A clinicians view on regeneration in spinal cord injuries

ESCIF

May 20, 2010

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Clinic for Spinal Cord Injuries, Rigshospitalet, and University of Copenhagen, Denmark

REMEMBER

ACHIEVEMENTS OF TODAY

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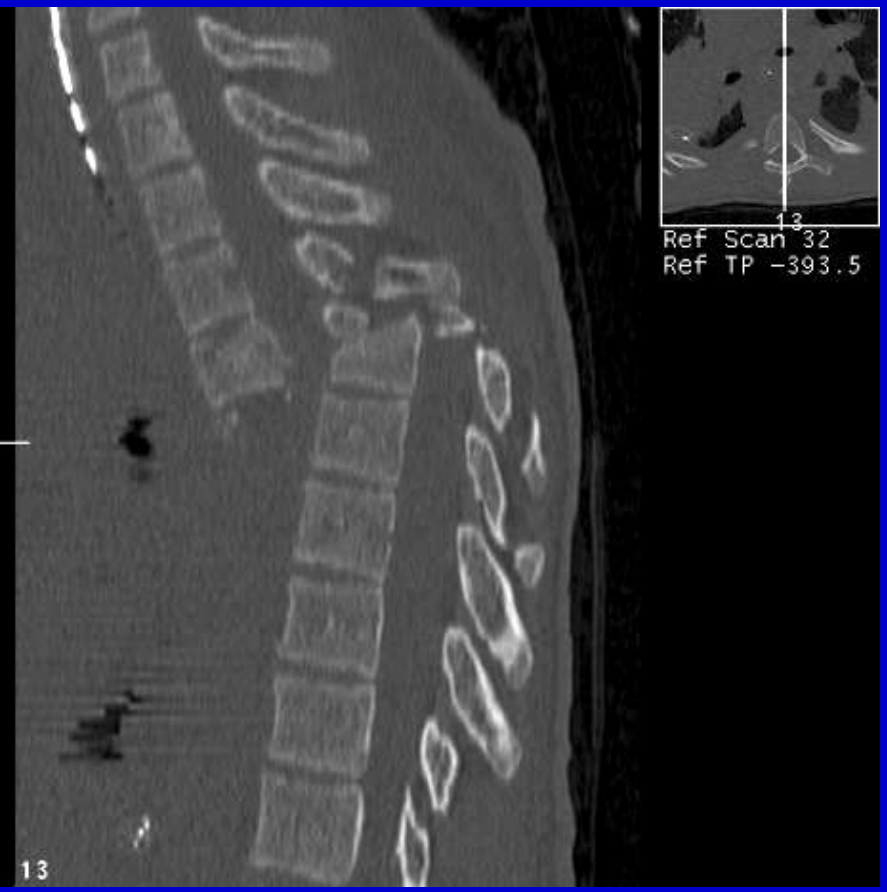
SURVIVAL



Before 2nd World War: 20-40%

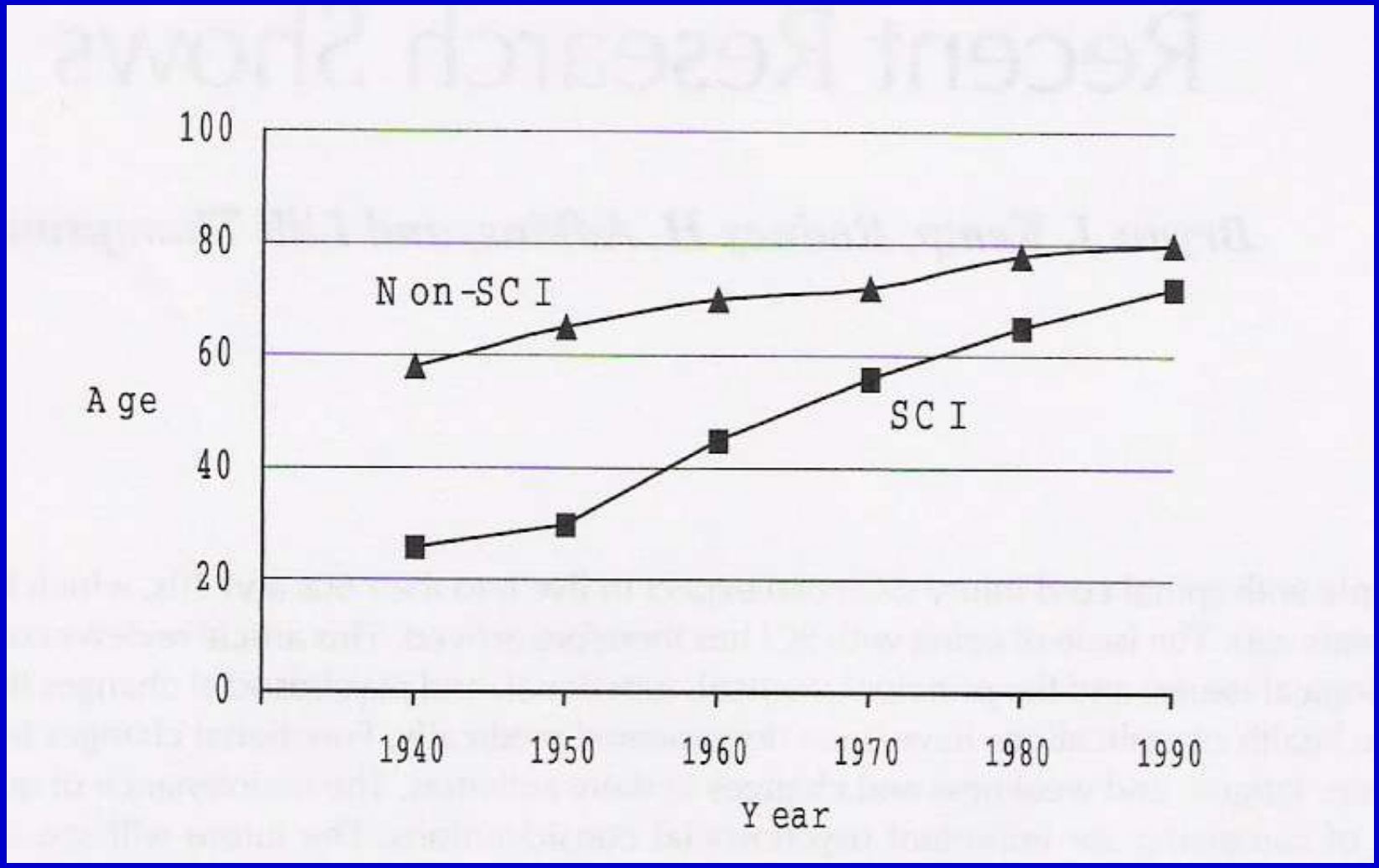
In the 1960s: 70%

In the 1970s: 85%

In the 1980s: 94%

Ducker TB. N Eng J Med 1990;322:1405-11

Life-expectancy of a 25-year-old person with and without SCI since 1940



Kemp et al. Top Spinal Cord Inj Rehabil 2004;10:175-97.

CLINICIANS CHALLENGE

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Enthusiasm for spinal regeneration research

Evoked stories of promise and hope in popular and scientific publications.

