain, Diarrhea, Joint Pain, Morning Stiffness, Memory Issues, Focus/Concentration Issues, Word Recollection Issues, Decreased Learning of New Knowledge, Confusion, Disorientation, Skin Sensitivity, Mood Swings, Appetite Swings, Sweats (especially night sweats), Temperature Regulation or Dysregulation Problems, Excessive Thirst, Increased Urination, Static Shocks, Numbness, Tingling, Vertigo, Metallic Taste, Tremors.



# Cytokine Storm Symptoms

Common Symptoms: Fatigue, Weakness, Aches, Muscle Cramps, Unusual Pain, Ice Pick Pain, Headache, Light Sensitivity, Red Eyes, Blurred Vision, Tearing, Sinus Problems, Cough, Shortness of Breath, Abdominal Pain, Diarrhea, Joint Pain, Morning Stiffness, Memory Issues, Focus/Concentration Issues, Word Recollection, Executive Function, Confusion, Disorientation, Skin Sensitivity, Mood Swings, Appetite Swings, Sweats (especially night sweats), Temperature Regulation Problems, Excessive Thirst, Increased Urination, Static Shocks, Numbness, Tingling, Vertigo, Metallic Taste, Tremors

Client Name: _____ Date: _____

Symptom Score: Pre HBO | HBO50 | HBO 100 | HBO150 | HBO200

| Symptoms Severity Score | 0-none | 1-mild | 2-moderate | 3-severe |
|---|---|---|---|---|
| Unexplained fevers, sweats, chills or flushing | | | | |
| Unexplained weight change (loss or gain) | | | | |
| Fatigue, tiredness, poor stamina | | | | |
| Unexplained hair loss | | | | |
| Swollen glands | | | | |
| Sore throat | | | | |
| Testicular or pelvic pain | | | | |
| Unexplained menstrual irregularity | | | | |
| Irritable bladder or bladder dysfunction | | | | |
| Unexplained milk production or breast pain | | | | |
| Sexual dysfunction or loss of libido (sex drive) | | | | |
| Upset stomach (Indigestion) or abdominal pain | | | | |
| Changes in bowel – constipation and or diarrhea | | | | |
| Chest pain or rib soreness | | | | |
| Shortness of breath or persistent cough | | | | |
| Heart palpitations or skipping heart | | | | |
| Stiffness of the back | | | | |
| Muscle pain, shooting pains or cramps | | | | |
| Twitching of face or other muscles | | | | |
| Headaches | | | | |
| Neck stiffness and or shooting pain arms | | | | |
| Tingling, numbness and or skin sensitivities | | | | |
| Facial paralysis or Bell's palsy | | | | |
| Joint pain or swelling | | | | |
| Vision – double, blurry, increased floaters and or light sensitivity | | | | |
| Ear or hearing – buzzing, ringing, pain, sound sensitivity | | | | |
| Light headedness, dizziness, unavoidable need to sit down | | | | |
| Tremor | | | | |
| Confusion and or difficulty thinking | | | | |
| Difficulty concentrating and or reading | | | | |
| Forgetfulness, short term memory loss, poor attention | | | | |
| Disorientation, getting loss and or going to wrong places | | | | |
| Difficulty with speech, or writing or name forgetting | | | | |
| Mood swings, irritability and or depression | | | | |
| Disturbed sleep, night awakening and or early awakening | | | | |
| TOTAL | | | | |

Prof Sam Shor (USA) Lyme Tick Borne Diseases Symposium 2014

 Patient Signature _____

# **Cytokine (Metabolic) Storm** associated with **multisystem inflammatory cascade.**

## But Cytokine Storm Masks the Injury Site

Cytokine Storm makes the entire body looks inflamed, injured and infected


CytoSorbents 24

## Cytokine Storm Is Common in the ICU

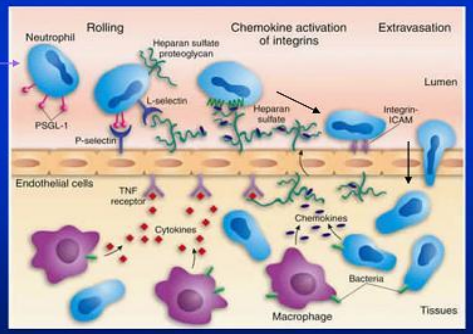

Cytokine Storm

CytoSorbents 14

## Cytokine Storm Also Causes "Immune Confusion"

An injury or infection usually leads to the local production of cytokines. Normally, these cytokines allow white blood cells to home in on the infection and migrate from the blood stream into the affected area.

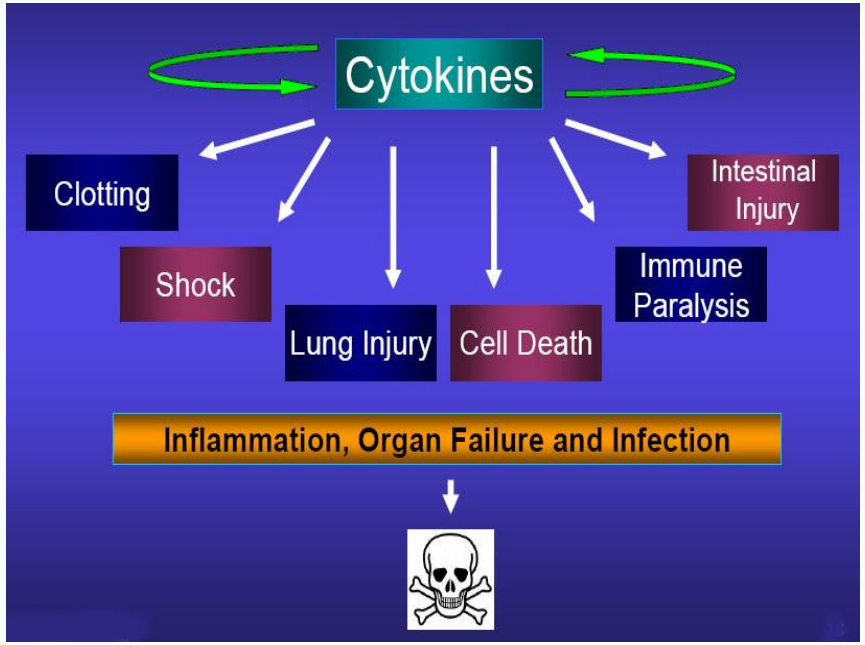
White Blood Cell

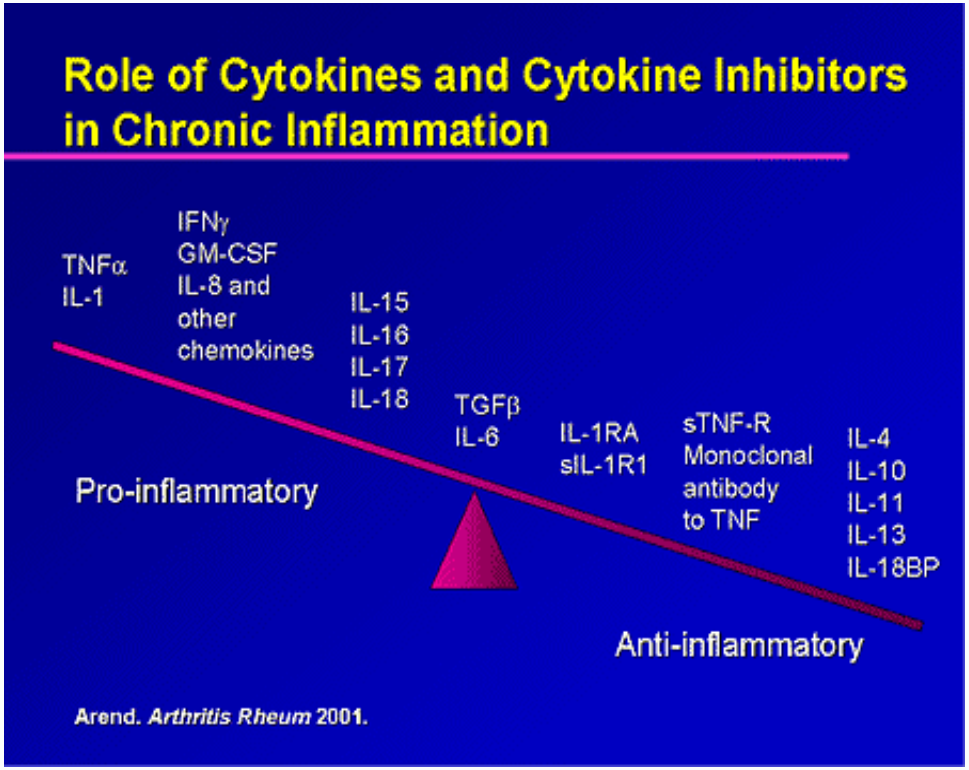


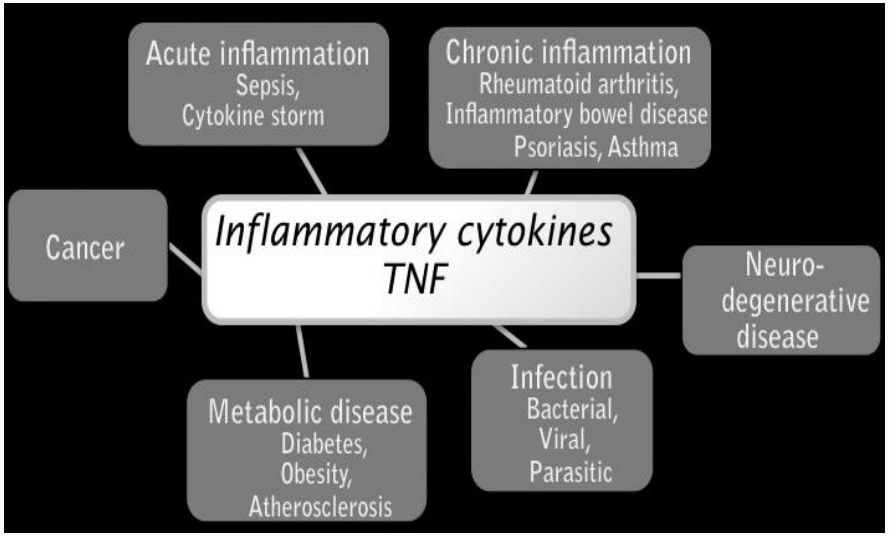

Blood Vessel (blood flow ⟶)

Tissue

CytoSorbents 23



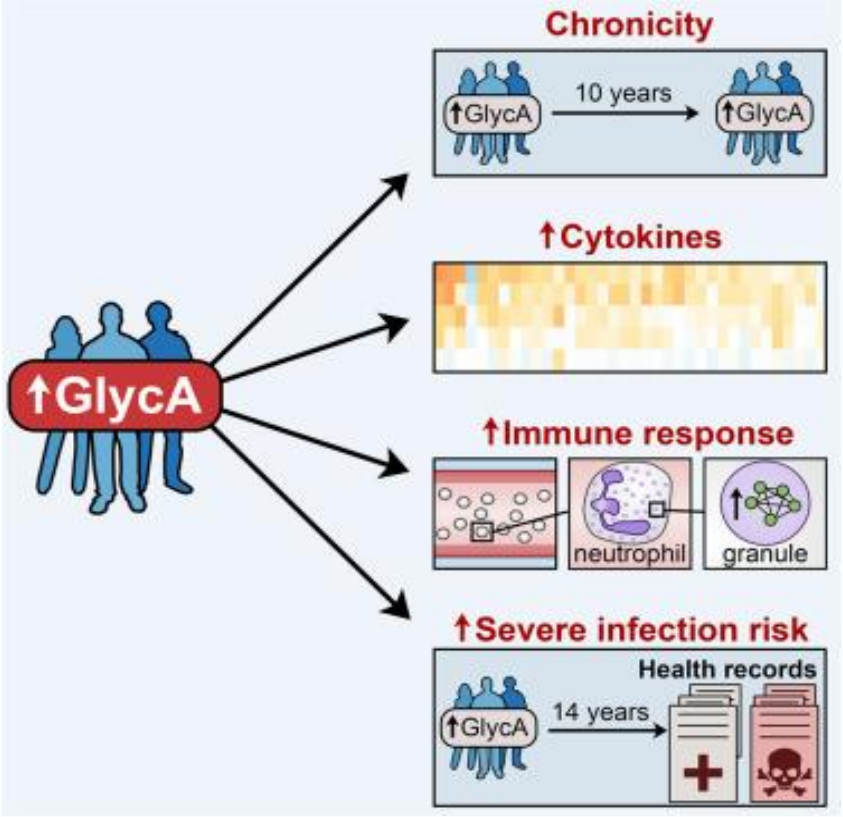


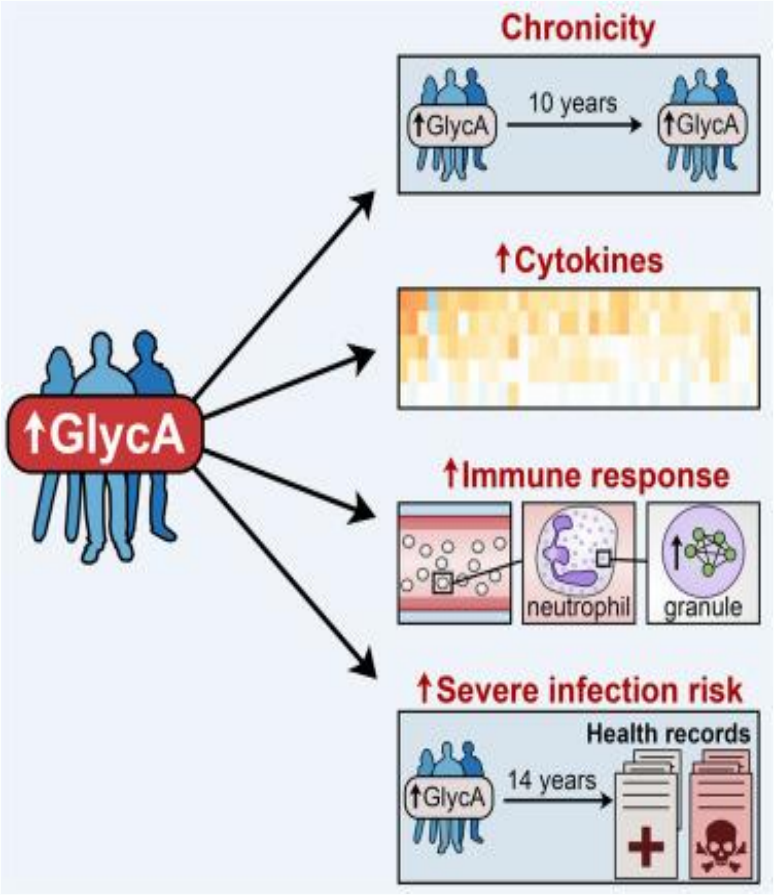




**S100B - Astrocyte Neurotrophic Cytokine**

S100B is a useful **neurobiochemical marker of brain damage** such as in circulatory arrest, stroke and traumatic brain injury. S100B is also associated with neurodegenerative diseases like Alzheimer's disease or other chronic neurological diseases.

**GlycA – The Biomarker GlycA (Glycoprotein Acetylation)** is associated with **chronic inflammation and predicts long term risk of severe infection.** Elevated GlycA in acute v chronic and myriad cascade of inflammatory cytokines. **Mortality within 14-years.** Ritchie et al, Cell Systems P293-301 Elsevier 2015.






**GlycA – The Biomarker GlycA (Glycoprotein Acetylation) is associated with chronic inflammation and predicts long term risk of severe infection.**
Ritchie et al 2015 Cell Systems P293-301 Elsevier 2015.

- Elevated GlycA in apparently **healthy patients** – for greater than **10-years is associated with chronic low grade inflammation.**
- Elevated GlycA was stable for up to a decade.
- GlycA marked the levels of **myriad inflammatory cytokines in circulation – Cytokine Storm.**
- A **gene network enriched for neutrophil** functions was associated with GlycA.
- GlycA strongly predicted **future risk of infection; increased hospitalisation and death from diverse infections within 14-years** – particularly **septicaemia and pneumonia** – that persists over a decade.
- Healthy individuals with elevation GlycA have persistent but clinically silent - **low grade chronic inflammation that mimics an antimicrobial response and myriad cascade of inflammatory cytokines.**

## Autoimmune diseases

Ankylosing spondylitis

Multiple sclerosis

Eczema

Hidradenitis suppurativa

Inflammatory bowel disease

Atopic dermatitis

Rheumatoid arthritis

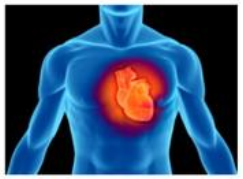
Psoriasis

Sarcoidosis

Scleroderma

Systemic lupus erythematosus

## Cardiovascular diseases



Atherosclerosis

Myocardial infarction

**TNF-α**

## Neurologic diseases

Alzheimer's disease

Epilepsy

Bipolar disorder

Parkinson's disease

Depression

## Osteoporosis

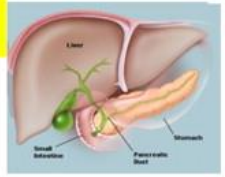
## Cancer

## Non-alcoholic fatty liver disease

## Metabolic diseases

Obesity

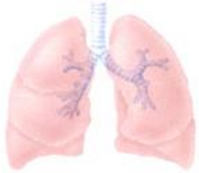
Diabetes, type 2



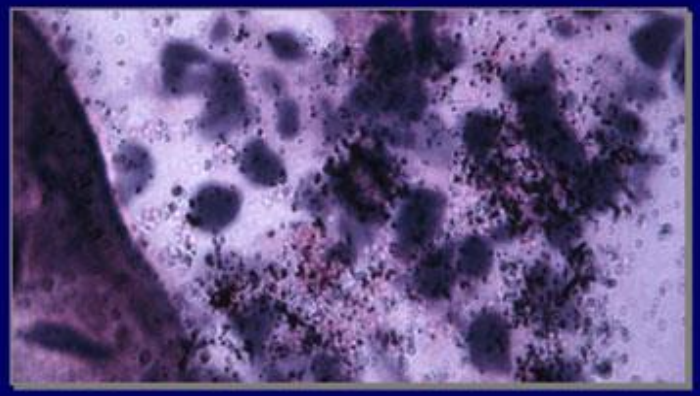
## Pulmonary diseases

Asthma

Chronic obstructive pulmonary disease

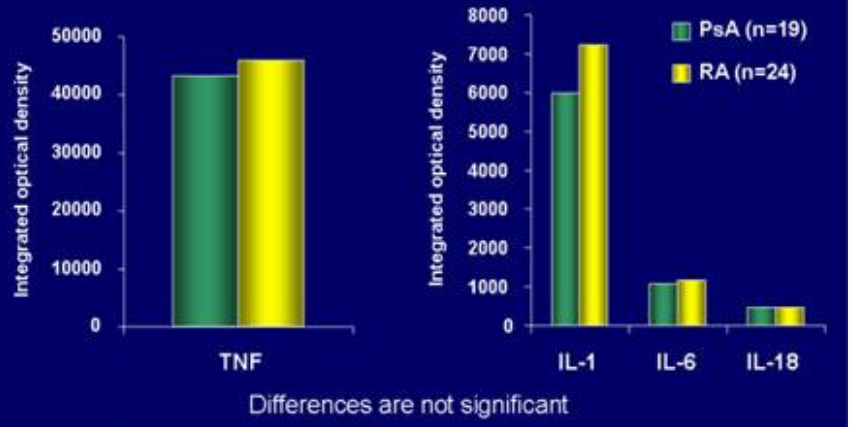


## TNF-alpha mRNA in a Sacroiliac Biopsy



Braun J. et al. *Arthritis Rheum.* 1995;38:499-505.

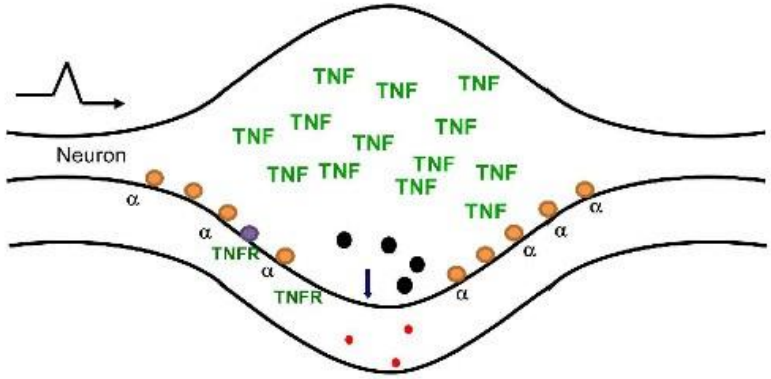
## Overexpression of Proinflammatory Cytokines in Inflamed Synovium



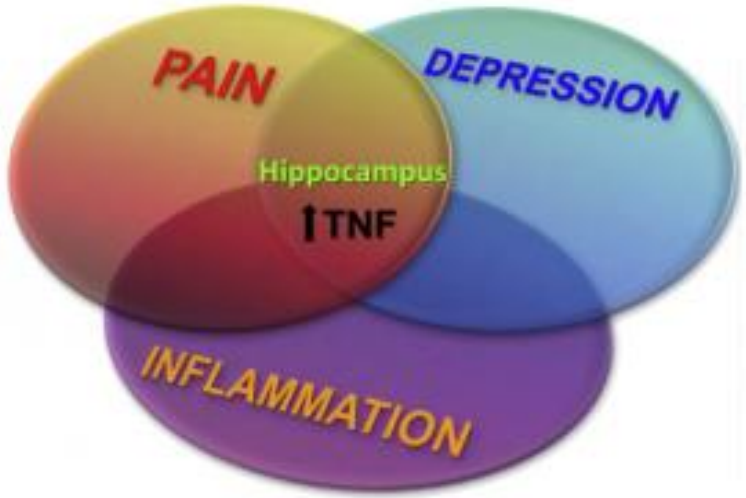

Differences are not significant

van Kuijk AWR, et al. Ann Rheum Dis. 2006;25; [Epub ahead of print] .