Predictions that basic findings could lead to clinical applications routinely accompany studies that report axonal regeneration and statistically significant behavioural recovery in **animal** studies of novel SCI strategies.

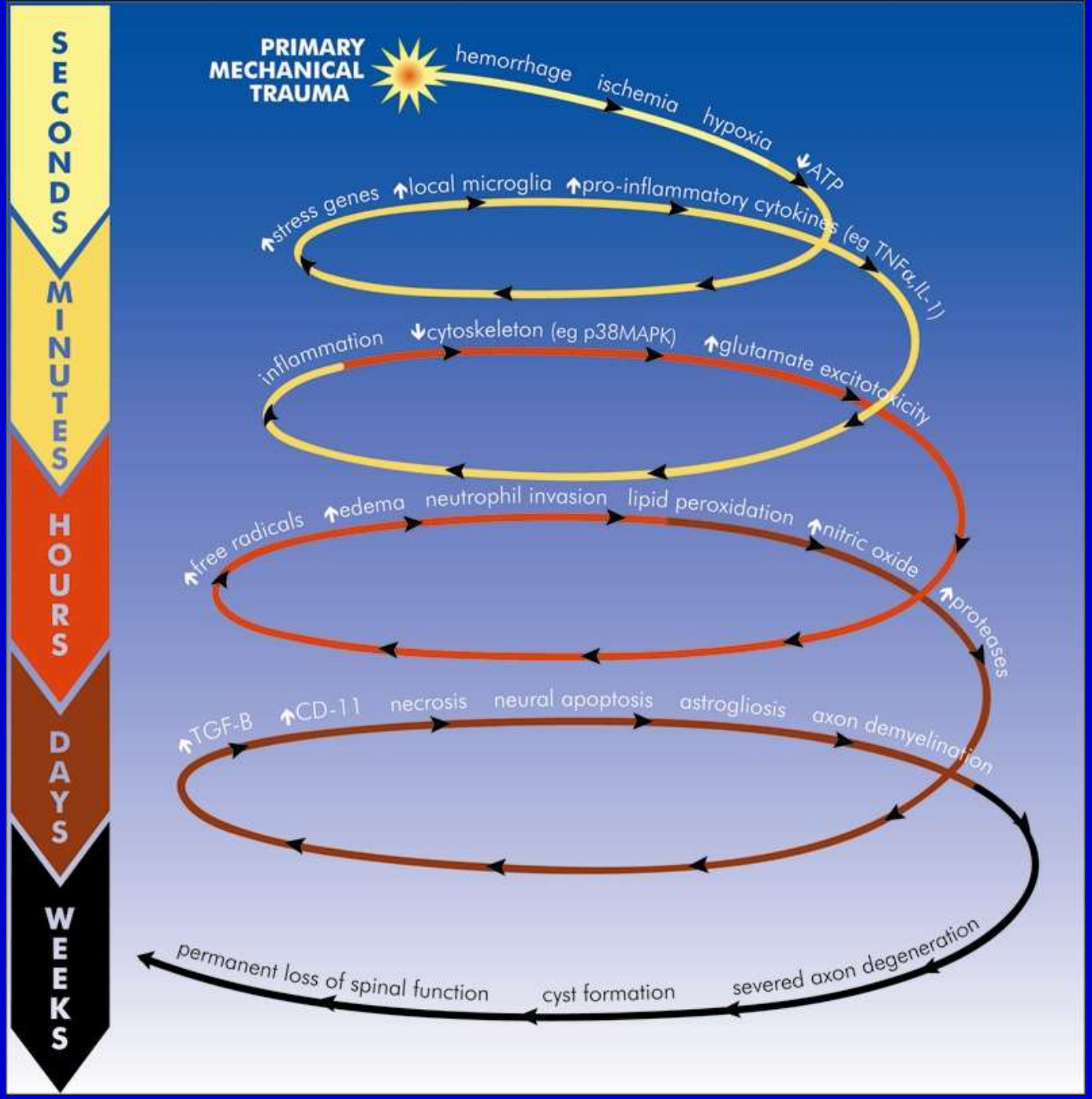
Kleitman N. J Spinal Cord Med 2004;27:311-8

PRIMARY MECHANISM

- At the time of injury
- Related to the acute compression, laceration, or contusion of the spinal cord

SECONDARY MECHANISM

- Delayed injury process
- Caused by various biochemical processes leading to ischemia, neurogenic shock, haemorrhage, vasospasm, ionic derangements, neurotransmitter accumulation, production of free radicals, inflammation, and apoptosis.



John Steeves

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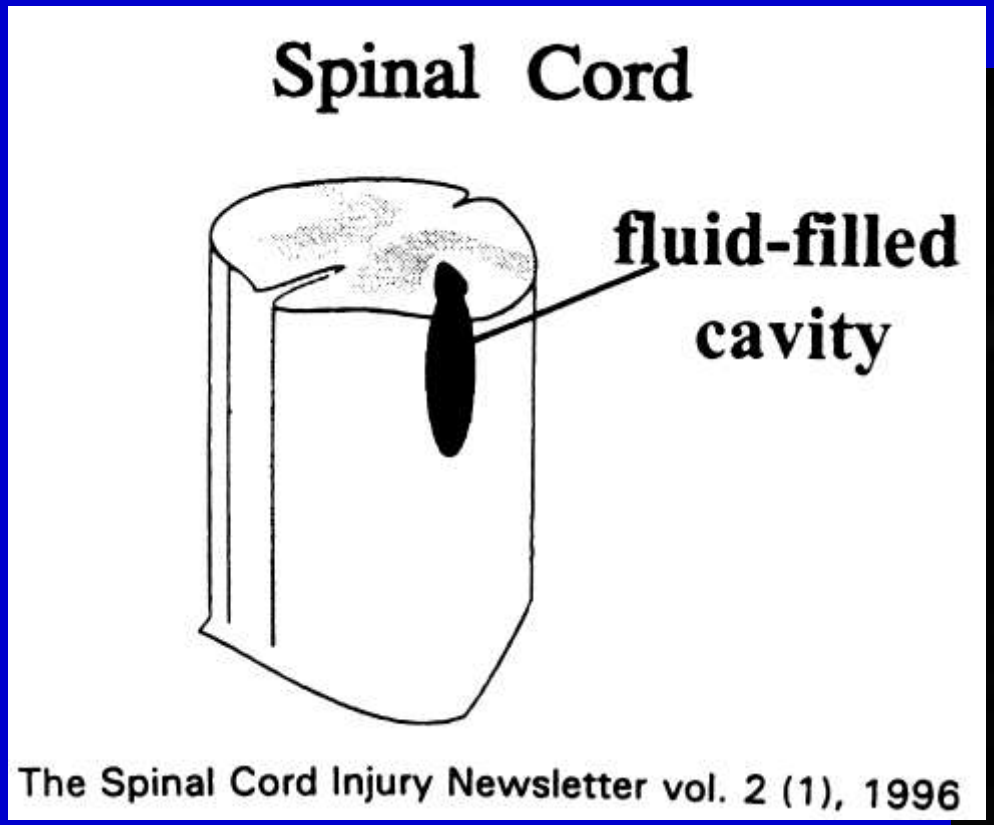
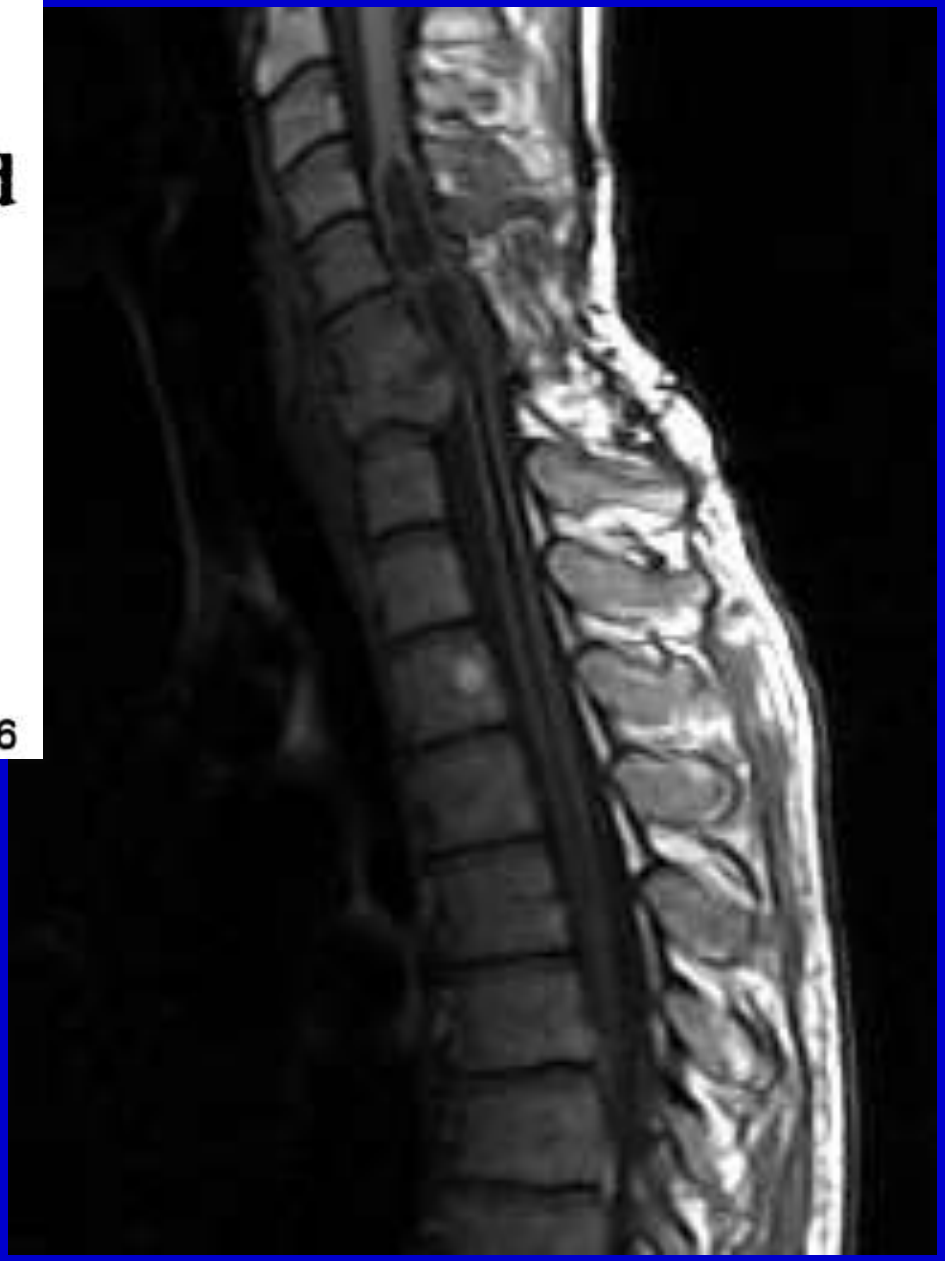
Chronic Injury Processes Days to Years

- Apoptosis (orthograde and retrograde)
- Receptor upregulation/activation
- Scaring/tethering
- Demyelination/conduction deficits
- Cyst formation
- Regeneration of cut axons
- Sprouting of intact axons
- Central sensitization
- Neural circuit changes

Hulsebosch ASIA, Dallas 2005





Post-traumatic syringomyelia

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Recovery mechanism

Mechanism	Time after injury
Resolution of acute injury events	Minutes to 7 days
Resolution of secondary injury processes	2 hours to 4 weeks
Regrowth or regeneration	24 hours to years

Hulsebosch ASIA, Dallas 2005

Research strategy

International Spinal Research Trust (ISRT) gave in 2000 their view on the directions the research should be directed to reach the goal:

Ramer et al. A refined strategy for the International Spinal Research Trust. Research review. Spinal Cord 2000;38:449-72

Research strategy

- Minimising the deleterious effects of early trauma, inflammation and scar deposition

Research strategy

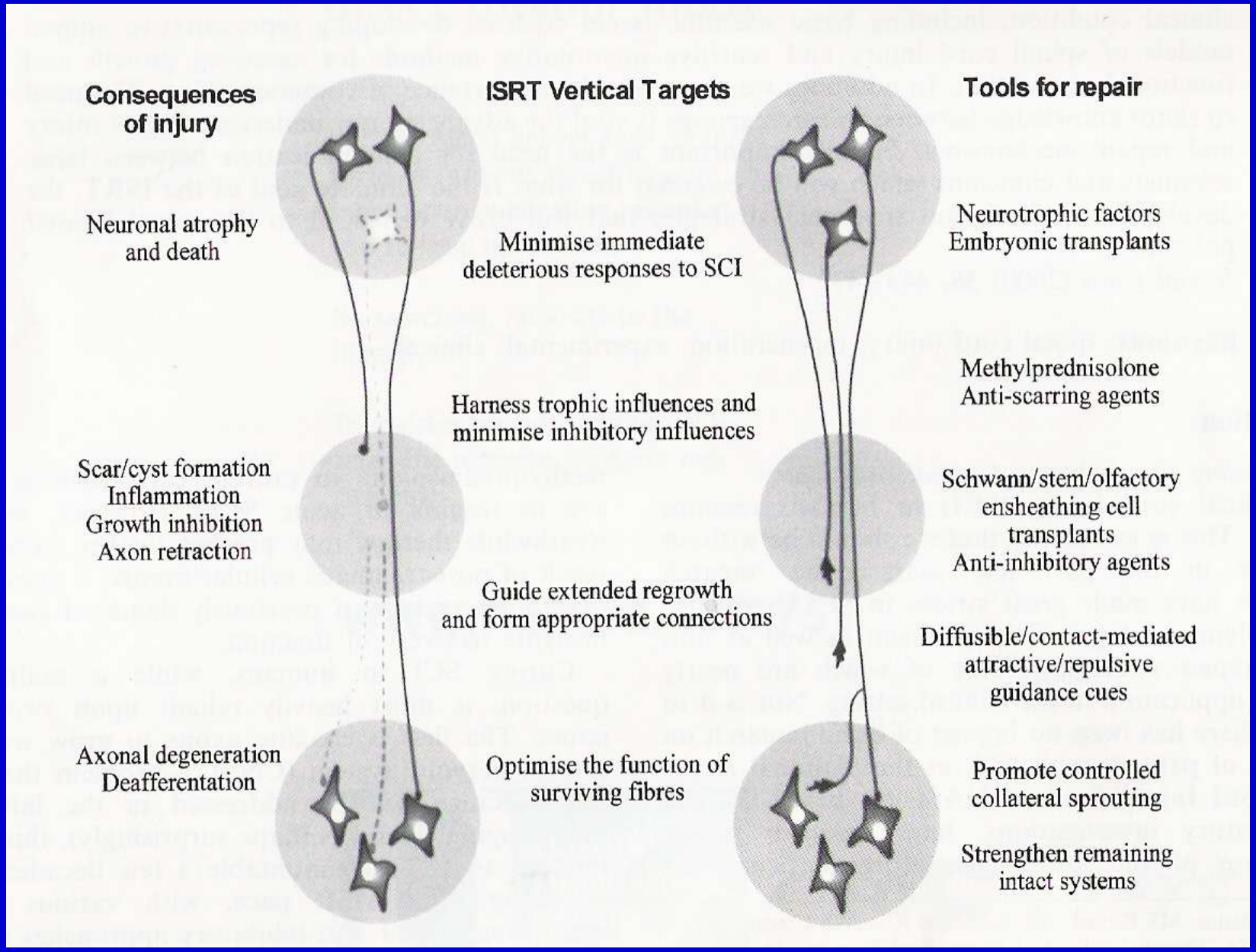
- Combining trophic support with blockade of inhibitory influences in the damaged cord to promote regeneration