## Chronic Pain

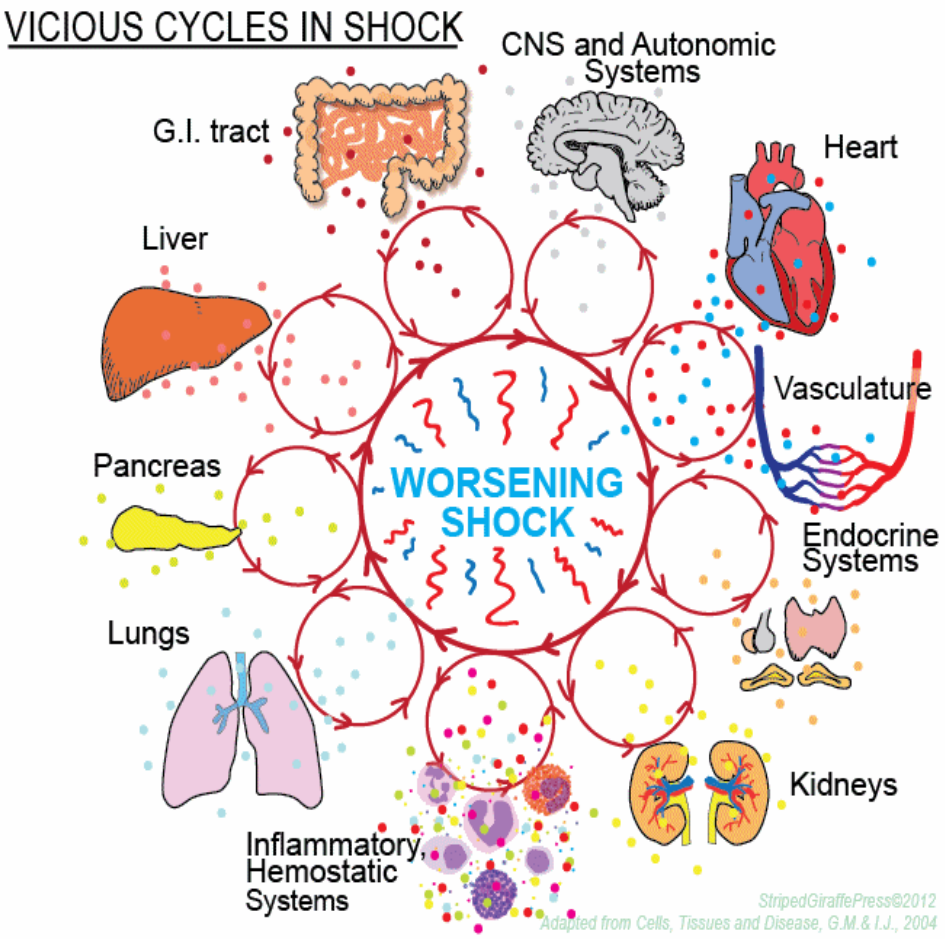


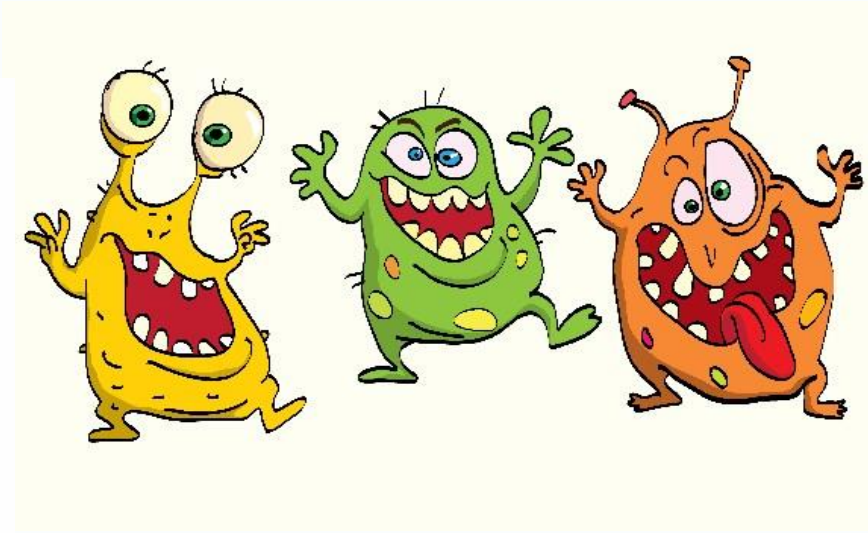

Post-synaptic Cell




Fasick, V., et al., The hippocampus and TNF: Common links between chronic pain and depression. Neurosci. Biobehav. Rev. (2015)

# The Typical Hyperbaric Patient – ‘the last hope’

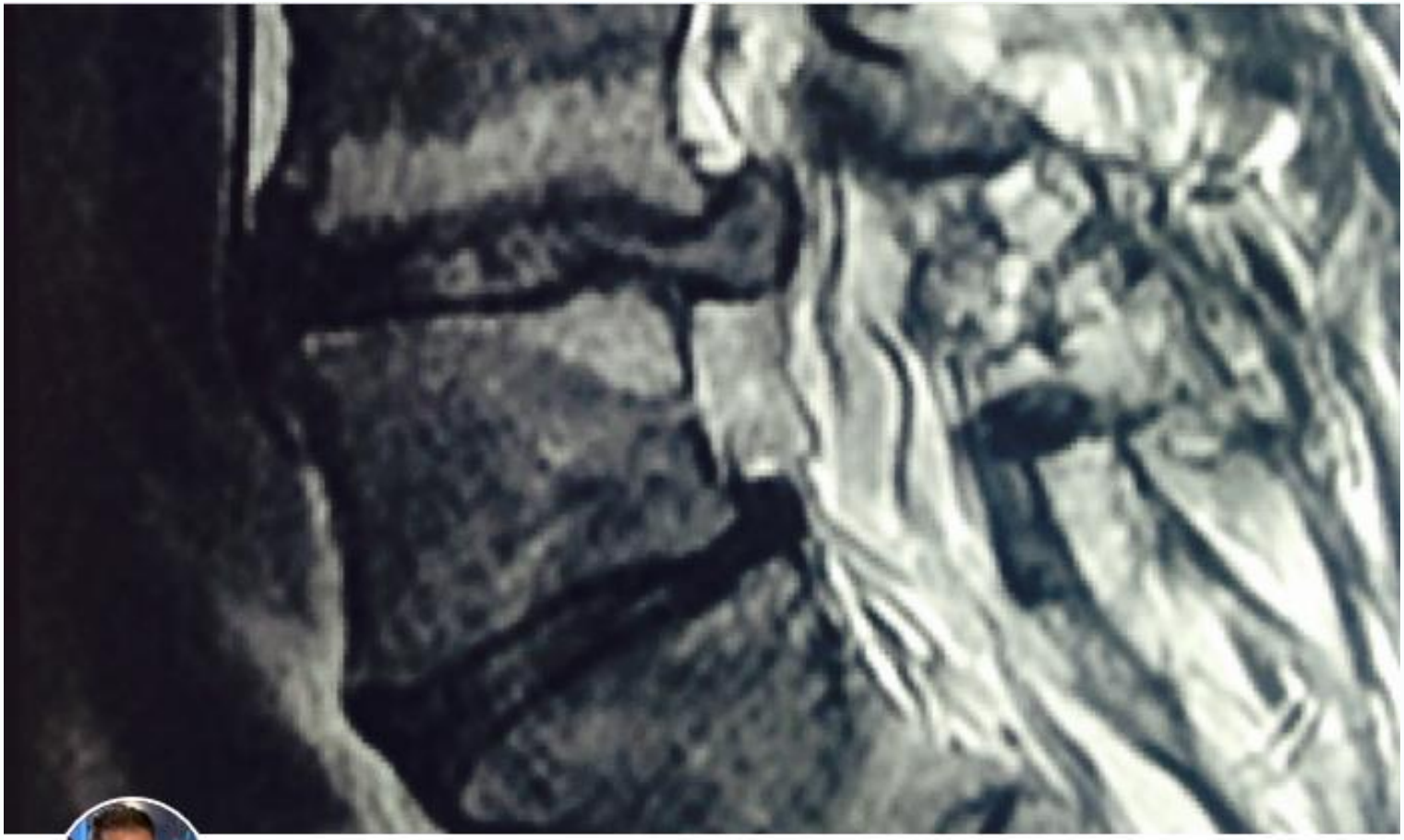


"Nurse, get on the internet, go to SURGERY.COM, scroll down and click on the 'Are you totally lost?' icon."

# CytoSorb®

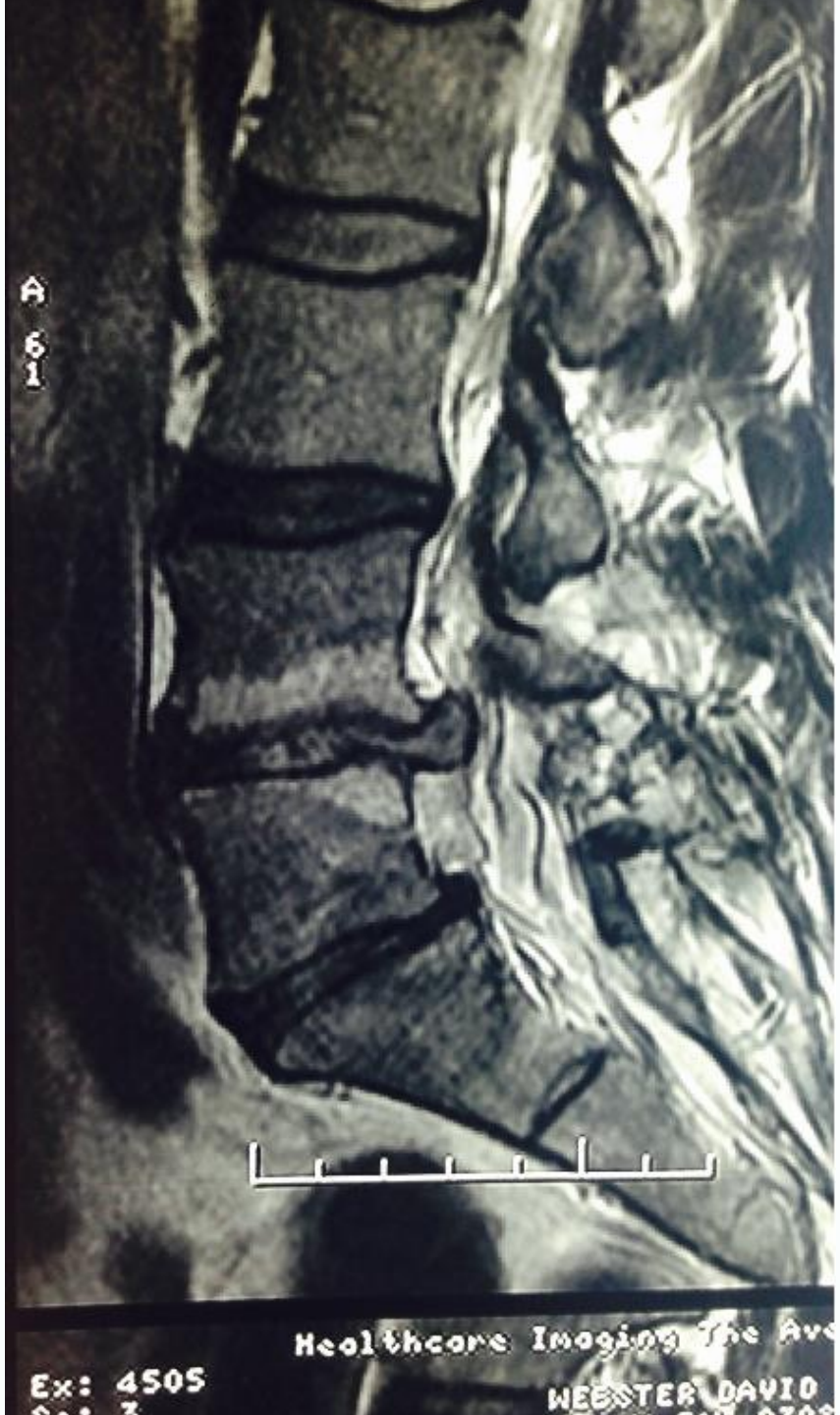
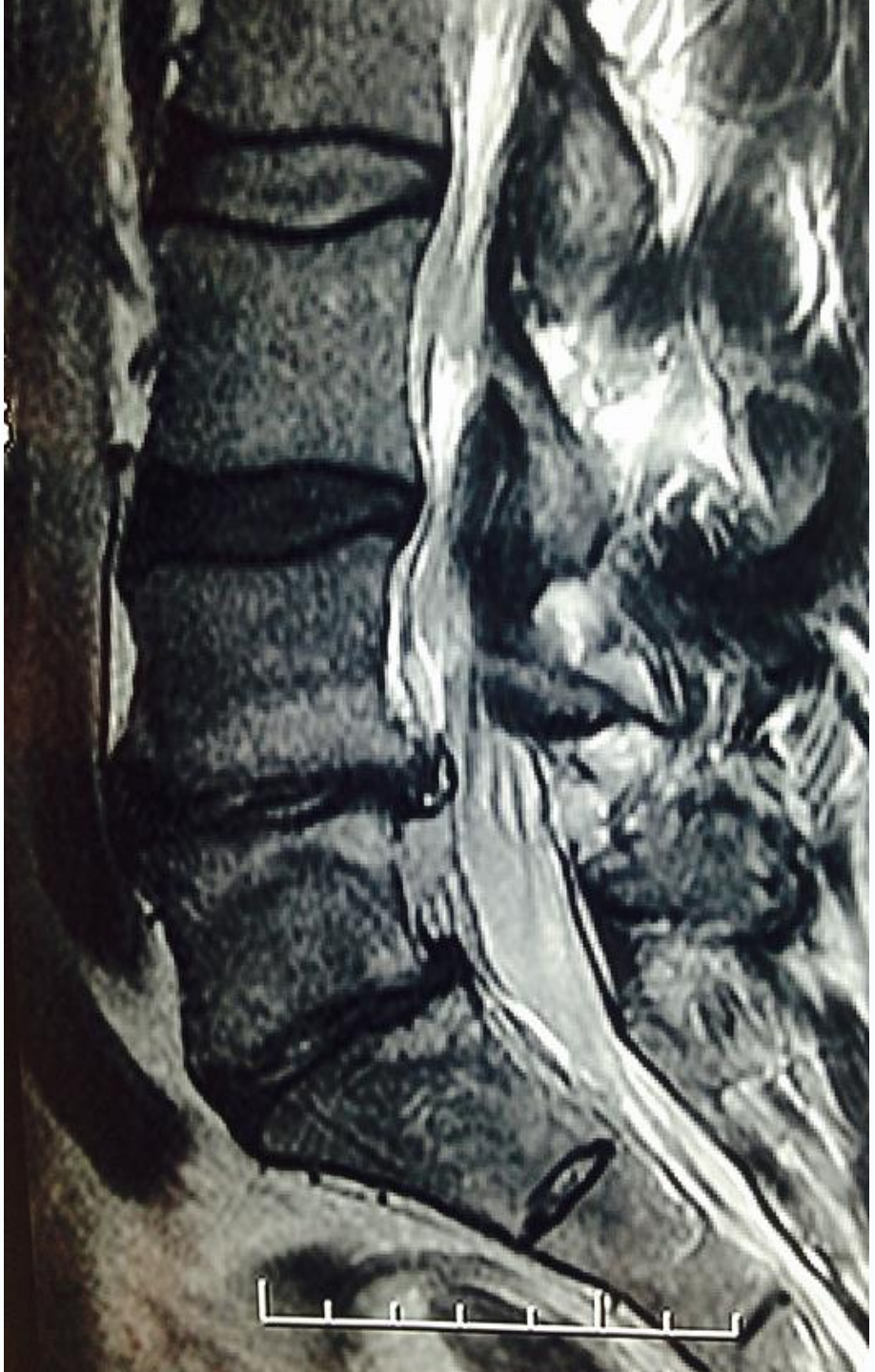
## A powerful new weapon in the fight against Cytokine Storm



Mal Hooper
HyperMED | OXYMED Australia | OXYGEN100 - Heal
The Warriors

Edit post View stats

# Hyperbaric Oxygen Impacts Failed Back Surgery - Cytokines, Interleukins Case Study - Mr DW


A
61
Healthcare Imaging
Ex: 4505
WEBSTER DAVID


NutriPATH
Integrative Pathology Services

P: 1300 688 522
E: info@nutripath.com.au
A: PO Box 442 Ashburton VIC 3142

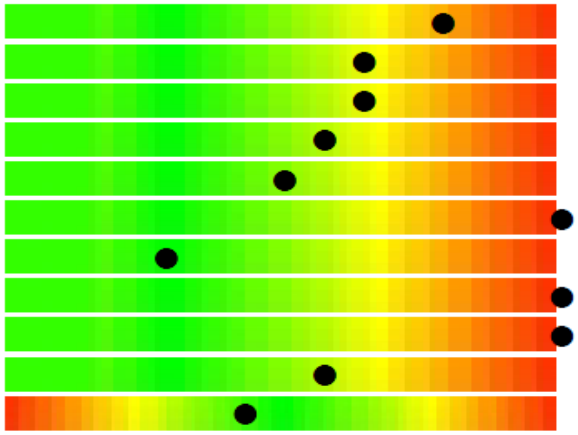
Date of Birth : 18-Mar-1961
Sex : M
Collected : 29-Jan-2015

Lab id: **3378314** UR#:

HYPERMED
643 CHAPEL STREET
SOUTH YARRA VIC 3141

## INTEGRATIVE MEDICINE

| BLOOD - SERUM | Result | Range | Units |
|---|---|---|---|
| **Hyperbaric Oxygen Therapy (HBO)** | **100.0** | | Hours |
| **CYTOKINES,Extensive Panel** | | | |
| **Interleukin 1** | **2.7** | 0.0 - 2.8 | pg/mL |
| **Interleukin 6** | **7.8** | 0.0 - 11.0 | pg/mL |
| **TNFa** | **10.56** | 0.00 - 13.00 | pg/mL |
| **TNFb** | **89.0** | 0.0 - 156.0 | pg/mL |
| **Interleukin 2** | **4.8** | 0.0 - 10.0 | pg/mL |
| **Interleukin 4** | ***40.2* *H** | 0.0 - 19.0 | pg/mL |
| **Interleukin 5** | **1.1** | 0.0 - 13.0 | pg/mL |
| **Interleukin 10** | ***12.1* *H** | 0.0 - 7.0 | pg/mL |
| **Interleukin 13** | ***12.6* *H** | 0.0 - 6.0 | pg/mL |
| **INFg** | **18.8** | 0.0 - 28.0 | pg/mL |
| **TGFb** | **43.0** | 28.0 - 64.0 | pg/mL |



**Mr DW: History prior to HBOT - 2 Failed Back Surgeries (L4/5 laminectomy and discectomy), Pain Management. Mr DW's Orthopaedic Surgeon recommended block fusion L3-S1.**

**Cytokine Profile - not available prior to Mr DW undertaking HBOT.**

- At 100-hours HBO Mr DW is virtually symptom free.
- **IL4 is markedly elevated 40.2 (0-19). IL10 & IL13 are also on the rise.**
- IL4 is anti-inflammatory cytokine and responsive to **neuropathic ischemic pain** i.e reflex sympathetic dystrophy, complex regional pain syndromes etc.