Research strategy

- Sustaining directed outgrowth, resulting in appropriate re-connection of damaged axons with targets

Research strategy

- In cases of partial cord damage, exploiting the function of surviving, intact fibres



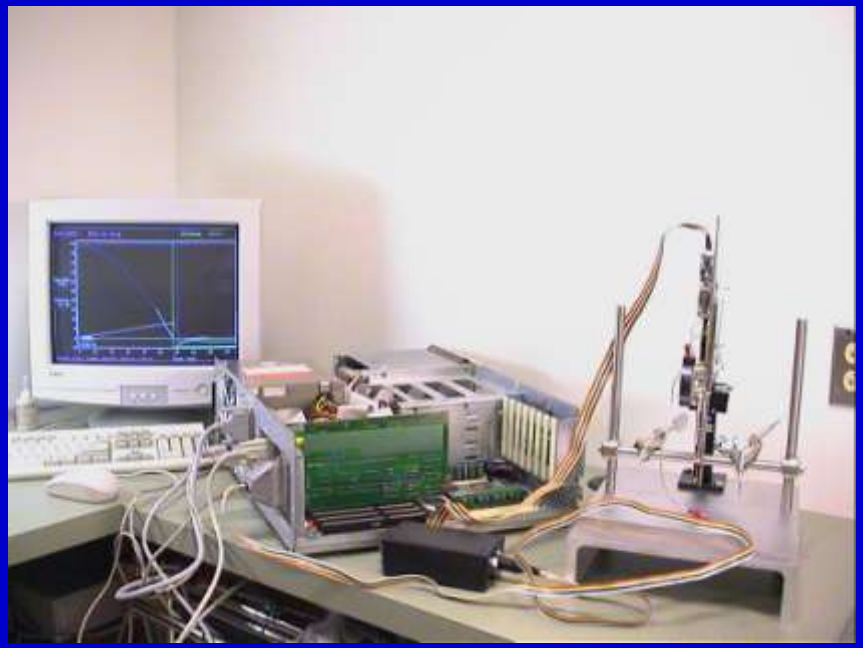
Ramer et al. Spinal Cord 2000;38:449-72

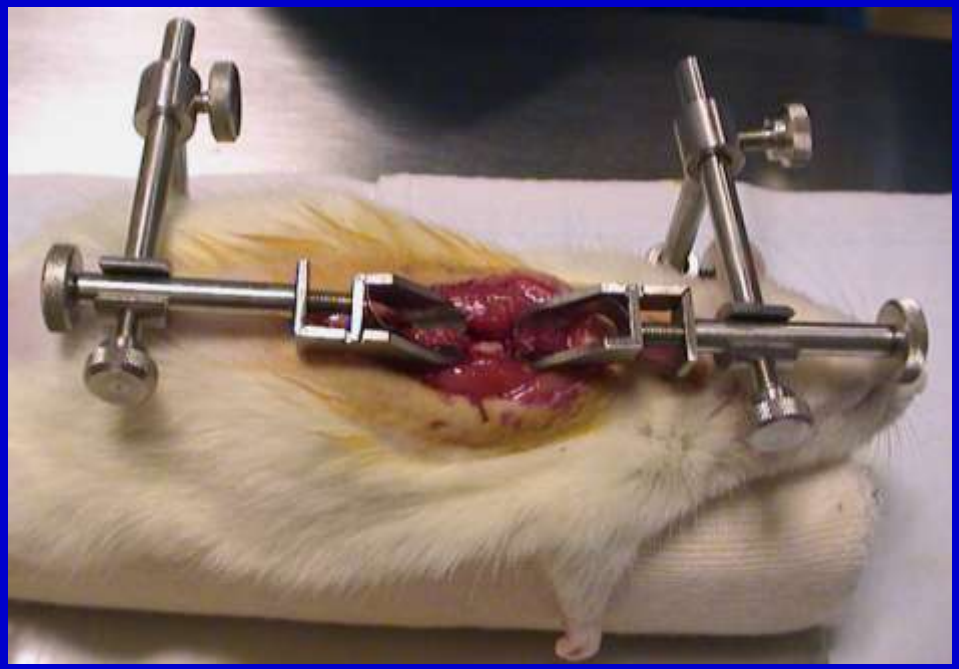
Research strategy

Capabilities' required to support these goals consist of:

Research strategy

- Developing representative animal models of spinal cord injury





New York University Impactor

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Research strategy

- Developing sensitive, quantitative methods for assessing axonal regrowth and functional recovery in the laboratory and in the clinic

More sensitive measures, optimized to evaluate specific clinical targets will be needed. Complicated by the fact that each treatment:

- Has a different biological action or targets.
- May be delivered at different times after SCI
- Is provided to people with distinctly different levels of SCI damage
- Will potentially have distinct benefits or detriments, since every person with SCI has a somewhat unique set of functional capabilities.

Steeves et al. Spinal Cord 2004;42:591-7

Trials in acute stages after SCI

The outcome is not known for the individual patients

- Considerable variability
- Large sample sizes, using a number of different outcome measures, with randomized controls and double-blind protocols

Steeves et al. Spinal Cord 2004;42:591-7

Trials in later stages after SCI

Over 2 years after SCI the situation is often relatively stable in terms of functional capability, and they have learned to report subtle functional changes and thus might serve as their own control group.

- More predictable outcome
- Smaller sample sizes needed to establish efficacy

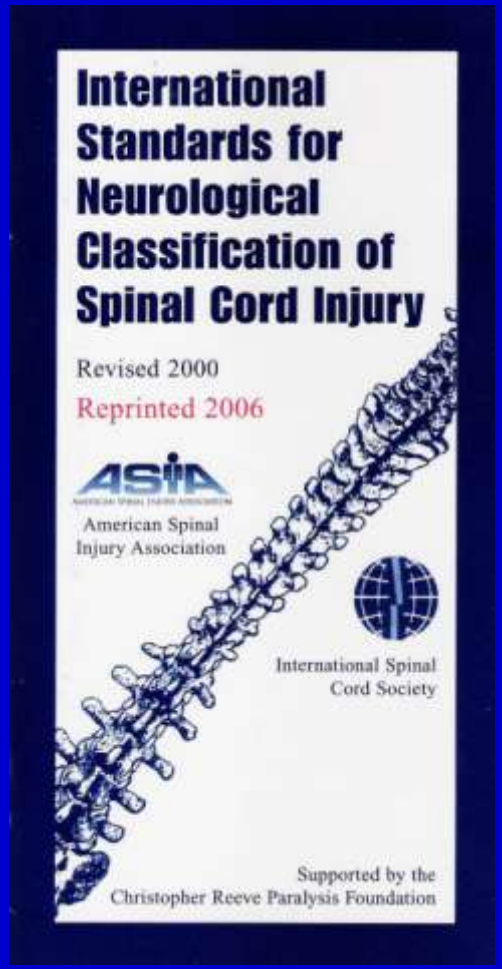
Steeves et al. Spinal Cord 2004;42:591-7

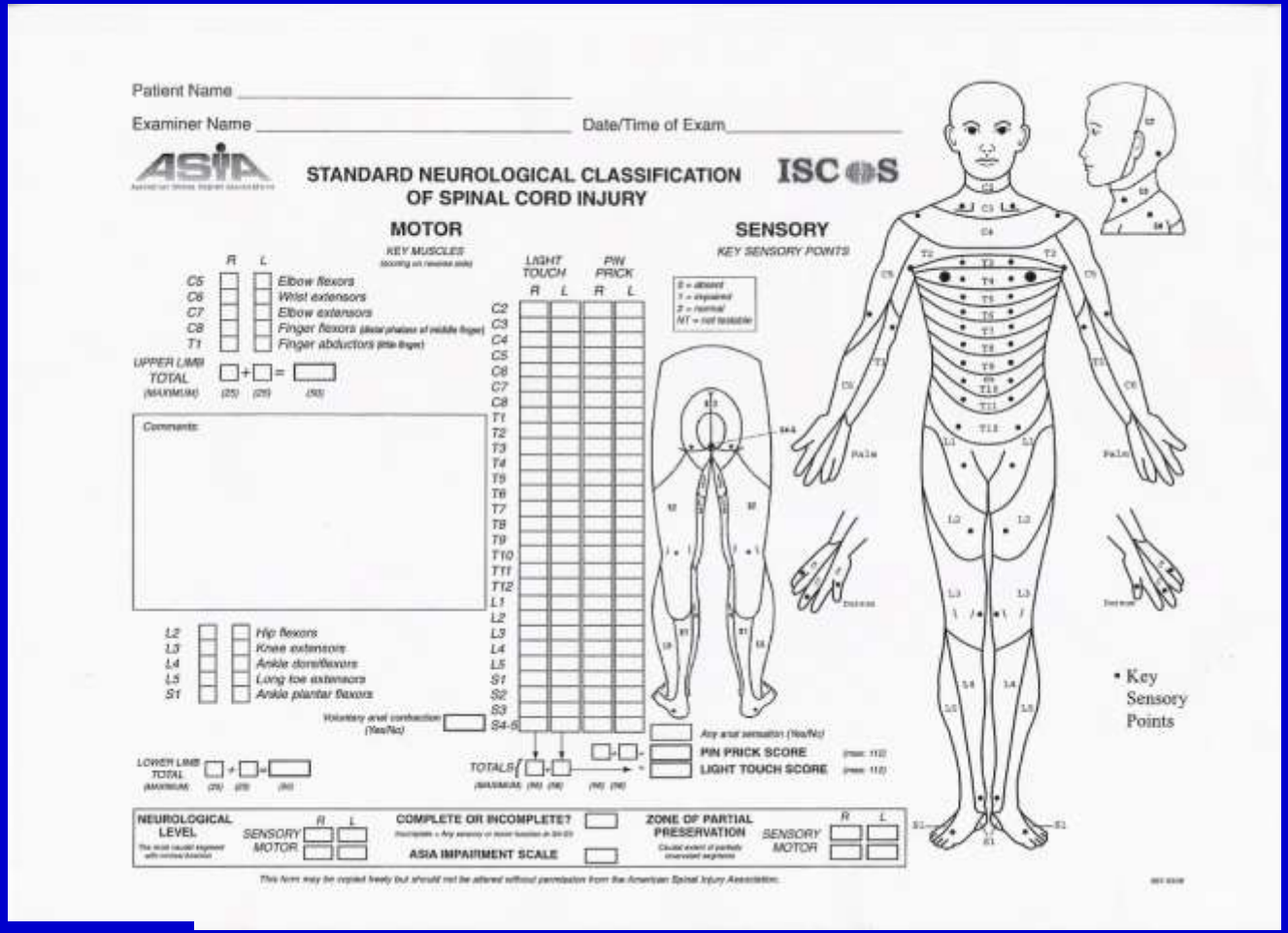
Assessment methods

ISRT team: Developing assessment methods aimed at thoracic level spinal cord injuries:

- Graded electrical skin stimulation for quantification of sensory thresholds
- EMG recordings of muscle activation triggered by cortical magnetic stimulation – intercostals/paraspinal

International Standards for Neurological Classification of Spinal Cord Injury





www.asia-spinalinjury.org

Marino RJ, Barros T, Biering-Sorensen F, Burns SP, Donovan WH, Graves DE, Haak M, Hudson LM, Priebe MM. International standards for neurological classification of spinal cord injury. J Spinal Cord Med 2003; 26(suppl.1): S50-S56.