BLOOD

*The Journal of The American Society of Hematology*

VOL 77, NO 9 MAY 1, 1991

REVIEW ARTICLE

## Interleukin-4: A Prototypic Immunoregulatory Lymphokine

By William E. Paul

- IL4 is a pleiotropic cytokine and a potent lymphoid cell growth factor that stimulates the growth and survivability of certain B cells and T cells. **IL-4 ameliorates non-resolving neuro-inflammation that causes neuropathic pain** after nerve injury (crush injury).
- The interleukin 4 receptor also binds to IL13 and may contribute to many overlapping functions of IL4 and IL13.
- IL-4 has striking **antitumor activities** raise the possibility that IL-4 or potential small molecule agonists may be potent biologic agents to **enhance immune elimination of certain tumor cells.**
- It is closely related and has functions similar to **IL10 & IL13.**

Pain. 2015 Jan 27. [Epub ahead of print]

**Peripheral interleukin-4 ameliorates inflammatory macrophage-dependent neuropathic pain**

Kiguchi N[1], Kobayashi Y, Saika F, Sakaguchi H, Maeda T, Kishioka S.
[1]aDepartment of Pharmacology, Wakayama Medical University, 811-1 Kimiidera, Wakayama 641-0012, Japan bDepartment of Pharmacology, Niigata University of Pharmacy and Applied Life Sciences, 265-1 Higashijima, Niigata 956-8603, Japan.

**Abstract**

There is increasing evidence that **inflammatory (M1-polarized) macrophages drive the non-resolving neuroinflammation that causes neuropathic pain after nerve injury.**

- **Interleukin-4 (IL-4) promotes the suppressive (M2-polarized) state in macrophages** and ameliorate M1 macrophage-dependent neuropathic pain.
- Perineural administration of IL-4 in mice ameliorated development and maintenance of tactile allodynia and thermal hyperalgesia.

We found that **neuropathic pain can be ameliorated by IL-4 treatment**, which exerts its therapeutic effect on accumulating macrophages via a STAT6-dependent pathway.
A shift in macrophage phenotype from the inflammatory to the suppressive phenotype-driven by IL-4R signaling-may have benefits in the treatment of neuropathic pain.

Anesth Analg. 2011 Sep;113(3):626-33. Epub 2011 May 19.

**Hyperbaric Oxygen Therapy alleviates chronic constrictive injury-induced neuropathic pain and reduces tumor necrosis factor-alpha production.**

Department of Anesthesiology, Upstate Medical University, Syracuse, NY, USA.

The development of hyperalgesia and allodynia after **chronic constrictive injury (CCI) is associated with increased tumor necrosis factor (TNF)-α and interleukin (IL)-1β.** Recently, a beneficial effect of hyperbaric oxygenation therapy (HBOT) in the treatment of pain disorders. Our study examined the hypotheses that (1) CCI-induced neuropathic pain may be associated with increased production of TNF-α and IL-1β, (2) HBOT may alleviate CCI-induced neuropathic pain, and (3) the alleviated neuropathic pain may be associated with reduced production of TNF-α and/or IL-1β.

**METHODS:**

HBO rats (n =18) exposed to pure oxygen for **1 hour at 2.4 atm once a day.** Non-HBO (n =18) and sham rats (n =6) were placed in the HBOT chamber breathing air. **TNF-α and IL-1β in the sciatic nerve were assayed with ELISA.** The presence of TNF-α protein in homogenates was verified by Western blot analysis.

**CONCLUSION:**

- HBOT alleviates CCI-induced neuropathic pain and inhibits endoneuronal TNF-α production, but not IL-1β in CCI-induced neuropathic pain.
- **Reduced TNF-α production may contribute to the beneficial effect of HBOT.**

**The Inflammatory Milieu of the Degenerate Disc: is Mesenchymal Stem Cell-Based Therapy for Intervertebral Disc Repair a Feasible Approach?**

Curr Stem Cell Res Ther. 2015 Feb 11. 1McGill University Health Centre, Department of Surgery, Montreal General Hospital, Abstract

- **Intervertebral disc degeneration is directly linked to chronic low back pain** a condition that affects multitudes of people worldwide with tremendous direct and indirect health costs. **Water-loss, inflammation, disruption of the extracellular matrix ultimately result in loss of tissue function and associated pain.** Cytokines present in degenerate tissue can upregulate protease activity and directly causes pain.
- Non-invasive therapies provide limited efficacy for pain management, and surgical intervention is often required. Disc removal can offer immediate pain-relief, however degeneration of adjacent segments can occur and pain can return.
- Stem cell therapy is investigated as a means to repair degenerating discs. **However, few studies have addressed whether stem cell therapies can modulate the inflammatory microenvironment or whether cytokines can affect the ability of the implanted cells to repair damaged tissue.** This review focuses on mechanisms of **disc degeneration and the role of an inflammatory milieu in this process.**
- **Stem cell differentiation can be negatively influenced by inflammatory cytokines**; stem cells can potentially have anti-inflammatory effects.
- Further investigation of stem cell interactions with the inflammatory microenvironment is required, and that ***priming of stem cells*** **under various conditions may be necessary for optimal therapeutic value for intervertebral disc repair and pain reduction.**

# Athletes and the Growing Injury List

NutriPATH
Integrative Pathology Services

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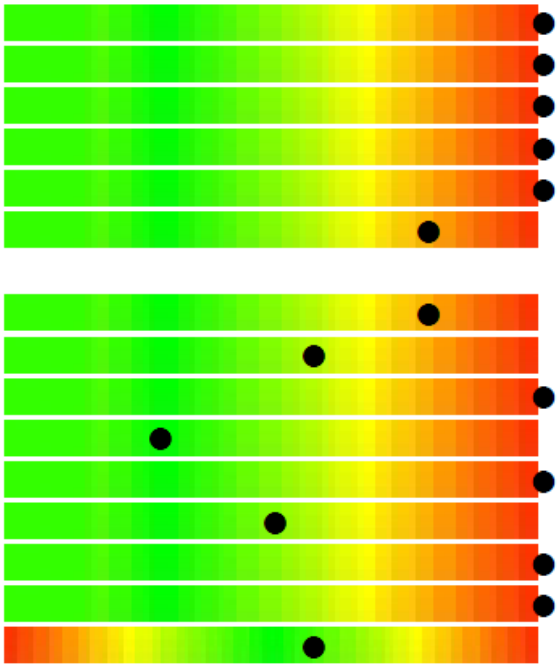
E: info@nutripath.com.au
A: PO Box 442 Ashburton VIC 3142

Date of Birth : 29-Apr-1978
Sex : M
Collected : 20-Jan-2016
C/O HYPERMED 643 CHAPEL STREET
SOUTH YARRA VIC 3141
Lab id: **3413608** UR#:

HYPERMED
643 CHAPEL STREET
SOUTH YARRA VIC 3141

## INTEGRATIVE MEDICINE

| BLOOD - SERUM | Result | Range | Units |
|---|---|---|---|
| **Hyperbaric Oxygen Therapy (HBO)** | **0.0** | | Hours |
| **CYTOKINES,Extensive Panel** | | | |
| **ProInflammatory Cytokines (TH1)** | | | |
| Interleukin 1 | ***161.0* *H** | 0.0 - 2.8 | pg/mL |
| Interleukin 6 | ***35.0* *H** | 0.0 - 11.0 | pg/mL |
| Interleukin 7 | ***23.3* *H** | 0.0 - 16.0 | pg/mL |
| Interleukin 8 | ***>2500.0* *H** | 0.0 - 28.0 | pg/mL |
| TNFa | ***39.10* *H** | 0.00 - 13.00 | pg/mL |
| TNFb | **149.0** | 0.0 - 156.0 | pg/mL |
| **AntiInflammatory Cytokines (TH2)** | | | |
| GM-CSF | **77.7** | 0.0 - 80.0 | pg/mL |
| Interleukin 2 | **6.8** | 0.0 - 10.0 | pg/mL |
| Interleukin 4 | ***26.2* *H** | 0.0 - 19.0 | pg/mL |
| Interleukin 5 | **1.6** | 0.0 - 13.0 | pg/mL |
| Interleukin 10 | ***10.1* *H** | 0.0 - 7.0 | pg/mL |
| Interleukin 12 | **7.5** | 0.0 - 14.0 | pg/mL |
| Interleukin 13 | ***13.2* *H** | 0.0 - 6.0 | pg/mL |
| INFg | ***75.2* *H** | 0.0 - 28.0 | pg/mL |
| TGFb | **50.6** | 28.0 - 64.0 | pg/mL |



**Actual Elite Athlete**

- Cytokine Blood test of an **36 year old male athlete entering the 'business end'** after a long and successful career. Note the marked elevation of pro-inflammatory cytokines. Undoubtedly the physical and mental toll of competing at the high end level of sports culminates with the never ending list of chronic injuries.
- However when the athlete retires instead of just sitting back and enjoying their success invariably they are now confronted with managing potentially serious health issues as a results of years of cytokine abuse.

- IL8 (>2500, ref 0-28) is an inflammatory cytokine linked with **systemic vascular inflammation and erosion.**

- 'TNFα is a cytokine produced by white blood cells which acts as the master regulator of the human inflammatory response.'
- **Chronic neuropathic pain includes elevated levels of the cytokine tumor necrosis factor-alpha (TNF) in the hippocampus**; area of the brain most notable for its role in learning and memory formation, plays a fundamental role in pain sensation.
- Neurogenesis refers to the growth and development of neurons. Research has shown that the human **hippocampus retains its ability to generate neurons throughout life.**
- **Hippocampal atrophy associated with many brain diseases, including depression, psychosis, addiction and dementia.**

# Athletes and the Growing Injury List

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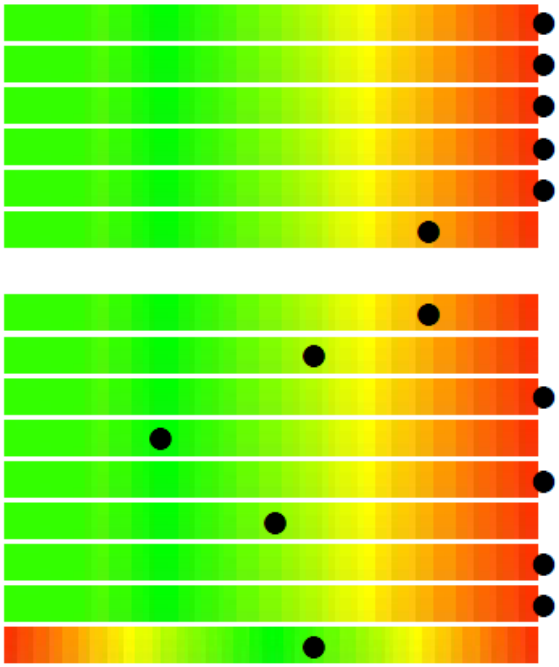


Cardiovascular Research (2009) 84, 353–360
doi:10.1093/cvr/cvp241

Review

# Interleukin 8 and cardiovascular disease

**Stavros Apostolakis, Konstantina Vogiatzi, Virginia Amanatidou, and Demetrios A. Spandidos***

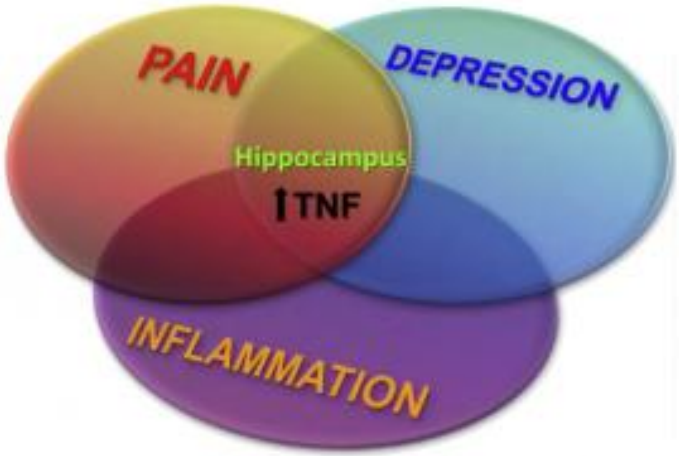
*Laboratory of Clinical Virology, Faculty of Medicine, University of Crete, 71409 Heraklion, Crete, Greece*

Received 9 May 2009; revised 1 July 2009; accepted 8 July 2009; online publish-ahead-of-print 18 July 2009

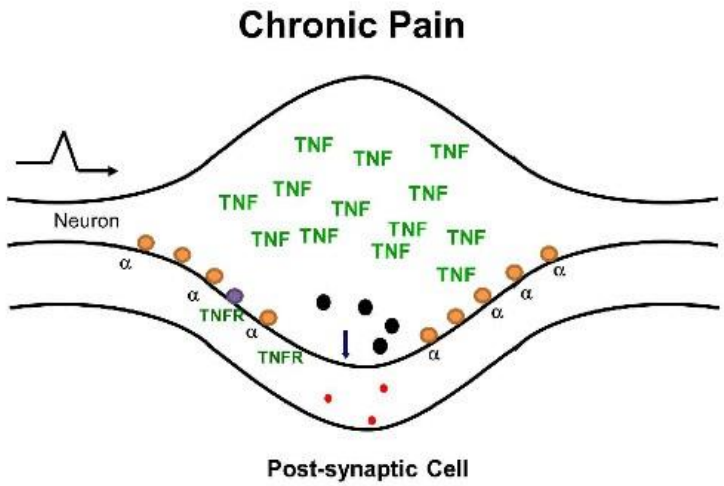
Time for primary review: 27 days

**KEYWORDS**
Chemokines;
Interleukin 8;
Cardiovascular disease;
Biochemical markers

Since the establishment of the inflammatory basis of atherosclerosis, several pro- or anti-inflammatory agents have been examined as potential mediators of the biochemical pathways of lesion formation. Interleukin (IL)-8 was first characterized in 1987. Since then, knowledge regarding its role in leucocyte trafficking and activation has advanced rapidly, especially in the field of cardiovascular disease. In the scientific literature, there is sufficient evidence to support beyond any doubt the involvement of IL-8 in the establishment and preservation of the inflammatory micro-environment of the insulted vascular wall. However, how the information derived from *in vitro* studies and animal models can be applied in clinical practice has yet to be determined. In the present review, the available evidence regarding the role of IL-8 in cardiovascular disease is presented, and future perspectives are discussed.




Fasick, V., et al., The hippocampus and TNF: Common links between chronic pain and depression. Neurosci. Biobehav. Rev. (2015)



**Efrati - Hypoxic Altitude Training - Risks Associated**

Crit Care. 2015 Sep 1;19(1):307. doi: 10.1186/s13054-015-1034-2.

Oxygen - a limiting factor for brain recovery & performance

Hadanny A[1,2], Efrati S[3,4,5,6].

[1]Sagol Center for Hyperbaric Medicine and Research, Assaf Harofeh Medical Center, Zerifin, 70300, Israel.

**Abstract Summary**

Effective brain metabolism is highly dependent on a narrow therapeutic window of oxygen. In major insults to the brain (e.g., intracerebral hemorrhage), **slight decrease in oxygen supply, as occurs in a hypobaric environment at high altitude, has devastating effects on the injured and performing brain tissue.**

- Conversely, increasing brain oxygenation, by the use of hyperbaric oxygen therapy, can **improve brain metabolism and its dependent regenerative & recovery processes.**

**In Flight Hypoxia (Long Haul Flights) Induces Inflammatory Cytokines In IBS**

Dig Dis. 2016;34(1-2):78-83. Epub 2016 Mar 16.

Vavricka SR[1], Rogler G, Biedermann L.

[1]Division of Gastroenterology and Hepatology, Triemli Hospital, Zurich, Switzerland.

**Abstract**

The importance of environmental factors in the pathogenesis including their disease-modifying potential are increasingly recognized in **inflammatory bowel disease (IBD)** patients, largely driven by the perception that the prevalence and incidence of IBD are on the rise within the last few years, especially in non-western countries.

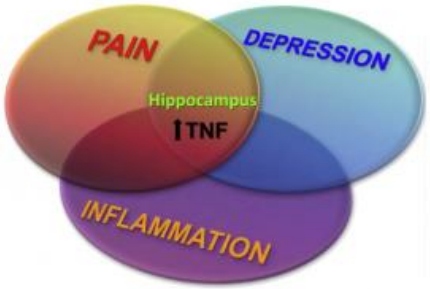
One of those factors is believed to be hypoxia. The role of hypoxia as a modifying or even causative factor in the genesis and maintenance of inflammation has been increasingly elucidated in recent years. **Hypoxia is believed to be a main inducing factor of inflammation.** This has been studied in different animal experiments as well as in humans exposed to hypoxia. In several studies **animals exposed to short-term hypoxia accumulated inflammatory cells in multiple organs and showed elevated cytokines in the blood.**

The study participants underwent a 3-hour exposure to hypoxic conditions simulating an altitude of 4,000 m above sea level

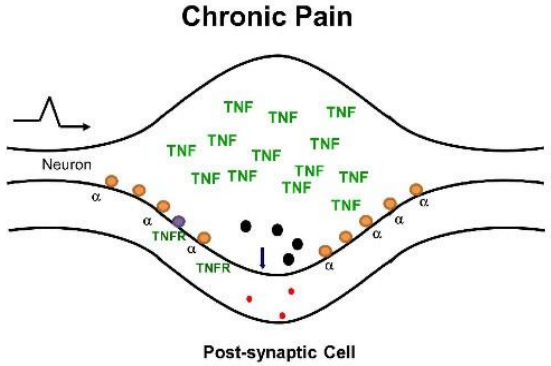
- According to these findings, we concluded that **aircraft flights and stays at high altitudes** are a risk factor for increased disease activity in IBD.

**Tumor Necrosis Factor-alpha**

- TNFα is a cytokine produced by white blood cells which acts as the master regulator of the human inflammatory response. **Proinflammatory TNF is a key mediator of chronic neuropathic pain pathogenesis.**
- TNF is elevated at sites of neuronal injury, in the spinal cord, and supraspinally during the initial development of pain.
- The hippocampus, an area of the brain most notable for its role in learning and memory formation, plays a fundamental role in pain sensation. Neurogenesis refers to the growth and development of neurons. Research has shown that the human hippocampus retains its ability to generate neurons throughout life.
- **Elevated TNF in the hippocampus results in atrophy** and is associated with many brain diseases, including depression, psychosis, addiction and dementia. Animal studies demonstrate that infusion of a anti-TNFα adjacent to the hippocampus completely alleviated pain.
- **Elevated pro-inflammatory markers Cytokines (IL1, IL6, IL7, IL8) and TNFα** are linked with chronic and progressive neurodegenerative disease - **Cytokine Storm** leading to multisystem inflammatory cascade (autoimmune erosion). The body due to autoimmune (confusion) dysfunction - attacks itself.




Fasick, V., et al., The hippocampus and TNF: Common links between chronic pain and depression. Neurosci. Biobehav. Rev. (2015)



**Effects of TNF-alpha in Neurologic disorders?**

- Excess TNF-alpha in the brain and spinal cord can disrupt synaptic communication. **Excess TNF-alpha triggers a cycle** whereby **toxic amyloid-beta** is produced. This results in greater levels of pro-inflammatory TNF-alpha.

- Increasing laboratory evidence implicate TNF-alpha in inflammatory molecular mechanisms producing **neurotoxicity, neuronal death, or neuronal dysfunction**. Elevated TNF-alpha has been linked with many **neurovascular and autoimmune disorders.**

**Etanercept is a TNFα blocker – E. TOBINICK**

- **Etanercept (Enbrel)** is a fusion of two proteins naturally occurring in the human body that was developed to treat various inflammatory diseases by **binding to TNF-alpha, effectively neutralizing its ability to act on cell membranes.**
- Enbrel treatment has a rapid effect, reversing cognitive impairment, and validating the role excess TNF-alpha has in the Alzheimer's disease and autoimmune TNFa related process. Brain dysfunction including neurodegenerative disorders such as Alzheimer's involve inflammatory disease of the brain.

- **Reducing neuroinflammation results in improvements in memory, mood, and cognitive function.**
- Etanercept is a powerful anti-inflammatory agent. The administration of **perispinal Etanercept can result in rapid and dramatic improvements in cognitive function in persons with Alzheimer's disease and numerous other neurodegenerative disorders.**

# Supporting evidence for using Perispinal Etanercept to inhibit TNFα when treating neuropathologies including dementia, chronic stroke, neuropathic pain or traumatic brain injury: Clinical outcomes and role of TNF in neuropathologies other than Alzheimer's Dementia (Part III)

**Stephen J. Ralph [1], Ian Clark [2]**

**1** School of Medical Science, Griffith University, Gold Coast, Australia **2** Research School of Biology, Australian National University, Canberra, Australia

## Abstract

Part III examines the evidence for the involvement of the pro-inflammatory cytokine, Tumour Necrosis Factor-alpha (TNFα) in neuropathologies other than Alzheimer's Dementia (AD), and for using an anti-TNF therapy, Etanercept (ENBREL), to target and treat these health problems, including chronic stroke, neuropathic pain or traumatic brain injury (TBI). All of these can become chronic illnesses and are of major incidence with a grossly unmet need to improve their treatment. The three-part review presents the overwhelming scientific and medical basis as to why research studies and more trials to evaluate the use of the perispinally administered anti-TNFα drug, Etanercept, are justified to allow it to become a front-line standard therapy. Part I established the role of TNFα as a direct regulator of neuronal synaptic activity. It is in this context, as detailed below, that targeting TNF in the brain holds major significance, not only for treating the dementias, but also its great benefits in reducing long term pain during rehabilitation from TBI or chronic stroke. Given the increasing numbers of families afflicted with Alzheimer's disease, chronic stroke, neuropathic pain or TBI, clinical studies are now imperative to improve the treatment of these life-threatening and debilitating illnesses.