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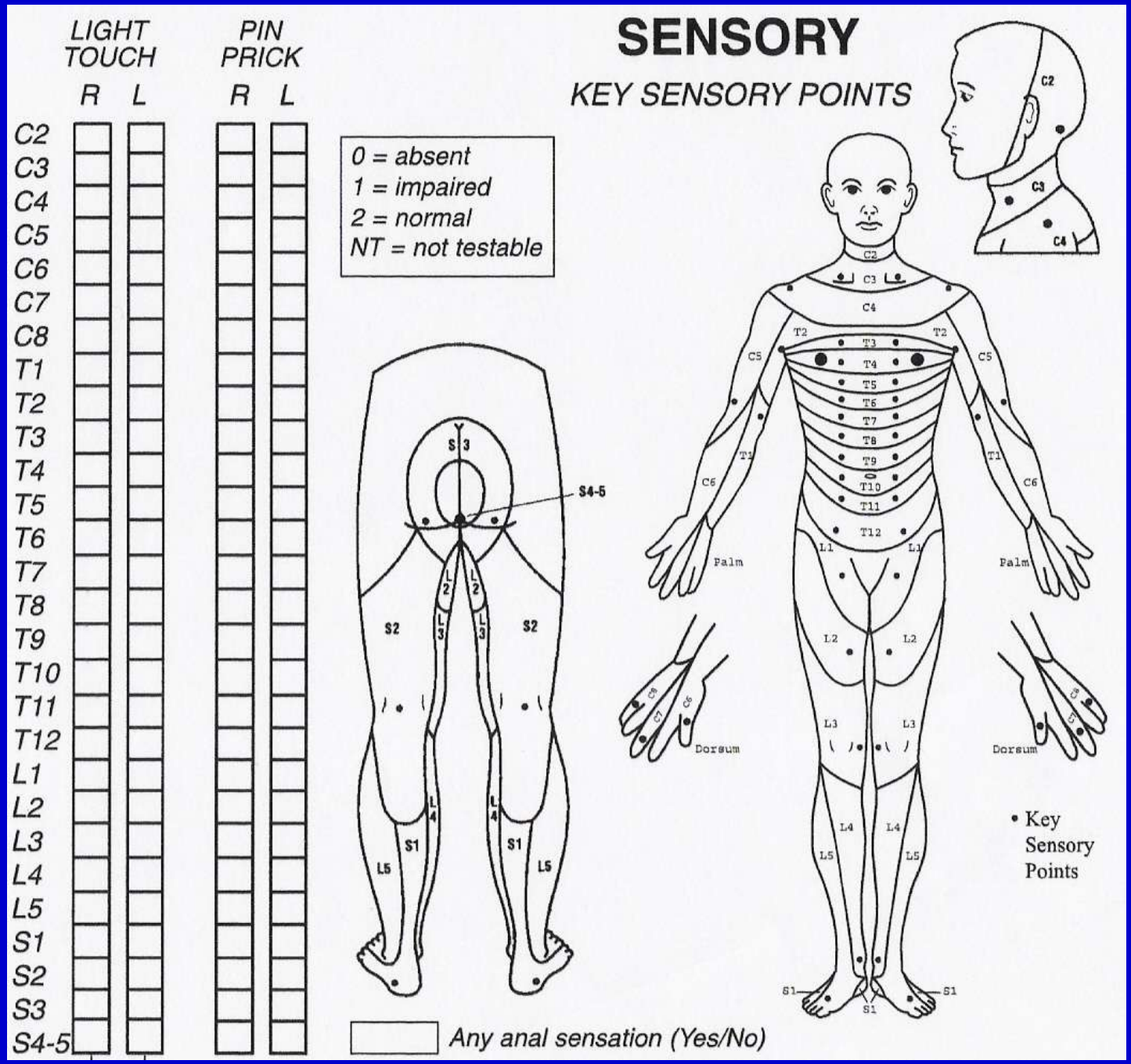

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Research efforts should incorporate functional outcome measures that include:

- Bladder and bowel function
- Measures of cardiovascular response (autonomic dysreflexia)
- Sexual function
- Elimination of chronic pain as well as locomotion and trunk stability measures

Anderson KD. J Neurotrauma 2004;21:1371-83.

Phase I trials

Involve a small number of patients and may not utilize controls.

- Safety
- Begin to establish pharmacokinetics
- Establish highest tolerated dose
- Some preliminary evidence of efficacy

Steeves et al. Spinal Cord 2004;42:591-7

Phase II trials

Larger with more exact protocols.

- Maintain safety (e.g. possible toxicity or deleterious side effects)
- Establish which instruments will be most useful in showing efficacy in phase III trials

Steeves et al. Spinal Cord 2004;42:591-7

Phase III trials

Large-scale multi-centre trials, rigorously comparing the efficacy of a new treatment with the current standard treatment.

- Clearly defined inclusion and exclusion criteria
- Small number of defined clinical end points and a blinded evaluation of accurate outcome measures

Steeves et al. Spinal Cord 2004;42:591-7

Timing of treatment

Neuroprotective treatment:

Soon after injury – window of opportunity defined

Axonal regeneration treatment:

might be effective weeks after injury – possible to predict neurological outcome if the individual is not treated

Plasticity-inducing rehabilitation:

might be effective months or years after incomplete injuries

Steeves et al. Spinal Cord 2004;42:591-7

Targets for development of restorative therapies in SCI The 6 R's

1. **Reduction** *of secondary cell death and axon damage (neuroprotection)*
2. **Replacement** *of lost cells, particular lower motor and/or propriospinal neurons*
3. **Repair and**
4. **Regeneration** *of damaged axonal systems*
5. **Remyelination** *of spared, demyelinated, axons or regenerating fibres*
6. **Rehabilitation** *to enhance plasticity, modulate reflexes, and improve function.*

Kleitman N. J Spinal Cord Med 2004;27:311-8

POTENTIAL TREATMENTS

1. ***Protection*** to prevent death of neural cells undamaged by the initial injury
2. ***Stimulation axonal growth***, either by enhancing the intrinsic regenerative capacity of spinal and supraspinal neurons or by blocking or removing endogenous inhibitors to repair
3. ***Bridging***, to provide a permissive substrate for elongating axons and to replace lost tissue
4. ***Enhancing axonal transmission***, to alleviate conduction block in spared or regenerated axons
5. ***Rehabilitation***, to enhance functional plasticity within surviving circuits and consolidate anatomical repair.

Ramer et al. Spinal Cord 2005:1-28

NEUROPROTECTION

- ***Methylprednisolone***
- ***GM-1 gangliosides***
- ***Tirilazad mesylate***
- ***Insulin***
- ***EPO***
- ***Minocycline*** (second generation tetracycline derivative) – antiinflammatory – inhibit microglial activation, to promote oligodendrocyte survival, to reduce lesion-induced cavity formation, and to prevent the retraction or dieback of injured axons.
- Direct application of ***neurotrophic factors*** may prevent neuronal atrophy, and stimulate expression of axonal growth-associated genes.

Critisims of NASCIS II

- Positive effect only in a post-hoc subgroup, but not in the initial patient population as a whole
- Small effect sizes
- Increased risk of sepsis

Remembered when criticizing NASCIS II

- No other clinically proven treatment options
- Even small effects can lead to a significant change in lifestyle for individuals with spinal cord injuries

NASCIS II & III

Several Societies:

- The use of steroids for acute SCI is a **treatment option** (unclear clinical certainty, based on Level II or III data)
- **Not** endorsed as either **standard** of care (supported by Level I study) **or** a **guideline** (moderate clinical certainty supported by at least one Level I study)

Stimulation axonal growth

Myelin inhibitor molecules (examples):

- NogoA
- Myelin-associated glycoprotein (MAG)
- Oligodendrocyte myelin glycoprotein (OMgp)

Signal through a common receptor – Nogo receptor NgR

Antagonists of NgR:

- NEP1-40
- NgREcto
- Anti-NgR monoclonal antibody

Ramer et al. Spinal Cord 2005;43:1-28

Stimulation axonal growth

Myelin-derived inhibition reduction at the site of SCI by transplantation of autologous macrophages:

Activated autologous macrophages entered clinical multicentre-trial (ProNeuron).