**Citation:** Ralph SJ, Clark I (2015) Supporting evidence for using Perispinal Etanercept to inhibit TNFα when treating neuropathologies including dementia, chronic stroke, neuropathic pain or traumatic brain injury: Clinical outcomes and the role of TNF in neuropathologies other than Alzheimer's Dementia (Part III). Healthy Aging Research 4:17. doi:10.12715/har.2015.4.17.

**Received:** December 22, 2014; **Accepted:** January 30, 2015; **Published:** February 24, 2015.



**Competing interests:** The authors have declared that no competing interests exist.

* Email: s.ralph@griffith.edu.au

CNS Drugs (2014) 28:679–697
DOI 10.1007/s40263-014-0174-2

LEADING ARTICLE

# Perispinal Etanercept for Post-Stroke Neurological and Cognitive Dysfunction: Scientific Rationale and Current Evidence

Tracey A. Ignatowski · Robert N. Spengler · Krishnan M. Dhandapani · Hedy Folkersma · Roger F. Butterworth · Edward Tobinick

Abstract : **There is increasing recognition of immune signalling molecule, tumor necrosis factor in the pathophysiology of stroke and chronic brain dysfunction.**

- TNF plays an important role in modulating synaptic function and in the pathogenesis of neuropathic pain.
- **Elevation of TNF & other proinflammatory cytokines without upregulation of anti-inflammatory cytokines were found in post-mortem brain tissue, CSF and blood of TBI** patients. Frugier T, Iflammatory mediators post mortem human brain tissue after TBI. J. Neurotrauma27(3),497–507 (2010). Goodman JC, Pro-inflammatory and pro-apoptotic neuroinflammatory response activated in TBI. Acta Neurochir. (2008).
- **Activated microglia** have been observed in human TBI brains from 3 days after injury. Mannix RC, Traumatic brain injury, microglia, and beta amyloid. Int. J. Alzheimers Dis.2012,608–732 (2012). and, as assessed by PET, showed a **widespread increase in the brain consistent with diffuse neuronal damage 6 months after TBI,** Folkersma H, Widespread and prolonged increase in (R)-(11)CPK11195 binding after traumatic brain injury. J. Nucl. Med.52(8),1235–1239 (2011). and were **enhanced in subcortical regions, but not at the original site of focal brain lesion, up to 17 years after TBI.** Ramlackhansingh AF. Inflammation after trauma: microglial activation and traumatic brain injury. Ann. Neurol.70(3),374–383 (2011)
- Recent observational studies have reported **rapid and sustained improvement in chronic post-stroke neurological and cognitive dysfunction following perispinal administration of Etanercept.**

**Table 1** Rapid improvement in chronic post-stroke neurological dysfunction following perispinal etanercept

| Clinical effect | Manifestations | Reference |
|---|---|---|
| Statistically significant improvements | | |
| Motor function | Increased strength, improved gait, stronger grip. Improvements in swallowing and dysarthria | [4, 5] |
| Spasticity | Decreased muscle tone, improved range of motion, decreased shoulder pain | [4, 5] |
| Sensation | Improved sensation | [4, 5] |
| Cognition | Improvements in cognitive testing scores and executive function | [4, 5] |
| Psychological/behavioral function | Improvements in mood, affect, and behavior. Reductions in depression and anxiety | [4, 5] |
| Aphasia | Improvements in speech and language function | [4, 5]; see also [11] |
| Pain | Reductions in post-stroke pain, including post-stroke shoulder pain and allodynia | [4, 5] |
| Case reports | | |
| Urinary incontinence | Regained bladder sensation and control | [5] |
| Pseudobulbar affect | Reduction in excessive emotionalism | [5] |

- The biological plausibility of these results is supported by independent evidence demonstrating **reduction in cognitive impairment, neuropathic pain, and microglial activation following the use of Etanercept designed to inhibit TNF.**

the NEUROSCIENCE center

PATHFINDER BRAIN SPECT IMAGING

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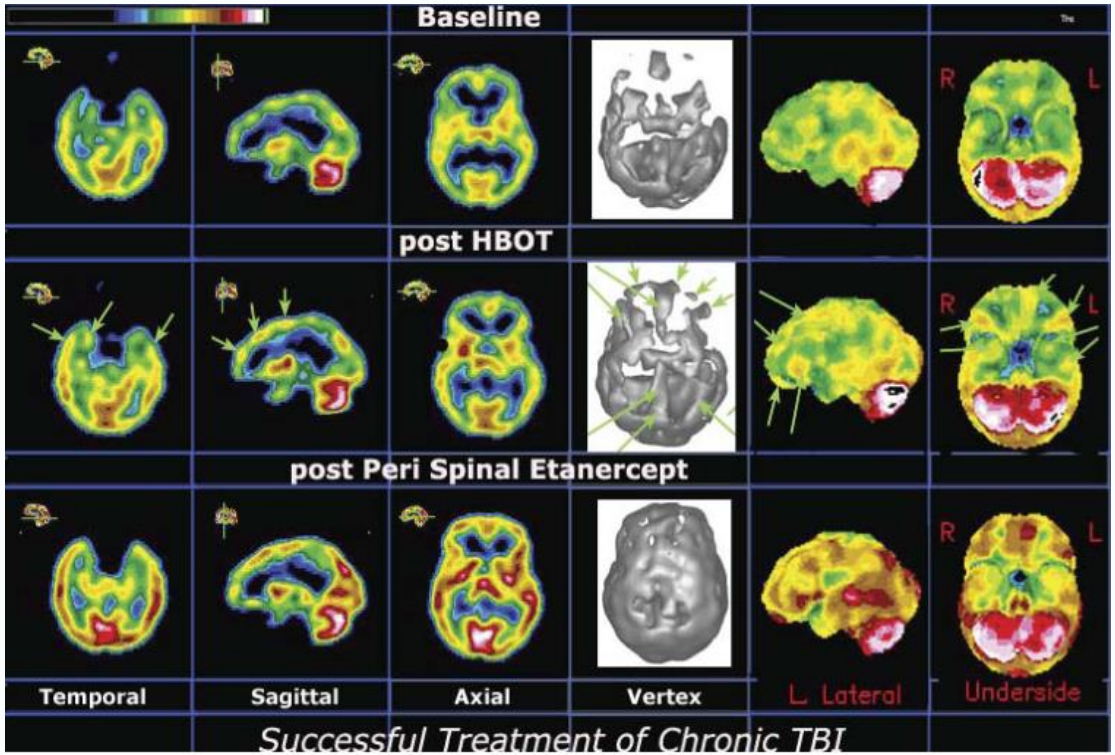
## Perispinal Etanercept Treatment (PSE)

PSE injections allow us to preferentially deliver small amounts of this antibody to the central nervous system (CNS). This in turn can neutralize a prime component contributing to the excessive inflammation caused by Stroke, Post Concussion Syndrome, Traumatic Brain Injury and also by Degenerative diseases.

In addition to causing ongoing damage to the nervous system, chronic inflammation causes a drain of metabolic energy, and also depletes the CNS of monoamines like dopamine, norepinephrine, and serotonin. When used in concert with hyperbaric oxygen therapy (HBOT) we can control inflammation, and stimulate stem cell activity thus improving the likelihood of recovery from the illness at hand.

The PSE technique is simple and practically painless.



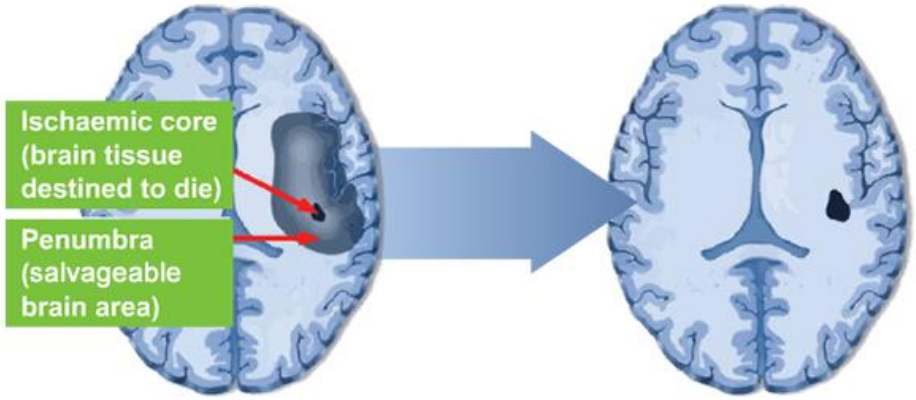

*Successful Treatment of Chronic TBI*

## Perispinal Etanercept Treatment

- Perispinal administration of etanercept, a TNF inhibitor, is a medical treatment used to treat chronic neurological, neuropsychiatric and clinical impairment.
- Perispinal administration is found to enhance etanercept delivery across the blood–CSF barrier.
- Especially effective in cases of chronic stroke and traumatic brain injury (TBI).
- Etanercept has the ability to improve microglial activation and modify the adverse synaptic effects of excess TNF.
- In many cases, people experience significant improvement in motor impairment, spasticity, sensory impairment, cognition, aphasia, pain and psychological/behavioral function.
- The number, and frequency, of doses are tailored to each patient's case.

**Mr GP age 64 Stroke R-sided MCA**
**Pre-HBO**

- **IL8 - 480.8** (0-14) IL8 is an inflammatory cytokine linked with systemic vascular inflammation and erosion
- **IL7 - 23.1** (0-16)
- **TNFα - 82.30** (0-54)

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A: PO Box 442 Ashburton VIC 3142

Date of Birth : 23-Jul-1950
Sex : M
Collected : 08-May-2015
1433 RIDDELL ROAD
RIDDELLS CREEK VIC 3431
Lab id: **3388514** UR#:

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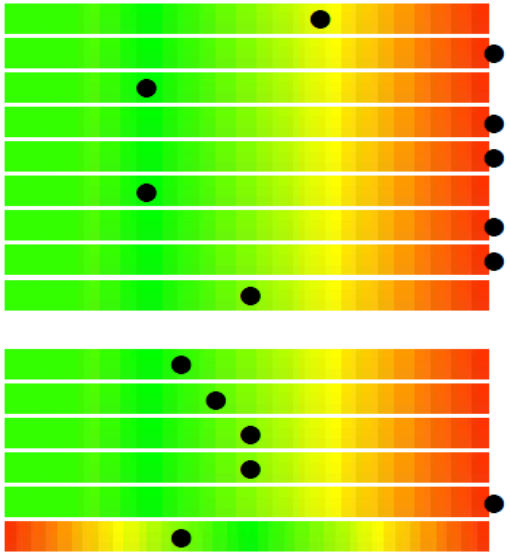
| CYTOKINES,Extensive Panel | | | |
| ProInflammatory Cytokines (TH1) | | | |
| GM-CSF | 64.3 | 0.0 - 88.0 | pg/mL |
| Interleukin 1 | *5.2* *H | 0.0 - 2.8 | pg/mL |
| Interleukin 2 | <1.0 | 0.0 - 10.0 | pg/mL |
| Interleukin 7 | *23.1* *H | 0.0 - 16.0 | pg/mL |
| Interleukin 8 | *480.8* *H | 0.0 - 14.0 | pg/mL |
| Interleukin 12 | <1.0 | 0.0 - 14.0 | pg/mL |
| INFg | *16.0* *H | 0.0 - 3.5 | pg/mL |
| TNFa | *82.30* *H | 0.00 - 54.00 | pg/mL |
| TNFb | 69.3 | 0.0 - 156.0 | pg/mL |
| AntiInflammatory Cytokines (TH2) | | | |
| Interleukin 4 | <3.7 | 0.0 - 19.0 | pg/mL |
| Interleukin 5 | 5.5 | 0.0 - 13.0 | pg/mL |
| Interleukin 6 | 5.6 | 0.0 - 11.0 | pg/mL |
| Interleukin 10 | <3.0 | 0.0 - 6.2 | pg/mL |
| Interleukin 13 | *12.8* *H | 0.0 - 6.0 | pg/mL |
| TGFb | 39.2 | 28.0 - 64.0 | pg/mL |



**Mr GP age 64 Stroke RMCA**
**Pre-HBO**

- **IL8 - 480.8** IL8 is an inflammatory cytokine linked with systemic vascular inflammation and erosion
- **IL7 - 23.1**
- **TNFα - 82.30**

**Mr GP**
**Post-HBO (50 hours)**

- **IL8 – 10.5**
- **IL7 – 12.5**
- **TNFα – 34.7**

NutriPATH
Integrative Pathology Services

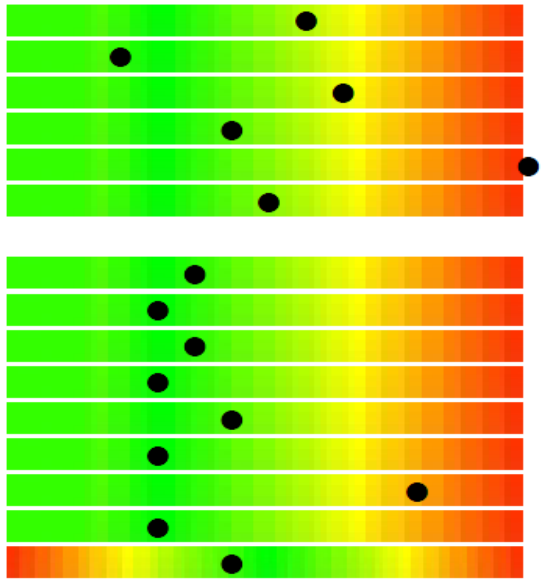
P: 1300 688 522
E: info@nutripath.com.au
A: PO Box 442 Ashburton VIC 3142

Date of Birth : 23-Jul-1950
Sex : M
Collected : 06-Aug-2015
1433 RIDDELL ROAD
RIDDELLS CREEK VIC 3431
Lab id: **3397095** UR#:

HYPERMED
643 CHAPEL STREET
SOUTH YARRA VIC 3141

## INTEGRATIVE MEDICINE

| BLOOD - SERUM | Result | Range | Units |
|---|---|---|---|
| **Hyperbaric Oxygen Therapy (HBO)** | **50.0** | | Hours |
| **CYTOKINES,Extensive Panel** | | | |
| **ProInflammatory Cytokines (TH1)** | | | |
| Interleukin 1 | 1.9 | 0.0 - 2.8 | pg/mL |
| Interleukin 6 | <0.4 | 0.0 - 11.0 | pg/mL |
| Interleukin 7 | 12.5 | 0.0 - 16.0 | pg/mL |
| Interleukin 8 | 10.6 | 0.0 - 28.0 | pg/mL |
| TNFa | *34.70* *H | 0.00 - 13.00 | pg/mL |
| TNFb | 82.6 | 0.0 - 156.0 | pg/mL |
| **AntiInflammatory Cytokines (TH2)** | | | |
| GM-CSF | 20.4 | 0.0 - 80.0 | pg/mL |
| Interleukin 2 | 1.5 | 0.0 - 10.0 | pg/mL |
| Interleukin 4 | <3.7 | 0.0 - 19.0 | pg/mL |
| Interleukin 5 | 2.2 | 0.0 - 13.0 | pg/mL |
| Interleukin 10 | <3.0 | 0.0 - 7.0 | pg/mL |
| Interleukin 12 | 1.7 | 0.0 - 14.0 | pg/mL |
| Interleukin 13 | 5.7 | 0.0 - 6.0 | pg/mL |
| INFg | 4.5 | 0.0 - 28.0 | pg/mL |
| TGFb | 41.0 | 28.0 - 64.0 | pg/mL |
| Cytokines Comment | | | |



**Mr TC age 28: Diffuse Brain Injury (Diffuse Global Gliosis) – MVA 3 years prior to commencing HBO. Cytokine Profile @ HBO 120 hours**

Note evidence of significant Up-Regulation of Anti-inflammatory Cytokines.

- Elevation of IL8 and IL7 NOT seen initially pre HBO is due to Cytotoxic (apoptosis) release from the damaged parts of the brain.
- As HBO penetrates the deeper afflicted neurovascular structures (penumbra and ischemic core) there is a **'dumping release' of inflammatory cytokine toxins, debris and apoptotic cells.** It is common to observe a corresponding elevation of the underlying cytokines and interleukins (IL, 6, IL7, IL8, TNF, S100B) that contributed to the originating injury cascade.

NutriPATH
INTEGRATIVE PATHOLOGY SERVICES

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A: PO Box 442 Ashburton VIC 3142

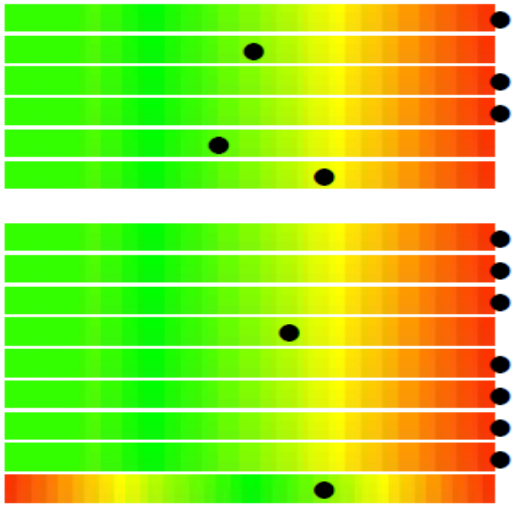
Date of Birth : 14-Feb-1987
Sex : M
Collected : 27-May-2015

Lab id: **3390241** UR#:

HYPERMED
643 CHAPEL STREET
SOUTH YARRA VIC 3141

**INTEGRATIVE MEDICINE**

| BLOOD - SERUM | Result | Range | Units |
|---|---|---|---|
| **Hyperbaric Oxygen Therapy (HBO)** | **120.0** | | Hours |
| **CYTOKINES,Extensive Panel** | | | |
| **ProInflammatory Cytokines (TH1)** | | | |
| Interleukin 1 | ***11.2*** *H | 0.0 - 2.8 | pg/mL |
| Interleukin 6 | **6.0** | 0.0 - 11.0 | pg/mL |
| Interleukin 7 | ***30.6*** *H | 0.0 - 16.0 | pg/mL |
| Interleukin 8 | ***124.7*** *H | 0.0 - 14.0 | pg/mL |
| TNFa | **18.30** | 0.00 - 54.00 | pg/mL |
| TNFb | **115.0** | 0.0 - 156.0 | pg/mL |
| **AntiInflammatory Cytokines (TH2)** | | | |
| GM-CSF | ***130.3*** *H | 0.0 - 88.0 | pg/mL |
| Interleukin 2 | ***21.7*** *H | 0.0 - 10.0 | pg/mL |
| Interleukin 4 | ***32.1*** *H | 0.0 - 19.0 | pg/mL |
| Interleukin 5 | **7.6** | 0.0 - 13.0 | pg/mL |
| Interleukin 10 | ***29.3*** *H | 0.0 - 6.2 | pg/mL |
| Interleukin 12 | ***21.7*** *H | 0.0 - 14.0 | pg/mL |
| Interleukin 13 | ***19.1*** *H | 0.0 - 6.0 | pg/mL |
| INFg | ***89.7*** *H | 0.0 - 3.5 | pg/mL |
| TGFb | **57.2** | 28.0 - 64.0 | pg/mL |



**Mr TC**
**Pre Jan16 HBO intensive**

NutriPATH
Integrative Pathology Services
P: 1300 688 522
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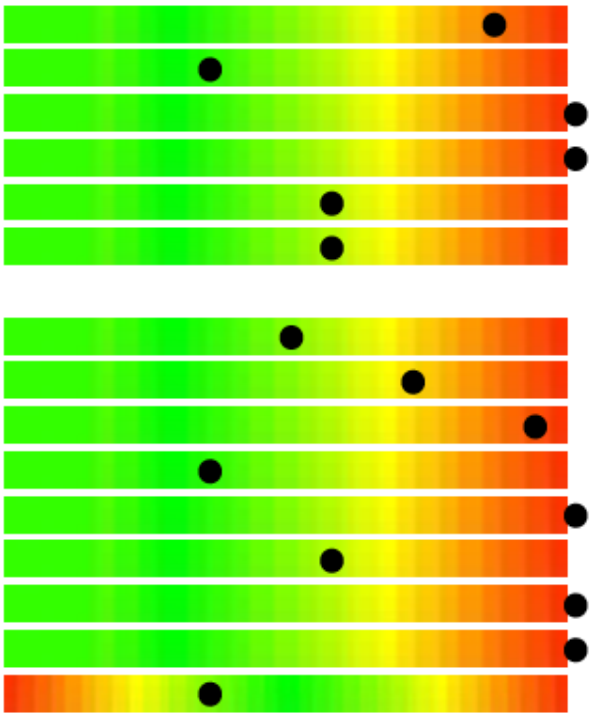
A: PO Box 442 Ashburton VIC 3142

Date of Birth : 14-Feb-1987
Sex : F
Collected : 05-Jan-2016
PO BOX 262
DUNSBOROUGH WA 6281
Lab id: **3412260** UR#:

HYPERMED
643 CHAPEL STREET
SOUTH YARRA VIC 3141

## INTEGRATIVE MEDICINE

| BLOOD - SERUM | Result | Range | Units |
|---|---|---|---|
| **CYTOKINES,Extensive Panel** | | | |
| **ProInflammatory Cytokines (TH1)** | | | |
| Interleukin 1 | *3.2* *H | 0.0 - 2.8 | pg/mL |
| Interleukin 6 | 2.1 | 0.0 - 11.0 | pg/mL |
| Interleukin 7 | *23.4* *H | 0.0 - 16.0 | pg/mL |
| Interleukin 8 | *452.0* *H | 0.0 - 28.0 | pg/mL |
| TNFa | 8.60 | 0.00 - 13.00 | pg/mL |
| TNFb | 98.5 | 0.0 - 156.0 | pg/mL |
| **AntiInflammatory Cytokines (TH2)** | | | |
| GM-CSF | 44.5 | 0.0 - 80.0 | pg/mL |
| Interleukin 2 | 9.1 | 0.0 - 10.0 | pg/mL |
| Interleukin 4 | *22.8* *H | 0.0 - 19.0 | pg/mL |
| Interleukin 5 | 3.3 | 0.0 - 13.0 | pg/mL |
| Interleukin 10 | *17.3* *H | 0.0 - 7.0 | pg/mL |
| Interleukin 12 | 8.5 | 0.0 - 14.0 | pg/mL |
| Interleukin 13 | *11.0* *H | 0.0 - 6.0 | pg/mL |
| INFg | *92.2* *H | 0.0 - 28.0 | pg/mL |
| TGFb | 37.2 | 28.0 - 64.0 | pg/mL |



**Mr TC**

**Post Jan16 HBO intensive** **(Feb riding bike, motor boat licence)**

NutriPATH
Integrative Pathology Services
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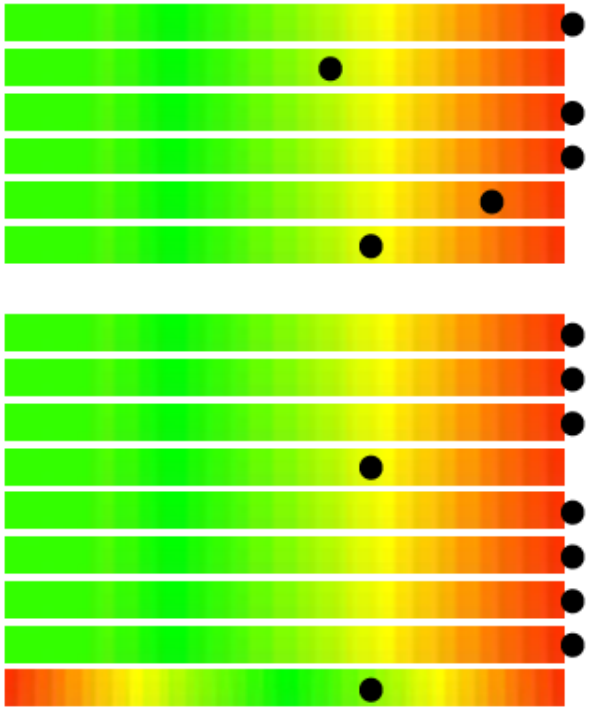
Date of Birth : 14-Feb-1987
Sex : F
Collected : 15-Jan-2016
PO BOX 262
DUNSBOROUGH WA 6281
Lab id: **3413289** UR#:

HYPERMED AUST
15 COLLINS ST, 13TH FLOOR
MELBOURNE VIC 3000

## INTEGRATIVE MEDICINE

| BLOOD - SERUM | Result | Range | Units |
|---|---|---|---|
| **Hyperbaric Oxygen Therapy (HBOT)** | **Not Stated (a)** | | Hours |
| **CYTOKINES,Extensive Panel** | | | |
| **ProInflammatory Cytokines (TH1)** | | | |
| Interleukin 1 | *10.7* *H | 0.0 - 2.8 | pg/mL |
| Interleukin 6 | 7.4 | 0.0 - 11.0 | pg/mL |
| Interleukin 7 | *57.1* *H | 0.0 - 16.0 | pg/mL |
| Interleukin 8 | *763.0* *H | 0.0 - 28.0 | pg/mL |
| TNFa | *15.00* *H | 0.00 - 13.00 | pg/mL |
| TNFb | 119.0 | 0.0 - 156.0 | pg/mL |
| **AntiInflammatory Cytokines (TH2)** | | | |
| GM-CSF | *137.7* *H | 0.0 - 80.0 | pg/mL |
| Interleukin 2 | *20.1* *H | 0.0 - 10.0 | pg/mL |
| Interleukin 4 | *54.9* *H | 0.0 - 19.0 | pg/mL |
| Interleukin 5 | 9.4 | 0.0 - 13.0 | pg/mL |
| Interleukin 10 | *38.6* *H | 0.0 - 7.0 | pg/mL |
| Interleukin 12 | *29.3* *H | 0.0 - 14.0 | pg/mL |
| Interleukin 13 | *28.4* *H | 0.0 - 6.0 | pg/mL |
| INFg | *209.0* *H | 0.0 - 28.0 | pg/mL |
| TGFb | 53.0 | 28.0 - 64.0 | pg/mL |



**Mr TC**

**Pre May16 HBO intensive (improved gait, stance)**

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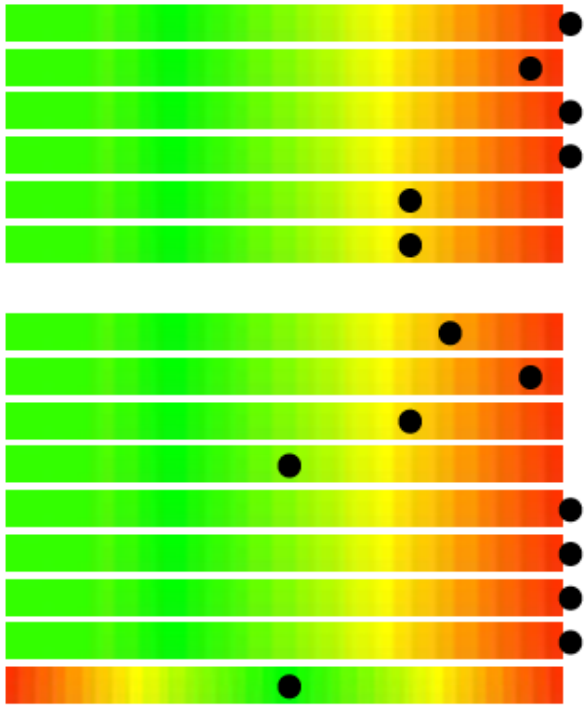
Sex : M
Collected : 03-May-2016
PO BOX 262
DUNSBOROUGH WA 6281
Lab id: 3427123 UR#:

HYPERMED
643 CHAPEL STREET
SOUTH YARRA VIC 3141

## INTEGRATIVE MEDICINE

| BLOOD - SERUM | Result | Range | Units |
|---|---|---|---|
| **Hyperbaric Oxygen Therapy (HBO)** | Pre intensive | | Hours |
| **CYTOKINES,Extensive Panel** | | | |
| **Proinflammatory Cytokines (TH1)** | | | |
| Interleukin 1 | *6.2* *H | 0.0 - 2.8 | pg/mL |
| Interleukin 6 | *14.4* *H | 0.0 - 11.0 | pg/mL |
| Interleukin 7 | *29.8* *H | 0.0 - 16.0 | pg/mL |
| Interleukin 8 | *132.0* *H | 0.0 - 28.0 | pg/mL |
| TNFa | 10.70 | 0.00 - 13.00 | pg/mL |
| TNFb | 129.0 | 0.0 - 156.0 | pg/mL |
| **Antiinflammatory Cytokines (TH2)** | | | |
| GM-CSF | *82.5* *H | 0.0 - 80.0 | pg/mL |
| Interleukin 2 | *12.2* *H | 0.0 - 10.0 | pg/mL |
| Interleukin 4 | 17.0 | 0.0 - 19.0 | pg/mL |
| Interleukin 5 | 6.4 | 0.0 - 13.0 | pg/mL |
| Interleukin 10 | *35.9* *H | 0.0 - 7.0 | pg/mL |
| Interleukin 12 | *36.3* *H | 0.0 - 14.0 | pg/mL |
| Interleukin 13 | *37.7* *H | 0.0 - 6.0 | pg/mL |
| INFg | *44.3* *H | 0.0 - 28.0 | pg/mL |
| TGFb | 47.0 | 28.0 - 64.0 | pg/mL |



**Mr TC**

**Post May16 HBO intensive**

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P: 1300 688 522
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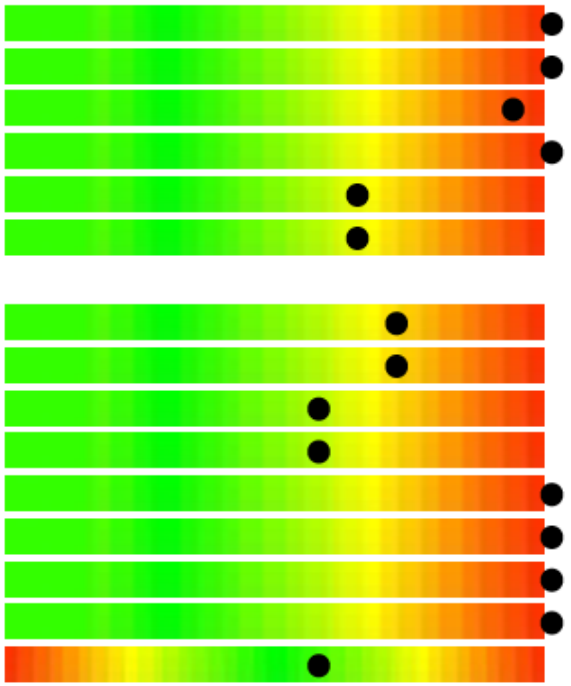
A: PO Box 442 Ashburton VIC 3142

Date of Birth : 14-Feb-1987
Sex : M
Collected : 17-May-2016
PO BOX 262
DUNSBOROUGH WA 6281
Lab id: **3429280** UR#:

HYPERMED
643 CHAPEL STREET
SOUTH YARRA VIC 3141

## INTEGRATIVE MEDICINE

| BLOOD - SERUM | Result | Range | Units |
|---|---|---|---|
| **Hyperbaric Oxygen Therapy (HBO)** | Post intensive | | Hours |
| **CYTOKINES,Extensive Panel** | | | |
| **Proinflammatory Cytokines (TH1)** | | | |
| Interleukin 1 | *4.0* *H | 0.0 - 2.8 | pg/mL |
| Interleukin 6 | *16.2* *H | 0.0 - 11.0 | pg/mL |
| Interleukin 7 | *19.9* *H | 0.0 - 16.0 | pg/mL |
| Interleukin 8 | *64.6* *H | 0.0 - 28.0 | pg/mL |
| TNFa | 10.10 | 0.00 - 13.00 | pg/mL |
| TNFb | 126.0 | 0.0 - 156.0 | pg/mL |
| **Antiinflammatory Cytokines (TH2)** | | | |
| GM-CSF | 65.6 | 0.0 - 80.0 | pg/mL |
| Interleukin 2 | 8.5 | 0.0 - 10.0 | pg/mL |
| Interleukin 4 | 11.7 | 0.0 - 19.0 | pg/mL |
| Interleukin 5 | 8.7 | 0.0 - 13.0 | pg/mL |
| Interleukin 10 | *56.1* *H | 0.0 - 7.0 | pg/mL |
| Interleukin 12 | *76.5* *H | 0.0 - 14.0 | pg/mL |
| Interleukin 13 | *24.7* *H | 0.0 - 6.0 | pg/mL |
| INFg | *55.7* *H | 0.0 - 28.0 | pg/mL |
| TGFb | 49.0 | 28.0 - 64.0 | pg/mL |



**Mr TC**
**Pre Sept16 HBO intensive**

NutriPATH
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P: 1300 688 522
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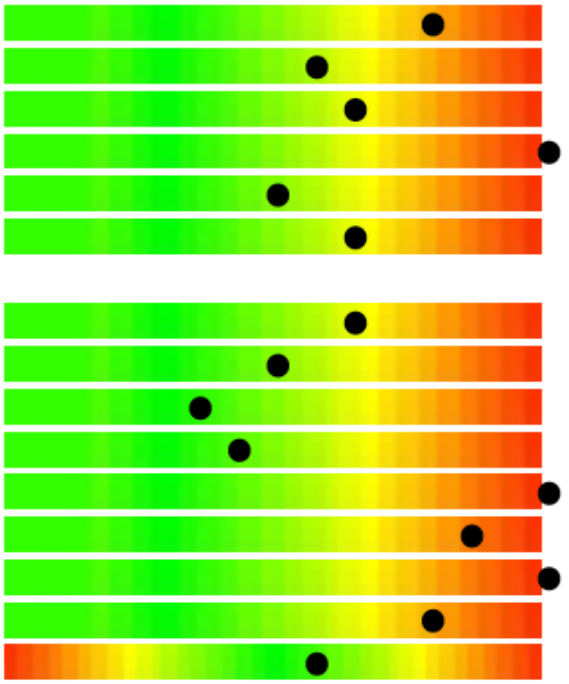
A: PO Box 442 Ashburton VIC 3142

Date of Birth : 14-Feb-1987
Sex : M
Collected : 01-Sep-2016
PO BOX 262
DUNSBOROUGH WA 6281
Lab id: **3444272** UR#:

HYPERMED
643 CHAPEL STREET
SOUTH YARRA VIC 3141

## INTEGRATIVE MEDICINE

| BLOOD - SERUM | Result | Range | Units |
|---|---|---|---|
| **Hyperbaric Oxygen Therapy (HBO)** | 0.0 | | Hours |
| **CYTOKINES,Extensive Panel** | | | |
| **Proinflammatory Cytokines (TH1)** | | | |
| Interleukin 1 | *2.9* *H | 0.0 - 2.8 | pg/mL |
| Interleukin 6 | 6.7 | 0.0 - 11.0 | pg/mL |
| Interleukin 7 | 13.0 | 0.0 - 16.0 | pg/mL |
| Interleukin 8 | *41.0* *H | 0.0 - 28.0 | pg/mL |
| TNFa | 6.90 | 0.00 - 13.00 | pg/mL |
| TNFb | 123.0 | 0.0 - 156.0 | pg/mL |
| **Antiinflammatory Cytokines (TH2)** | | | |
| GM-CSF | 57.0 | 0.0 - 80.0 | pg/mL |
| Interleukin 2 | 5.6 | 0.0 - 10.0 | pg/mL |
| Interleukin 4 | <3.7 | 0.0 - 19.0 | pg/mL |
| Interleukin 5 | 4.6 | 0.0 - 13.0 | pg/mL |
| Interleukin 10 | *22.1* *H | 0.0 - 7.0 | pg/mL |
| Interleukin 12 | *15.9* *H | 0.0 - 14.0 | pg/mL |
| Interleukin 13 | *14.9* *H | 0.0 - 6.0 | pg/mL |
| INFg | 27.3 | 0.0 - 28.0 | pg/mL |
| TGFb | 52.0 | 28.0 - 64.0 | pg/mL |



**Mr TC TBI**

**Cytokine Profile "Rounding Off"** (Harch/Fogerty 2016)

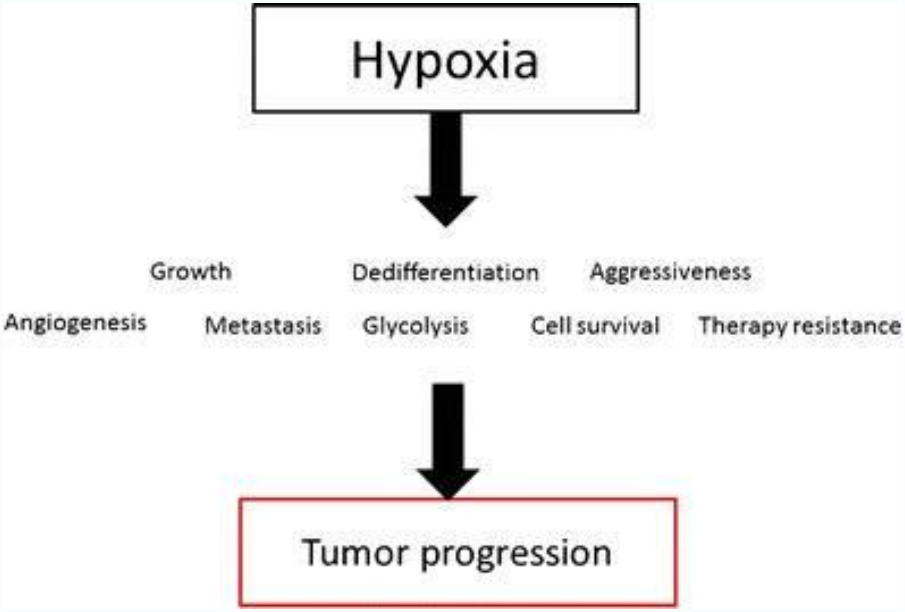
| **Pro Inflammatory** | May15 | Pre Jan16 | **Post Jan16** | Pre May16 | **Post May16** | Pre Sept16 |
|---|---|---|---|---|---|---|
| • **IL1** (0-2.8) | **11.2** | **3.2** | **10.7** | **6.2** | **4** | 2.9 |
| • **Il6** (0-11) | 6 | 2.1 | 7.4 | **14.4** | **16.2** | 6.7 |
| • **Il7** (0-16) | **30.6** | **23.4** | **57.1** | **29.8** | **19.9** | 13 |
| • **Il8** (0-28) | **124.7** | **452** | **763** | **132** | **64.6** | **41** |
| • **TNFα** (0-13) | **18.3** | 8.6 | **15** | 10.7 | 10.1 | 6.9 |
| **Anti Inflammatory** | | | | | | |
| • **GM-CSF** (0-80) | **130.3** | 44.5 | **137.7** | **82.5** | 65.6 | 57 |
| • **Il2** (0-10) | **21.7** | 9.1 | **20.1** | **12.2** | 8.5 | 5.6 |
| • **Il4** (0-19) | **32.1** | **22.8** | **54.9** | 17 | 11.7 | 3.7 |
| • **Il10** (0-7) | **29.3** | 7.3 | **38.6** | **35.9** | **56.1** | **22.1** |
| • **Il12** (0-14) | **21.7** | 8.5 | **29.3** | **36.3** | **76.5** | **15.9** |
| • **Il13** (0-6) | **19.1** | **11** | **28.4** | **37.7** | **24.7** | **14.9** |
| • **INFg** (0-28) | **89.7** | **92.2** | **209** | **44.3** | **55.7** | **27.3** |

# Hyperbaric Oxygen: Does it promote growth or recurrence of malignancy?

J. FELDMEIER[1], U. CARL[2], K. HARTMANN[3], P. SMINIA[4].

*[1]Radiation Oncology Department, Medical College of Ohio, Toledo, OH, USA;[2]Department of Radiation Oncology and Nuclear Medicine, Diakoniekrankenhaus Rotenberg, Germany; [3]Department of Radiation Oncology, Heinrich Heine University, Duesseldorf, Germany; [4]Department of Radiation Oncology, VU University Medical Center, The Netherlands*

iii. Interleukin-8 release is increased by hypoxia[68] This has been demonstrated in human glioblastoma cells in culture. IL-8 has been shown to have angiogenic properties in this model. The work of Shi and associates[69] confirms an increase in IL-8 by hypoxia and acidosis and suggest this contributes significantly to the aggressive biology of pancreatic cancer.




**IL8 release is increased by hypoxia and acidosis** and suggests this contributes to the aggressive biology of pancreatic cancer.

Mal Hooper
HyperMED | OXYMED Australia | OXYGEN100 - Heal
The Warriors

Edit post View stats

# Hyperbaric Oxygenation Impacts Hypoxic Glioblastoma Multiforme Cells & Potentiates the Killing Effect of Interleukin-13 based Cytotoxin

# Reoxygenation of Hypoxic Glioblastoma Multiforme Cells Potentiates the Killing Effect of an Interleukin-13-Based Cytotoxin

Tie Fu Liu,[1,2] Jiaozhong Cai,[2] Denise M. Gibo,[1] and Waldemar Debinski[1]

**Abstract** **Purpose:** Hypoxia is a cause for resistance to cancer therapies. Molecularly targeted recombinant cytotoxins have shown clinical efficacy in the treatment of patients with primary brain tumors, glioblastoma multiforme, but it is not known whether hypoxia influences their antitumor effect.