All patients received the treatment within 14 days of SCI – therefore initial clinical outcome difficult to interpret. In spite:

Phase II multi-centre trial ongoing.

Small pilot positive, but in the randomized trial it did not work! (2009)

Stimulation axonal growth

Neurotrophic factors:

Ability to induce regeneration-associated gene (RAG) expression and to promote elongation of neurons.

Mostly the growth-enhancing effect of neurotrophic factors at the site of SCI were tested in conjunction with other manipulations, e.g. fetal cord transplants or peripheral nerve grafts.

Ramer et al. Spinal Cord 2005;43:1-28

Bridging the site of SCI

Cellular transplants:

- For axonal growth and behavioural recovery
- Deliver neurotrophic factors
- Remove inhibitory debris at the lesion site
- To stimulate remyelination

Ramer et al. Spinal Cord 2005;43:1-28

Bridging the site of SCI

For axonal growth and behavioural recovery

- **Graft of peripheral nerve**, in humans less encouraging – today → cellular transplants (better defined, can be injected and genetically modified)
- **Schwann cells** – however, supraspinal axons that enter the bridge typically do not exit caudally

Ramer et al. Spinal Cord 2005;43:1-28

Bridging the site of SCI

For axonal growth and behavioural recovery

Olfactory ensheating cells (OECs)

- glia that support growth of olfactory neurons
- permit axonal growth across a PNS-CNS interface in adults
- several clinical trials worldwide
- nasal biopsy permit autologous transplantation
- protect spinal tissue from secondary damage and cavitation (? *Chhabra et al. Spinal Cord. 2009 Dec;47(12):887-95.*), enhance vascularisation, and promote branching of neighboring axons spared by the injury

Larger trials are ungoing – up to now no well performed trials with positive results (2010)

Bridging the site of SCI

For axonal growth and behavioural recovery

Grafts of fetal spinal cord

In posttraumatic syringomyelia – final reports not published. Ethical challenge

Multipotent and progenitor cells

Neural differentiation has been limited, vast majority become glia. May be associated with tissue sparing. Russian trial difficult to interpret.

Ramer et al. Spinal Cord 2005;43:1-28

Bridging the site of SCI

For axonal growth and behavioural recovery

Several challenges for clinical translation:

- Timing of cellular transplantation
- Cell source
- Cellular maintenance/manipulation
- Immunological compounds – graft rejection

Important inherent variables that may preclude comparison of results from clinical trials at different centres.

Ramer et al. Spinal Cord 2005;43:1-28

Bridging the site of SCI

For axonal growth and behavioural recovery

Synthetic implants:

- Identical and reproducible in composition
- Immunologically inert
- Absorbable
- May be used to contain/deliver neurotrophic factors or cells at the injury site and/or guide axons growing through the biosynthetic graft

Ramer et al. Spinal Cord 2005;43:1-28

Overcoming conduction block

- Schwann cells – remyelinate axons – also endogenous Schwann cells
- OECs – remyelinate axons – less!
- Progenitor cells – enhance endogenous oligendendrocyte remyelination
- Stem-like cells derived from bone marrow reported to myelinate spinal axons – i.v.?
- 4-aminopyridine (Fampridine), potassium channel blocker – restores conduction in de- or dysmyelinated axons – in clinical trial in chronic SCI (Acorda Therapeutics) ??2010

Ramer et al. Spinal Cord 2005;43:1-28

Rehabilitation and CNS plasticity

- Innate and remarkable ability for the damaged CNS to undergo spontaneous or activity-dependent plastic changes
- Synapse ‘unmasking’: loss of input from the periphery can result in the rapid appearance of expanded receptive fields of the remaining cortical neurons
- Long-term changes by sprouting or rewiring of synaptic connections

Ramer et al. Spinal Cord 2005;43:1-28

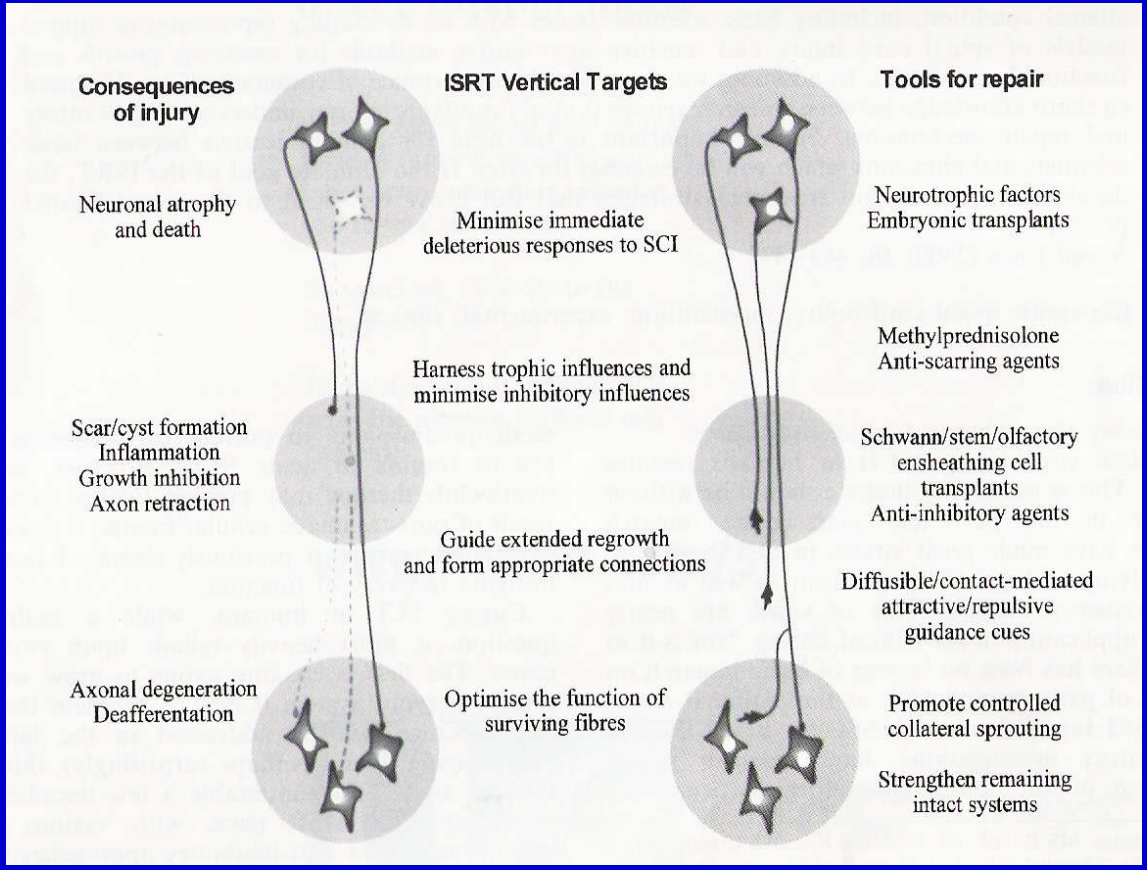
Rehabilitation and CNS plasticity

- Important to recognize that even if regeneration of injured axons is successful, or if synaptic spaces can become newly occupied by intact axons, the target in both cases is profoundly altered by injury. As a consequence, functional recovery will inevitably require some form of retraining

Ramer et al. Spinal Cord 2005;43:1-28

THERE MAY BE A LONG WAY

- DISTANCE
- TIME



A useful **preclinical research** method is to model human disease in animals so that detailed information can be obtained regarding the effects of experimental treatments on injury and disease.