Clin Cancer Res 2009;15(1) January 1, 2009

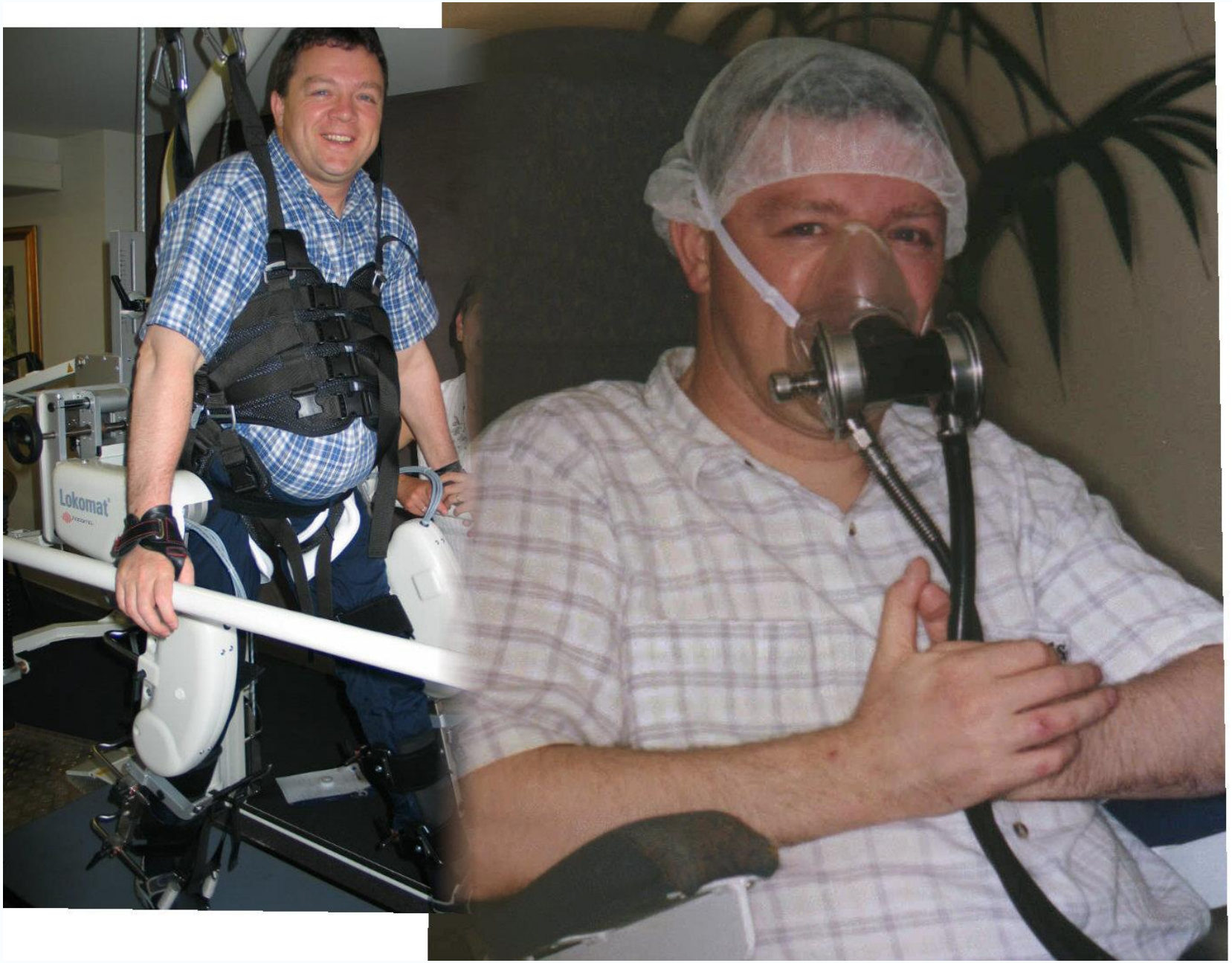
**Glioblastoma Multiforme** a high-grade aggressive form of brain tumors. The treatment of patients with GBM a major challenge - **median survival rate is 14.5 months** since diagnosis.

- 'Similarly to other solid tumors, **GBM exhibit resistance to radiotherapy and chemotherapy largely in part due to the hypoxic tumor microenvironment'.** The aggressive invasive nature of GBM is the unique property of tumor hypoxia. Hypoxia is an important factor affecting the efficacy of current orthodox treatments in GBM.
- 'Hypoxia influences the behaviour of tumor cells and **empowers hypoxic tumour cells a higher resistance** to radiotherapy and certain chemotherapies and a **higher mutation rate and potential for a more metastatic** and malignant phenotype'. The tumor oxygenation is negatively associated with increasing grade of human astrocytomas.
- **Solid tumors like GBM exhibit strong resistance to radiotherapy and chemotherapy due to the hypoxic tumor microenvironment**.

- **Undersea Hyperb Med. 2013** Hyperbaric Oxygen Therapy impacts cellular Oxygen tension and inflammatory cascades and has been shown to **'enhance the efficacy of radiotherapy and chemotherapy for the treatment of malignant tumors'.**
- Several clinical trials have been done with Hyperbaric Oxygen or hypoxic cell radiosensitizers intending to overcome the problem of the radioresistance of hypoxic tumor cells (7–9). The results of these trials have shown benefit of proper oxygenation for glioblastoma multiforme radiotherapy.

- The **reoxygenated anoxic GBM** were **2- to 10-fold more sensitive** to DT-IL13QM killing than normoxic glioblastoma multiforme cells.
- **IL-13 expression in GBM is dependent on Oxygenation status.**
- **IL-13 is up-regulated with HBO.**
- **Reoxygenation causes a rebound or even a further increase in protein levels of IL-13Ra2** and active furin in GBM cells subjected to anoxia or hypoxia.
- 'Results show that a recombinant cytotoxin directed against GBM cells kills these cells much less efficiently under anoxic/hypoxic conditions.

- The HBO reoxygenation brings unexpected additional **rebound benefit (IL13) making GBM cells even more responsive to the killing effect of a (IL13) cytotoxin.'**


Lokomat

**The Final Frontier - 'Repair and Functional Restoration' (Hooper 2005)**

- Hyperbaric Oxygenation primes the body and provides a **fertile neurovascular platform** for mobilizing the patient's own immune and circulating stem cell capacity whilst preparing the body for further stem cell implantation techniques. Hyperbaric Oxygenation activates dormant and inactive nerve cells, promotes plasticity hastening recovery.

- **The final frontier** in the treatment of complex degenerative neurovascular disorders including brain and spinal cord injury is focused on **'repair and functional restoration'.** This involves the use of **growth factors** including Neurotropic Cerebryolysin, Gangliosides (GM1) and target specific peptides (TB4) to **promote axonal sprouting, activation of idling and non-functional neurons whilst promoting neovascularization** (new capillary formation) of damaged areas.

- **Research efforts to bridge spinal cord and brain cell lesions** are also underway experimentally, using **transplanted tissues and bridging devices**. HOWEVER the ultimate success in these reconstructive methods and efforts are directly dependent on tissue vitality (neurovascular integrity).

Mal Hooper
HyperMED | OXYMED Australia | OXYGEN100 - Heal
The Warriors

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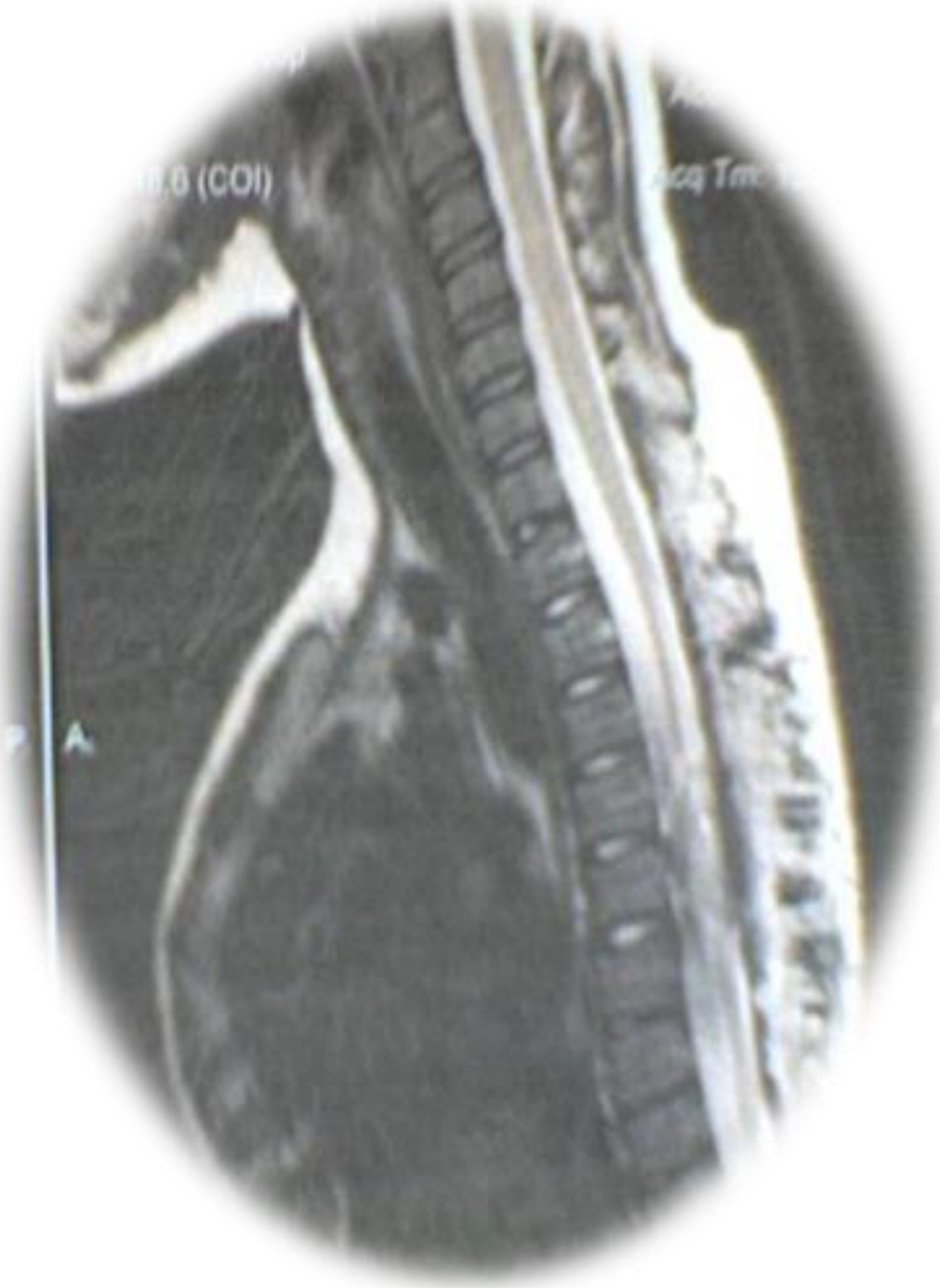
# Hyperbaric Oxygenation & Lokomat (Robotic Assisted Walking) Impacts Chronic Spinal Cord Injury - Case Study IM



**MRI (left) PRIOR to commencing at HyperMED dated 13-03-07**

'Comparison is made with the last examination dated 10-10-05. Again demonstrating the enhancing intraspinal lesion posteriorly in the spinal canal at the level of T4-T6. It is again seen to measure 2.8cm cranio caudal and 1cm AP.
The T2 imaging again shows cord atrophy with hydromyelia from T1 to at least the inferior border of the lesion'.
Classification: T4 complete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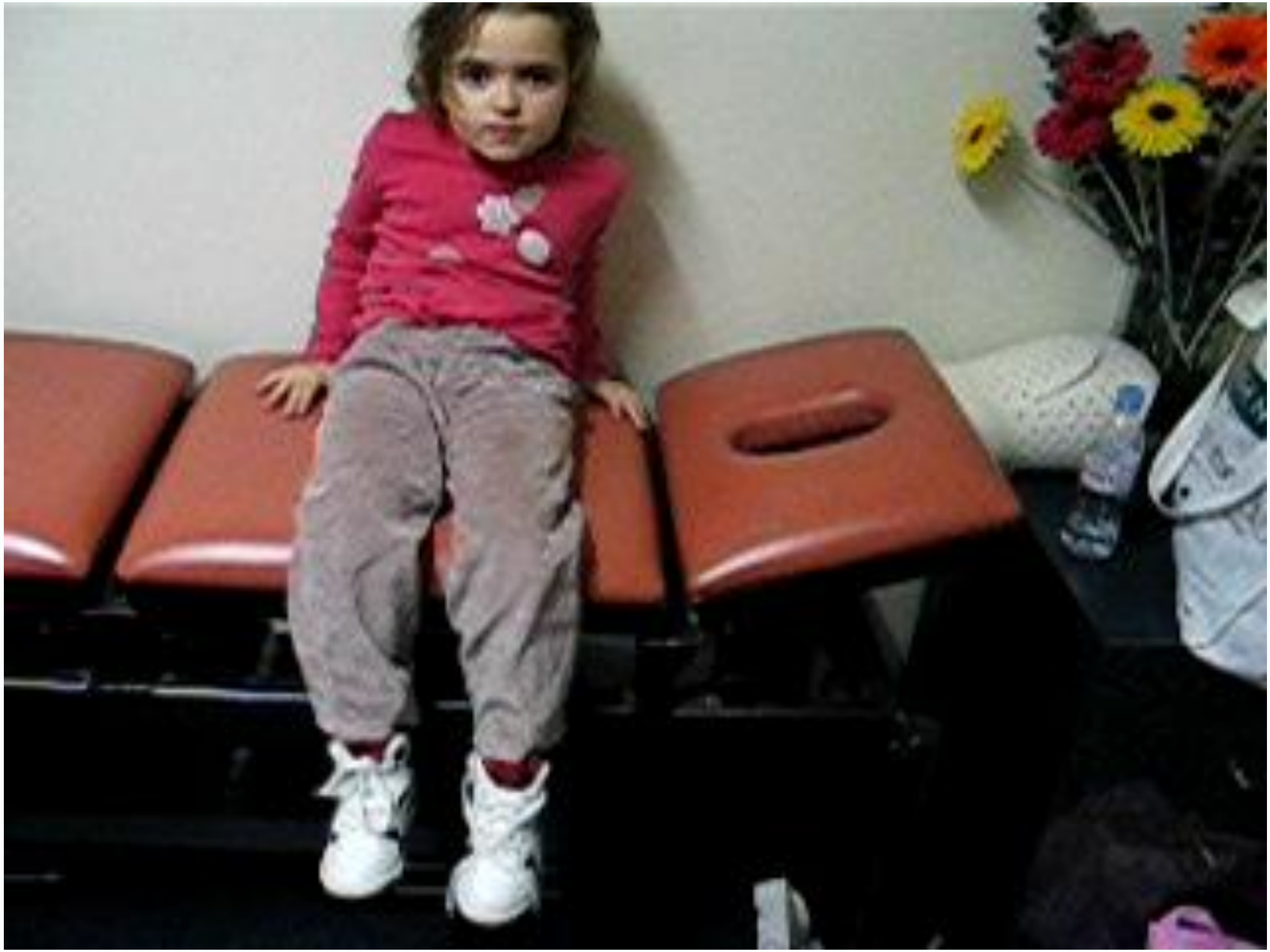



HyperMED NeuroRecovery Channel 7 News July 07- Drov


The Lokomat walking machine

**Spinal Cord Injury Research: Past Identifying Results in Animal Studies of SCI Between 1960-2000. Is Progressive Necrosis Occurring In The Contused Spinal Cord Reversible?**

**Professor John Yeo AO. Senior consultant, Spinal Injuries Unit, Royal North Shore Hospital**
**Associate Professor, Department of Surgery, University of Sydney**

Between 1960-2000 basic and clinical research identified that trauma to the spinal cord causes indirect as well as direct damage to the neurons and glial tissue.

METHODS: 1964 Hughes (UK) identified presence of central haemorrhage, dilatation of small blood vessels as well as oedema at the level of the spinal cord trauma. This study (Yeo) identified 63 papers between 1960-2000, confirmed haemodynamic changes in the spinal cord and/or progressive necrosis in the neuronal and glial tissue occurring within hours of spinal cord injury.

RESULTS: The studies detail extravasation of red blood cells with migrating white blood cells occurring within hours of the injury. **Secondary ischemia and hypoxia were shown to contribute to the initial damage from spinal cord contusion**. The outcomes of various treatments, including hyperbaric oxygen and the use of steroids, will be discussed.

CONCLUSION: The details of the pathological processes leading to the loss of normal efficient haemodynamics within the microvasculature of the injured spinal cord have yet to be identified. The question remains – why does the post-traumatic inflammatory process within the central nervous system appear to be so disadvantageous to the recently injured spinal cord?

- Any future modifications to the damage from secondary ischaemia and hypoxia, through achieving adequate spinal cord haemodynamics must significantly improve prognosis in the patient with a contusion injury to the spinal cord.

**The Smoking Gun**

- Brain Injury & Spinal Cord insult causes a **cascade of secondary degeneration (apoptosis) due to hypoxia and pro-inflammatory cytokines** including (not limited): IL1, IL6, IL7, IL8, MMP9 (Matrix metalloproteinase 9), TNFa, S100B, Caspase-3, TLR4/NF-kB signal pathways. HBO Alleviates Secondary Injury After Brain Trauma Through Inhibition of TLR4/NFkB Signaling Pathway Shu-Yi Pan (AS) Med Sc Monit, 2016.

- The resulting neuro-inflammation can lead to progressive glial and neuronal cell death. In addition remains a chronic ***'smouldering'*** **(cytokine) inflammation in the CNS continues to affect the spinal cord microenvironment.**

- Pro-inflammatory cytokines can kill cells, but they are also important in mobilizing reparative and regenerative responses. Further, cytokines can affect synaptic strength and synaptic plasticity, and 'in excess' can contribute to maladaptive plasticity, including chronic pain.

- The extent of neurovascular deterioration can be significantly diminished with **Hyperbaric Oxygenation (HBOT) which 'expands the therapeutic window'.**

**What About Stem Cells?**

- **Inflammatory Cytokines block stem-readiness and stem cell differentiation.**
- Cytokine imbalance inhibit stem cell therapies and proper stem cell differentiation. It is critical to correct the Cytokine Storm prior to proposed stem cell therapies. **Curr Stem Cell Res Ther. 2015**

J Neurotrauma. 2010 Jun;27(6):1121-7.

**Attenuating experimental spinal cord injury by hyperbaric oxygen: stimulating production of vasculoendothelial (VEGF) and glial cell line-derived (GDNF) neurotrophic growth factors and interleukin-10.** Institute of Clinical Medicine, Taipei Medical University, Taiwan.

Abstract: The present study was carried out to further examine the mechanisms underlying the **beneficial effects of hyperbaric oxygen (HBOT) on experimental spinal cord injury.** Rats were divided into three major groups: (1) sham operation (laminectomy only); (2) laminectomy + SCI + normobaric air (NBA; 21% oxygen at 1 ATA); and (3) **laminectomy + SCI + HBO(2) (100% oxygen at 2.5 ATA for 2 h).** 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. HBO(2) therapy was begun immediately after SCI. Behavioral tests of hindlimb motor function as measured by the Basso, Beattie, and Bresnahan (BBB) locomotor scale was conducted on days 1-7 post-SCI. Cells positive for glial cell line-derived neurotrophic nerve growth factor (GDNF) and vascular endothelial growth factor (VEGF) and cytokines in the injured spinal cord were assayed by immunofluorescence and commercial kits, respectively.

- **HBO(2) therapy significantly attenuated SCI-induced hindlimb dysfunction, and spinal cord infarction and apoptosis, reducing the overproduction of spinal cord interleukin-1beta and tumor necrosis factor-alpha.**
- **GDNF-positive and VEGF-positive cells and production of spinal cord interleukin-10 after SCI were all significantly increased by HBO(2).**
- These data suggest that **HBO(2) may attenuate experimental SCI (infarction & apoptosis) by stimulating production of GDNF, VEGF, and interleukin-10.**

J Neurotrauma 2013 Jun 3.

**The Therapeutic Role of Interleukin-10 after Spinal Cord Injury**

Source: University of Wisconsin , Neurological Surgery, Wisconsin, United States.

Abstract

Spinal cord injury (SCI) is a devastating condition affecting 270,000 people in USA.

- **A potential treatment for decreasing the secondary inflammation, excitotoxic damage, and neuronal apoptosis associated with SCI is the anti-inflammatory interleukin-10.**
- The best characterized effects of **IL-10 are anti-inflammatory; IL10 down-regulates pro-inflammatory species** IL-1β, IL-2, IL-6, tumor necrosis factor-α, interferon-γ, matrix metalloproteinase-9, nitric oxide synthase, myeloperoxidase, and reactive oxygen species. Pro-apoptotic factors cytochrome c, caspase 3, and Bax are down-regulated by IL-10, whereas **anti-apoptotic factors Bcl-2 and Bcl-xl are up-regulated by IL-10.**

- **IL-10 also provides trophic support to neurons** through the IL-10 receptor.
- **Increased tissue sparing, functional recovery, and neuroprotection are seen with an immediate post-SCI systemic administration of IL-10.**
- Treatment of SCI with IL-10 has been used successfully in **combination with Schwann cell** and olfactory glial cell grafts as well as methylprednisolone.
- **Minocycline + hyperbaric oxygen treatment all increase IL-10 levels in a SCI models and result in increased tissue sparing and functional recovery.** A chronic systemic administration of IL-10 does not appear to be beneficial to SCI recovery and causes increased susceptibility to septicemia, pneumonia, and peripheral neuropathy.
- IL-10 shows promise as a treatment for SCI, although research on local IL-10 delivery timeline and dosage needs to be expanded upon.


WALKING
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**The Final Frontier – 'Repair and Functional Restoration'**

- **Hyperbaric Oxygenation provides the available fuel** to damaged nerve cells and acts as a positive catalyst reversing spinal cord hypoxic degeneration.

- HBO | Robotic combination **protocols 'awakens' dormant neural pathways and provides accurate neurological repetition enhancing and re-training connections and pathways in the brain and spinal cord.**

- **HBO upregulates VEGF, BDNF, GDNF combined with exogenous growth factors** including Neurotropics - **Cerebryolysin, Gangliosides (GM1) and target specific peptides (ThymosinB4)** to promote axonal sprouting, activation of idling and non-functional neurons whilst promoting neovascularization (new capillary formation) of damaged areas.

- Patients have the ability to 'salvage back' what has been damaged - the capacity to **wake-up dormant pathways, rewire, retrain and reconnect function improving brain and spinal cord function.**

**Cerebrolysin – BDNF, GDNF, NGF**

- **Cerebrolysin Ever Neuro Pharma (2010) - 84 pages**
- **Cochrane Review - 2013**

- CL is a porcine (pig) **brain derived peptide preparation with a mixture of different neurotrophic factors including: brain-derived neurotrophic factor (BDNF), glial cell line derived neurotrophic factor (GDNF), nerve growth factor (NGF), ciliary neurotrophic factor (CNTF) and other peptide fragments.**
- CL facilitates **neurotrophic activity which has been shown to improve cognitive performance, clinical global function and increased activities of daily living** were observed in numerous neurodegenerative disorders and mental illness.
- CL potentiates **brain alpha activity, reduces slow EEG delta frequencies and improves memory performance** in healthy elderly humans, suggesting that this compound activates cerebral mechanisms related to attention and memory processes.
- CL is a safe product administered either **intravenous and or intramuscular injection**. The oral Cerebrolysin product is not as effective.

- **CL improves the cognitive deficits and global function in patients with mild to moderate progressive neurodegenerative disease including Multiple Sclerosis, Parkinson's Disease, Alzheimer's Disease, Dementia, Acute and Chronic Stroke victims. Cerebrolysin also demonstrated significant improvement in victims of post-acute traumatic brain injury.**

- CL demonstrated significant benefit in **childhood autism** (89%) and **cerebral palsy** (mild to complex anoxic encephalopathy).

- **CL protects against induced motor neuron damage and reduced imposed nerve death. Studies involving induced spinal cord and nerve root damage revealed significant motor recovery with Cerebrolysin**.

- CL exerts a **neuro-immunotrophic activity reducing the extent of chronic nerve cell inflammation and accelerated neuronal death** under pathological conditions such as those observed in acute traumatic and chronic progressive neurodegenerative diseases (progressive arthritis).

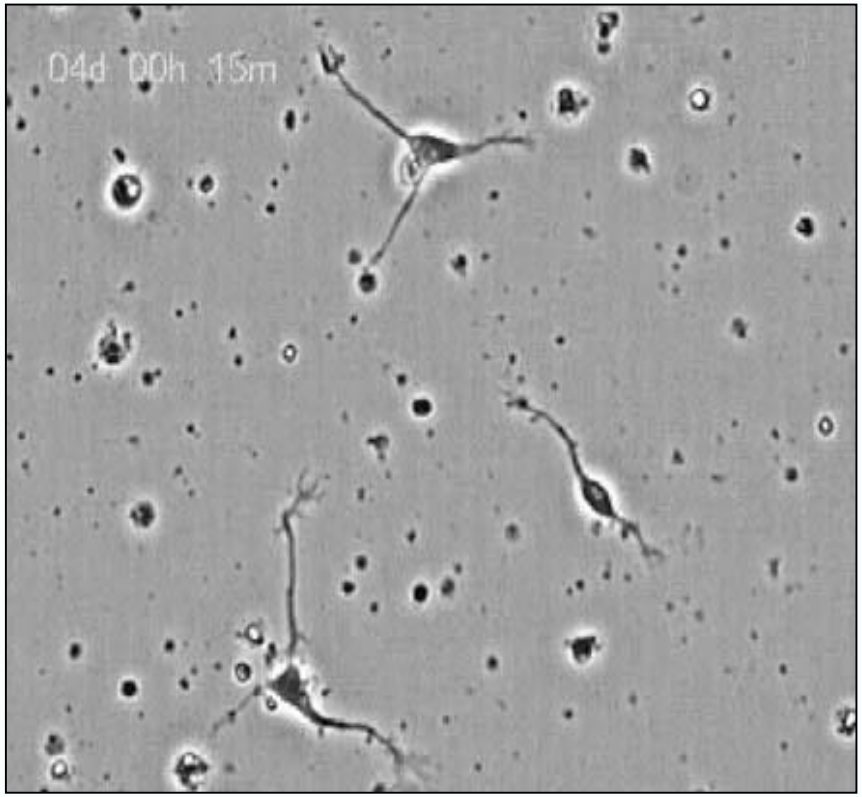
- CL demonstrates **'anti-aging'** with **benefits 'improving cognition, memory function, brain metabolism with capacity'.**

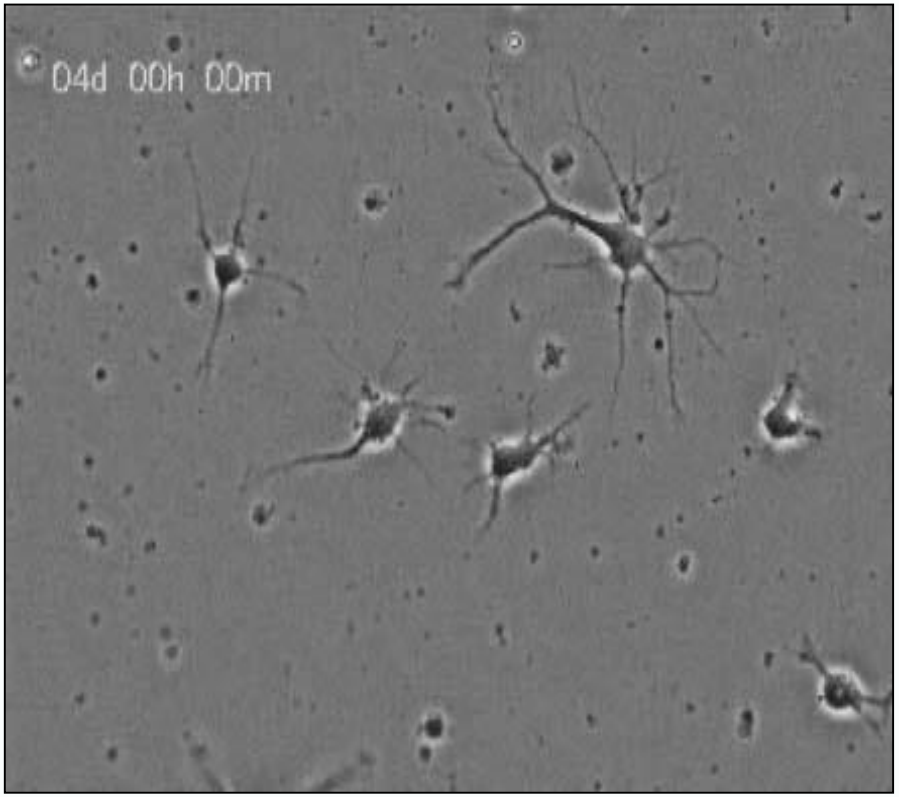
**Peptidergic Drugs for the Treatment of Traumatic Brain Injury**

X Antón Álvarez, Jesús Figueroa, Dafin Muresanu Future Neurology. 2013;8(2):175-192.

- CL has **neuroprotective and neurorestorative properties** - low molecular weight peptides able to **cross the BBB** and mimic action of endogenous neurotrophic factors.
- CL acts as a multimodal drug **exerting synergistic actions : positive effects on Aβ and tau pathologies, neuroinflammation, neurotrophic factors, oxidative stress, excitotoxicity, neurotransmission, brain metabolism, neuronal apoptosis and degeneration, neuroplasticity, neurogenesis as well as cognition,** experimental and human
- **Reduces brain Aβ deposition, tau phosphorylation** and Aβ- and tau-related neuropathology by regulating GSK-3β and CDK-5 activity
- **Modulates neuroinflammation, attenuating microglia activation and IL-1β release** in vitro and in vivo, **reducing the elevated serum levels of TNF-α** and TNF R1 in AD patients
- Displays **neurotrophic-like actions on neuronal survival and neurite outgrowth and increases circulating IGF-1 and BDNF levels** in humans
- Protects against oxidative and excitotoxic damage, at least in part by inhibiting lipid peroxidation and calpain activation
- Influences synaptic transmission mediated by GABAB, adenosine A1 and glutamate receptor subunit 1 receptors and exhibits cholinotrophic activity
- **Enhances the supply of glucose to the brain and ameliorates the slowing of brain bioelectrical activity**
- **Promotes neural plasticity and prevents dendritic and synaptic loss**
- **Promotes neuronal survival protecting neurons from apoptosis and degeneration**
- **Stimulates neurogenesis,** probably through Akt activation
- **Improves learning and memory**

- The true mechanism, by which this drug work in such a degenerative disease is still unknown, but probably the **neuronal differentiation (sprouting of axons and dendrites) and the maintenance of the functional integrity of the nerve cell** play a major role in the improvement encountered in this trial. [A. Mubaidin, A. Shurbaji, A. Hadid, N. Shishani: Cerebrolysin in Steel: Richardson-Olszewski Syndrome. The Internet Journal of Neurology. 2003. Volume 2 Number 1]



**The Victorian Neurotrauma Initiative (VNI) Final Report 'The economic cost of spinal cord injury and traumatic brain injury in Australia ' (2009)**

Dr Alex Collie Director VNI

- The lifetime cost of new cases of brain and spinal cord injury occurring in 2008 alone is **$10.5 billion in Australia**. The largest cost is attributed to burden of disease, direct costs such as provision of attendant care and healthcare services are also significant.
- The **burden of disease** includes Medical complications. The most common complications of SCI include urinary tract infections, bacterial infections and pressure ulcers. Other medical complications include bladder and bowel dysfunction, circulation problems, inability to control temperature, autonomic dysreflexia, respiration difficulties, sexual dysfunction, spasms, contracture and pain (musculoskeletal and neuropathic).
- **Approximately 70% of patients admitted to a hospital with a TBI/SCI had more than one complication.**

**Activity Based Restorative Therapies: Concepts and Applications in Spinal Cord Injury Related Neurorehabilitation.**

Dev Disabilities Research Reviews 15: 112–116 (2009)

Cristina L. Sadowsky and John W. McDonald International Center for Spinal Cord Injury, Department of Physical Medicine and Rehabilitation, Kennedy Krieger Institute, Johns Hopkins School of Medicine, Baltimore, Maryland, USA.

- The field of neurorehabilitation is changing. After years of evidence from the basic science data, the old, deep rooted rehabilitative principles of compensation and adaptation are slowly starting to change.
- Strategies for stimulating the nervous system are being used to optimize functional recovery.
- From basic science/animal model we have learned that the **adult injured central nervous system (CNS) is capable of reorganization at multiple levels.** The **reorganization** occurs at all different levels: **cortical, subcortical, spinal cord, and in the peripheral nervous system.**
- The repair process can happen through various mechanisms: **synaptic plasticity in pre-existing connections (peripheral and central), sprouting, and formation of new connections.**
- **Remyelination and new cell birth also occurs, correcting, restoring, and replacing the damaged nervous system. Both reorganization and repair seem to be dependent on maintaining an optimal level of neurological activity.**

**Effect of Activity on New Cell Birth - Neurogenesis**

Under normal conditions, neurogenesis only occurs in two ‘‘privileged’’ regions of the human adult brain: **hippocampus** and olfactory system.

- In the hippocampus, **physical activity stimulates neurogenesis by acting on the proliferation of neuronal stem cells** [Kempermann et al., 2000].
- In addition to stimulating neurogenesis, **exercise and activity also reverses the decline in neurogenesis commonly associated with aging** [van Praag et al., 2005].
- **Activation of neighboring axons** plays a major role in the proliferation of oligodendrocyte precursor cells in the developing rat optic nerve [Barres and Raff, 1993].

**Role of Activity in Neurorestoration**

- There is no doubt that spinal cord injuries induce a dramatic decrease in the amount of physical activity that an individual exerts [van den Berg-Emons et al., 2008].
- Maintaining an adequate level of physical activity is undoubtedly helpful with **cardiovascular function, muscle and bone mass, longevity** [Paffenbarger et al., 2001], **cognition** [Angevaren et al., 2008] **quality of life** [Kell et al., 2001].
- Regular physical activity can **significantly reduce the risk of coronary heart disease colon cancer, diabetes, and high blood pressure** [Thompson et al., 2003].
- Regular physical activity also helps to: (1) control weight, (2) contribute to healthy bones, muscles, and joints, (3) reduce falls among the elderly, (4) reduce the pain of arthritis, (5) reduce symptoms of anxiety and depression, (6) reduce the need for medication, and (7) reduce hospitalizations and physician visits [Fernhall et al., 2008]

- Individuals with paralysis related to SCI have an added degree of **cardiovascular challenge on top of deconditioning**; their autonomic nervous system is markedly affected by the spinal injury, especially if the injury is **above T6-T9 level**, where the major splanchnic autonomic outflow emerges.
- **Cardiovascular conditioning can be achieved and maintained in individuals with SCI related paralysis utilizing a robotic device** that delivers a quantified amount of workload.
- Robotic exercise produced a **2-fold increase in the oxygen uptake, a 3-fold increase in ventilation rate and a five beats/min increase**. Bhambhani and Maikala [2000]
- The physical activity and exercise improves muscle and bone mass in SCI. The effect of 1 year FES training in 10 individuals with chronic C6 to T4 SCI - **proximal tibia bone mineral density increased by 10% and the bone mass gain was reversed after 6 months of subsequent inactivity.** Mohr et al. [1997].

- **Recovery of 30% lost bone mass at the proximal tibia level and significant muscle strength gains following a 24 weeks resisted quadriceps strengthening utilizing electrical stimulation.** Belanger et al. [2000]

- The fact that the bone and muscle gains disappear after discontinuation of activity point to the need for sustained, **preferably home-based intervention to maintain physiological gains.** [Chen et al., 2005]

**Effect of Activity in Neurorestoration**

- Exercise becomes an important tool when used in individuals with neurological paralysis. It is a treatment that enhances neurological function by affecting musculoskeletal and neural plasticity.
- **Passive or FES-assisted lower extremities ergometry in pediatric population improves bone mineral density, muscle volume, stimulated quadriceps strength, and lowers the resting heart rate** [Johnston, 2008]
- FES is delivered by a **robotic device, ensuring repetitive accuracy.** Robotic gait training devices have been built: the Lokomat and Pediatric Lokomat (Hocoma AG, Switzerland), the Autoambulator (HealthSouth, Birmingham, AL), REOAmbulator (Motorika Ltd.) but in clinical practice they do not yet deliver the same results like therapist guided gait training [Edgerton and Roy, 2009; Hidler et al., 2008].

**Future Thoughts**

- **Activity- based interventions are not ‘‘the cure’’ for paralysis** and might indeed appear expensive, but they are needed and **assist with the multitude of complications that ultimately increase morbidity and mortality.**
- ABRTs are evidence-based rehabilitative interventions that are applied according to a new conceptual paradigm that uses activity as a tool for neurological recovery, and not only as a means to achieve compensatory function.

## Gait Assisted Walking

- **Neural plasticity refers to the natural ability of the neurons in the nervous system to generate and develop new connections** aimed at repairing the neuronal damages.

- In the other word, they can **learn new tasks**. Based on this fact, **locomotor training focuses on retraining the nervous system through simulating and repetition of walking gait,** in order to regain their function and/or enhance their existing potentials.

- By repetitively stimulating the muscles and nerves in the lower body 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 independently 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!

**Do Wheel Chairs Inhibit Recovery?**
Kentucky Spinal Cord Injury Research Center, University of Louisville. Presented: National Neurotrauma Society Symposium in Orlando, Florida. NewScientist Aug 2008


Injured rats strapped to tiny "wheelchairs" that restrict their movements recovered less limb function and coordination than those left to fend for themselves.

- This might mean that people with a spinal cord injury would recover better if they were encouraged to use their limbs sooner after injury and relied less on wheelchairs.

“Wheelchair restriction definitely impairs functional recovery in rats, and logically it would seem to apply also to humans," David Magnuson of the **Kentucky Spinal Cord Injury Research Center, University of Louisville.** There seems to be an optimal time period following spinal cord injury during which the brain is better able to relearn some of the functions lost. Missing this "window of opportunity" is thought to reduce the amount of movement an injured person can recover, says Magnuson. ‘Some studies suggest putting body weight onto the legs is best, while others stress moving the feet, for example’.

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

His team created rat-sized wheelchairs. The wheelchairs restricted their hind legs but the rats wheeled themselves around on their forelegs. The other rats were left to move about freely. After another eight weeks, in which all the animals were allowed free movement, their walking and swimming abilities were assessed using standard tests that measure joint movements, weight support, limb coordination, foot placement and gait stability. The team also filmed the rats while they had reflective tape stuck to their joints, so they could analyze their movements in detail.

They found that rats given wheelchairs recovered significantly less function than those left to move about as best they could. The team presented their results at the **National Neurotrauma Society Symposium in Orlando, Florida**.

"Most people when they see the rat wheelchair, their first response is to chuckle, because it does look comical, but then they realize we are trying to address some pretty important questions," says Magnuson.

While the study points to the importance of movement during spinal cord recovery, and suggests **less reliance on wheelchairs might help.** "This study indicates the importance of providing the appropriate feedback to the damaged cord to get the best functional outcome," says Mark Bacon, head of research at Spinal Research, a UK charity. "It remains to be seen what rehabilitation regime will be the most appropriate for humans."

**Locomotor Gait Assisted Training** - **"If you don't use it you will lose it …"**

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

**Activity Based Rehabilitation relies on three KEY 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). **Plasticity occurs in neural pathways that are active – (penumbra state).**

Figure 1: Patient suspended with manual BWSTT

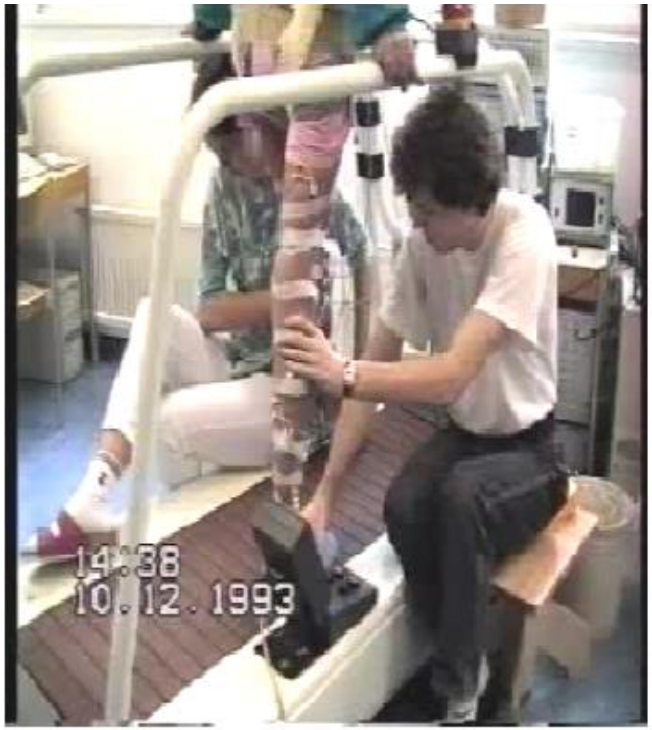



Figure 2: Video courtesy of University Hospital Balgrist, Zurich

# LOKOMAT Australian Experience: Robotically Gait Assisted Body Weight Support Treadmill Training (BWSTT) – Lokomat Gait Training.

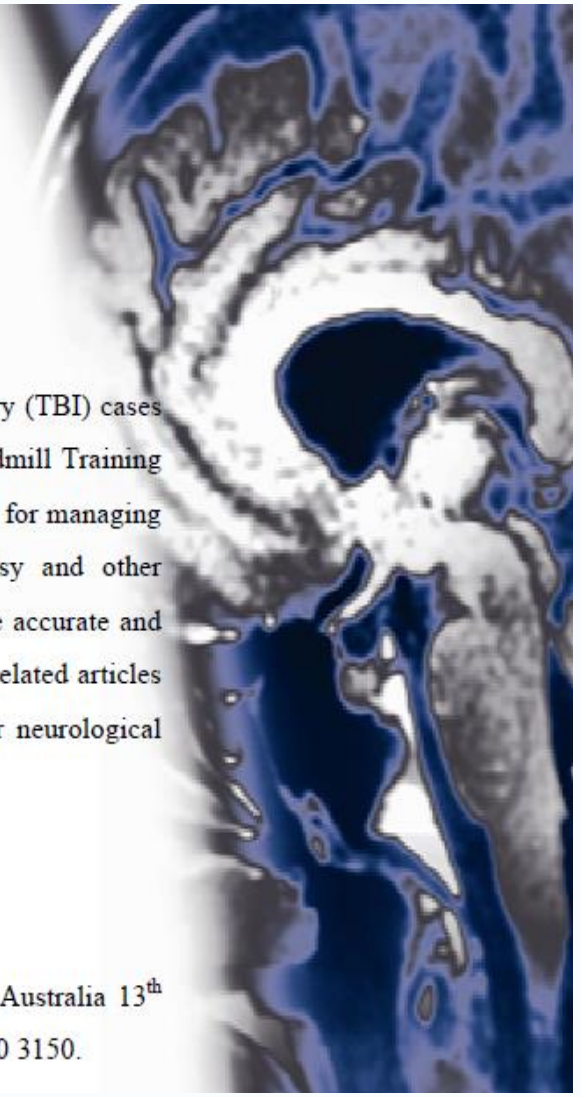
## Is it an effective and financially feasible treatment?

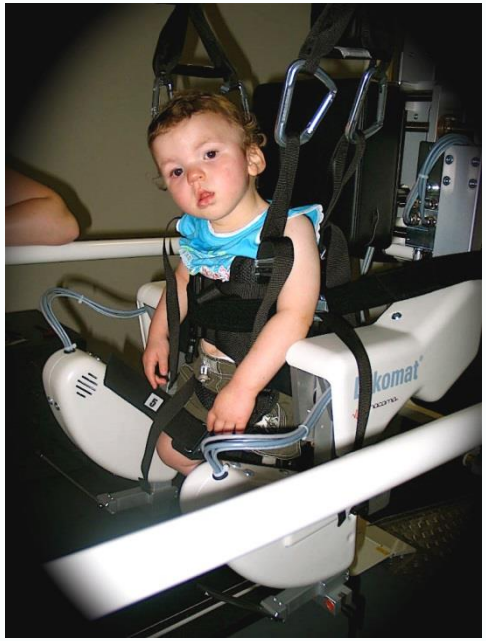
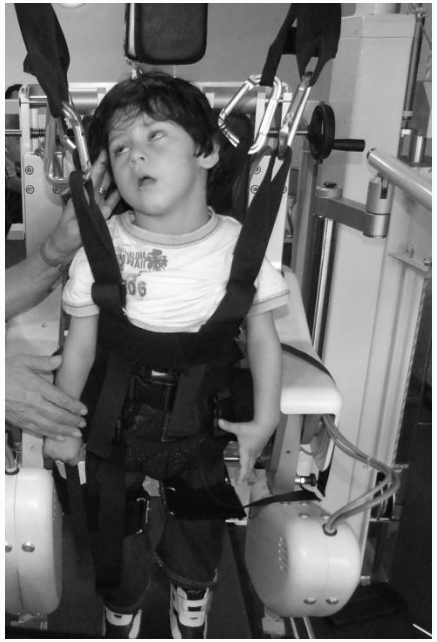
HyperMED NeuroRecovery Centre – Melbourne, Australia. M. R. Hooper, T. Chamacham 2008.

**Abstract:** Growing number of adult and pediatric spinal cord injury (SCI) and traumatic brain injury (TBI) cases each year indicates an increasing need for treatment modalities, like Body Weight-Supported Treadmill Training (BWSTT) to assist functional recovery. In addition to treatment of SCI cases, BWSTT has been used for managing other various neurological diseases such as stroke and multiple sclerosis (MS), cerebral palsy and other neurodegenerative states. Robotically Gait Assisted BWSTT (Lokomat) has been shown to be more accurate and financially feasible, compared to the other BWSTT modalities. In this article, we intend to review related articles and evidence to explain the medical and financial feasibility of using this treatment modality for neurological diseases.

**Keywords:** locomotion, exoskeleton, locomotor training, bodyweight support, robotics

**Corresponding author:** Malcolm R. Hooper Director Rehabilitation HyperMED NeuroRecovery Australia 13th floor 15 Collins St Melbourne 3001. Email info@hypermed.com.au T: +61 3 9650 3136 F: +61 3 9650 3150.



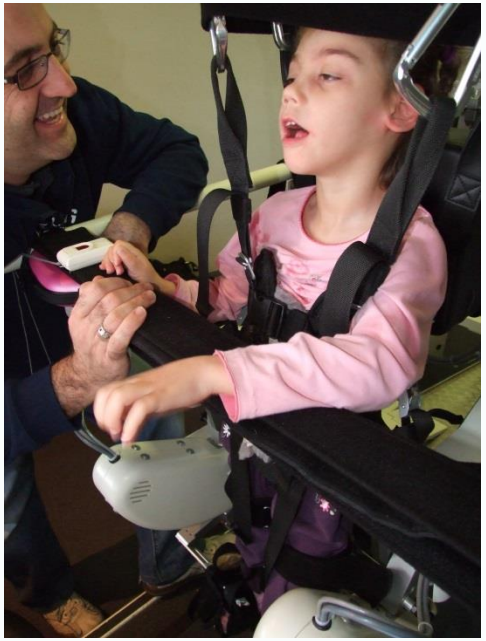
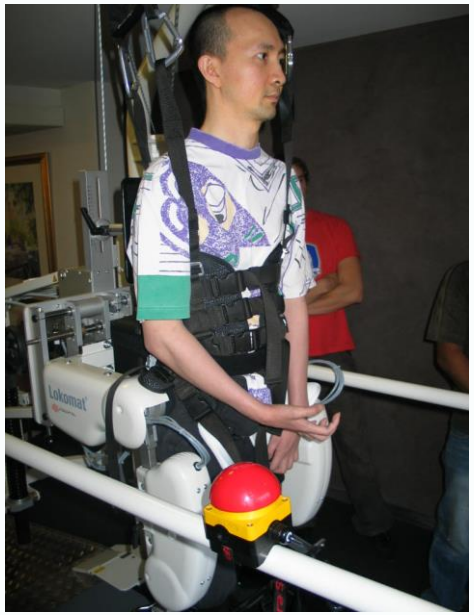
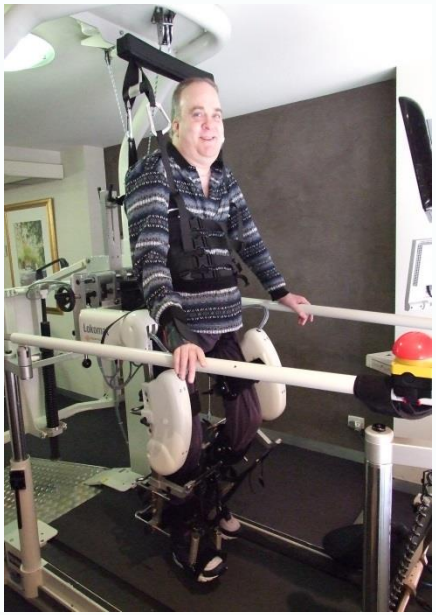
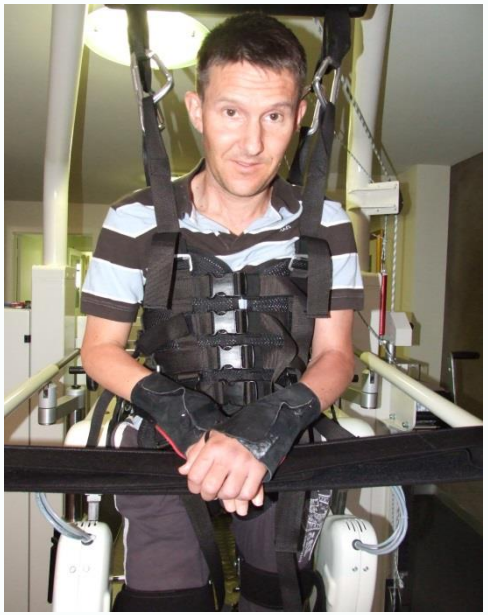






Figure 4: HyperMED Spinal Cord Injured patient on Lokomat[43]

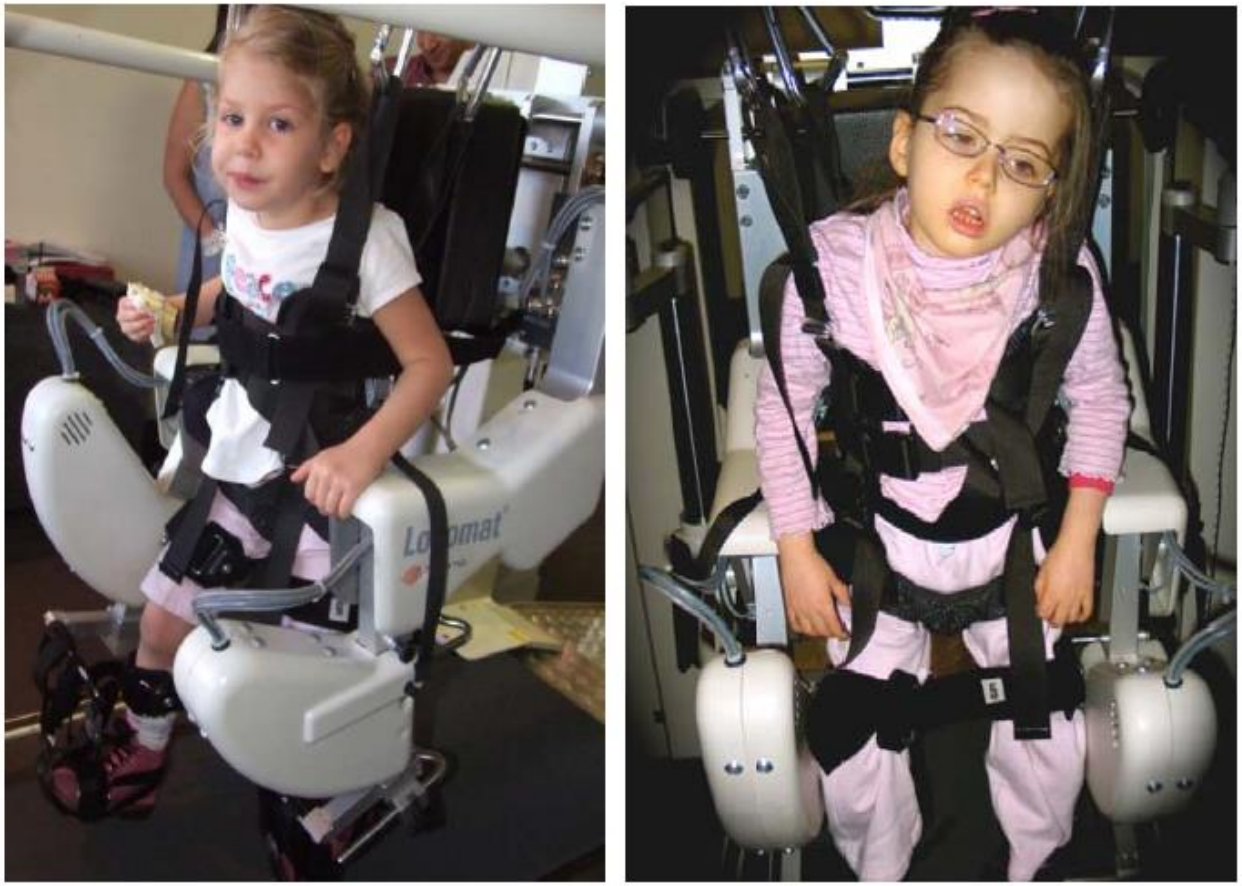


Figure 3: HyperMED cerebral palsy patients on Pediatric Lokomat [43]

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

## What Is The Evidence To Support Lokomat vs Gait Assisted Physiotherapy?

Cochrane Collaboration (2010)

- Many people who have had a stroke have difficulties with walking, and improving walking is one of the main goals of rehabilitation. Electromechanical-assisted gait training uses specialist machines to assist walking practice.
- **This review of 23 trials, which included 999 participants, found evidence that electromechanical-assisted gait training combined with physiotherapy may improve recovery of independent walking in people after stroke.**
- Specifically, people in the first three months after stroke and those who are not able to walk appear to benefit most from this type of intervention.



**Mechanically assisted walking with body weight support results in more independent walking than assisted overground walking in non-ambulatory patients early after stroke: a systematic review**

Louise Ada, Catherine M Dean, Janine Vargas and Samantha Ennis

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**Question**: Does mechanically assisted walking with body weight support result in more independent walking and is it detrimental to walking speed or capacity in non-ambulatory patients early after stroke? **Design**: Systematic review with meta-analysis of randomised trials. **Participants**: Non-ambulatory adult patients undergoing inpatient rehabilitation up to 3 months after stroke. **Intervention**: Mechanically assisted walking (eg, treadmill, electromechanical gait trainer, robotic device, servo-motor) with body weight support (eg, harness with or without handrail, but not handrail alone) versus assisted overground walking of longer than 15 min duration. **Outcome measures**: The primary outcome was the proportion of participants achieving independent walking. Secondary outcomes were walking speed measured as m/s during the 10-m Walk Test and walking capacity measured as distance in m during the 6-min Walk Test. **Results**: Six studies comprising 549 participants were identified and included in meta-analyses. Mechanically assisted walking with body weight support resulted in more people walking independently at 4 weeks (RD 0.23, 95% CI 0.15 to 0.30) and at 6 months (RD 0.23, 95% CI 0.07 to 0.39), faster walking at 6 months (MD 0.12 m/s, 95% CI 0.02 to 0.21), and further walking at 6 months (MD 55 m, 95% CI 15 to 96) than assisted overground walking. **Conclusion**: Mechanically assisted walking with body weight support is more effective than overground walking at increasing independent walking in non-ambulatory patients early after stroke. Furthermore, it is not detrimental to walking speed or capacity and clinicians should therefore be confident about implementing this intervention. **[Ada L, Dean CM, Vargas J, Ennis S (2010) Mechanically assisted walking with body weight support results in more independent walking than assisted overground walking in non-ambulatory patients early after stroke: a systematic review. *Journal of Physiotherapy* 56: 153–161]**

**Key words**: Stroke, Treadmill, Walking, Systematic review, Meta-analysis, Randomised controlled trials

## Mobile Exoskeletons With Variable Assist

**NeuroRecovery**

# OXYGEN100 *for* Traumatic Brain Injury, Shock Blast Injury, Post Traumatic Stress Disorder, Concussion Injury

*Free Hyperbaric Oxygen Therapy for immediate returning Aussie War Veterans suffering the effects of TBI, Shock Blast, PTSD and Concussion Syndrome*

# HEAL THE WARRIORS

Traumatic Brain Injury (TBI) | Post-Concussion Syndrome (PCS)

Post-Traumatic Stress Disorder (PTSD)

Hyperbaric Oxygen Therapy - Fighting to treat the effects of TBI and PTSD

# Take Home Message

- Key factors driving autoimmune illness and treatment resistance include Hypoxia associated with elevated inflammatory 'biomarkers' Cytokines (IL1, 6, 7, 8) including Tumour Necrosis Factor alpha (TNFα), GlycA, S100B, chronic anaerobic and fungal infections, high carbohydrate, high glucose diet ...

- HBO impacts up to 8101 Genes after a single exposure (1.5-2ATA @ 100% O2) (Courtesy: HBO in Chronic TBI: Oxygen Pressure, and Gene Therapy - Harch 2015).

- **Up~Regulated genes** were primarily '**growth and repair hormones**' and the **'anti-inflammatory genes**'. **Down~Regulated genes** were the **'pro-inflammatory and apoptotic genes**'.

- HBO **Up~Regulates** the patients own target specific Stem Cells {an 8-fold (800%) increase in circulating CD34+}; HBO enhances Mitochondrial function, HBO proliferates Vascular Endothelial Growth Factors (VEGF) & Neural Growth Factors (BDNF & GDNF), Anti-inflammatory Interleukins including IL4, IL10, IL12, IL13 and INFγ (positive feedback loop). HBO reduces Telomeres degeneration and more ...

- HBO **Down~Regulates** toxic intra and extra cellular inflammatory Cytokines (IL1, 2, 6, 7, 8), Tumour Necrosis Factor Alpha (TNFα), chronic opportunistic Anaerobic (MRSA, VRE) and co-infections (Viral, Bacterial, Parasitic), Cell Sepsis and more ...

# Hyperbaric oxygen therapy for traumatic brain injury: bench-to-bedside

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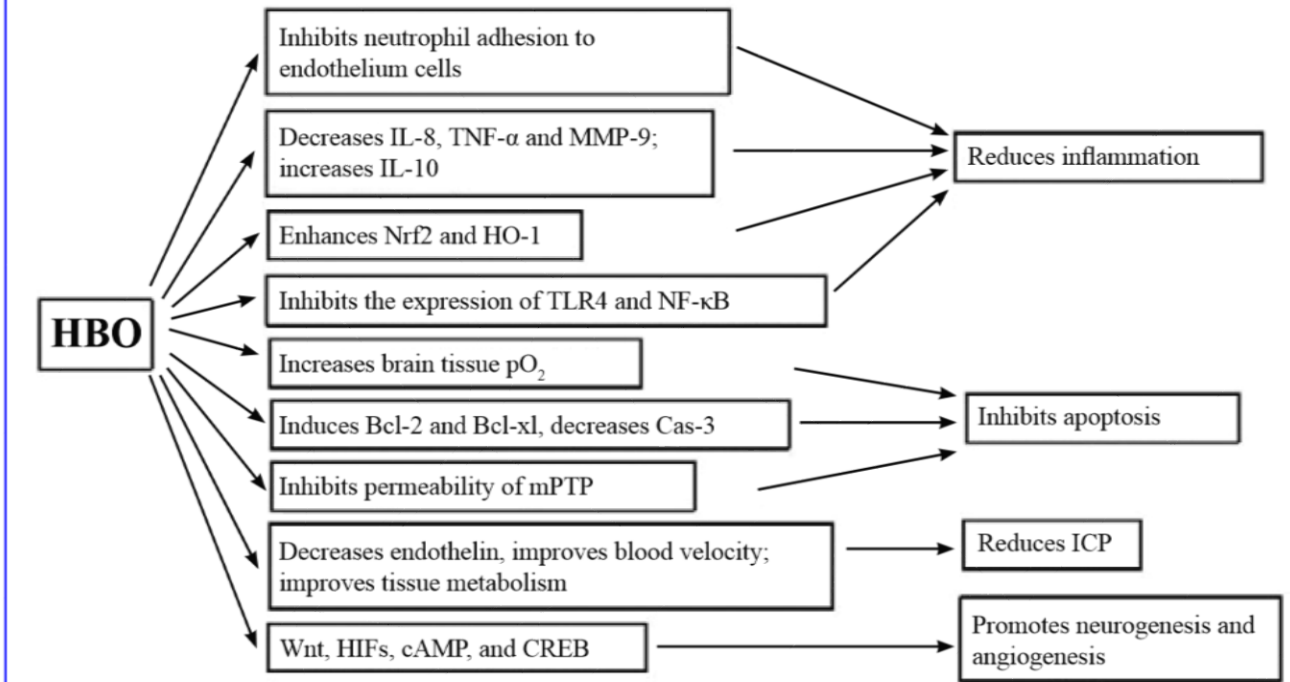


**Figure 1: Potential mechanisms of HBO therapy.**

Note: Many of the pathways work parallel, or together, to induce neuroprotection in the brain. These mechanisms include: increasing tissue oxygenation, reducing inflammation, inhibiting apoptosis, reducing ICP, and promoting neurogenesis and angiogenesis. HBO: Hyperbaric oxygen; ICP: intracranial pressure; CBF: cerebral blood flow; CSF: cerebrospinal fluid; $pO_2$: partial pressure of oxygen; IL-8: interleukin-8; IL-10: interleukin-10; TNF-α: tumor necrosis factor-α; MMP-9: matrix metalloproteinase-9; mPTP: mitochondrial permeability transition pore; Cas-3: caspase-3; HIFs: hypoxia-inducible factors; CREB: cAMP response element-binding; Nrf2: nuclear factor (erythroid-derived 2)-like 2; HO-1: heme oxygenase-1; TLR4: Toll-like receptor 4; NF-κB: nuclear factor-kappaB.

- **The human frame is Oxygen dependent.** Approximately 20-30% of the body's consumption of Oxygen occurs within 3-5% of the body mass – the brain and spinal cord structures. These structures are extremely sensitive to Oxygen deficiency.

- Oxygen is essential to quality of life and essential to drug delivery.

- HBO drives neuroplasticity and accelerates immune responses.

- HBO is non-invasive.

- HBO is the 'integrative bridge' between orthodox medicine and complimentary approaches.

- This multifactor internal healing response is 'unique' to Hyperbaric Oxygenation.

**Thankyou.**