Translational medicine is feedback oriented, i.e. iterative (clinical knowledge -> hypothesis and preclinical research testing -> clinical testing -> refinement of hypothesis and additional preclinical testing, etc.)

Clinical trials are human experiments where the ability of a new treatment to improve outcome from a disease is tested in comparison to the best previously established alternative, or placebo treatment if no established treatment exists.

Rehabilitation and CNS plasticity

- Appropriate training to enhance recovery after damage
- Overactivity or stressful regimes can impede rather than enhance functional recovery
- Central pattern generators – humans also?
- Suggestion that the isolated spinal cord can learn – maintenance necessary!

Rehabilitation and CNS plasticity

- Treadmill training used with considerable success in incomplete SCI – improvements maintained years after weeks to months training
- Complete SCI unable to maintain stepping movements after training stopped

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Combination of treatments

Combination of treatments required to address the complex issues of SCI – designing such a treatment strategy is incredible daunting:

1. Identify the best performers regarding
   - Neuroprotection
   - Stimulating axonal growth
   - Bridging the gap
   - Conducting – enhancing axonal transmission
   - Rehabilitation
2. Find the appropriate spatial and temporal combination

PERSPECTIVES

There have to be developed methods to make it possible to evaluate the effect on humans without risk of loss of function.

PERSPECTIVES

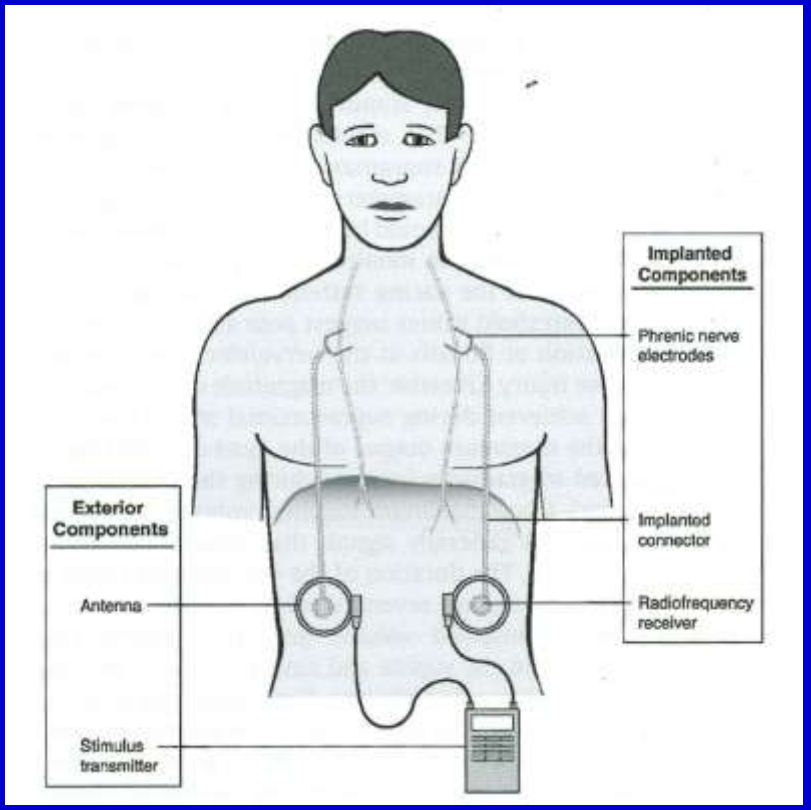
Until it become possible to reestablish and reconnect the neural pathways the practical development and research will try to find possibilities to improve functions still without becoming as before the SCI.

PERSPECTIVES

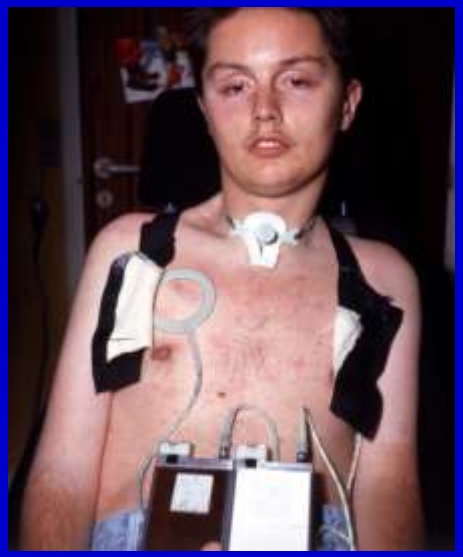
One possibility is Functional Electrical Stimulation (FES). The future development within this area will be towards smaller, lighter, more efficient, safer, more cosmetic, easier to use for the user and the clinician.

PERSPECTIVES

In FES systems we will see the use of an array of feed-back systems, which will make the systems better. Indications for the use of FES may also gradually be extended so more SCI individuals can have use of this technology.



Phrenic nerve stimulator - Diaphragm-pacemaker



Phrenic nerve stimulation significantly reduces frequency of respiratory infections compared to mechanical ventilation. Quality of speech is significantly better. Easier nursing.

Hirschfeld et al. Mechanical ventilation or phrenic nerve stimulation for treatment of spinal cord injury-induced respiratory insufficiency. Spinal Cord 2008;46(11):738-42.

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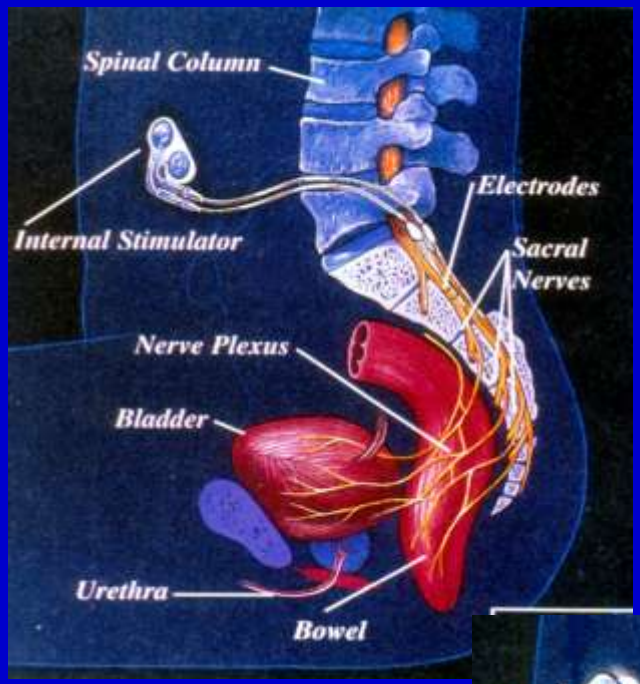
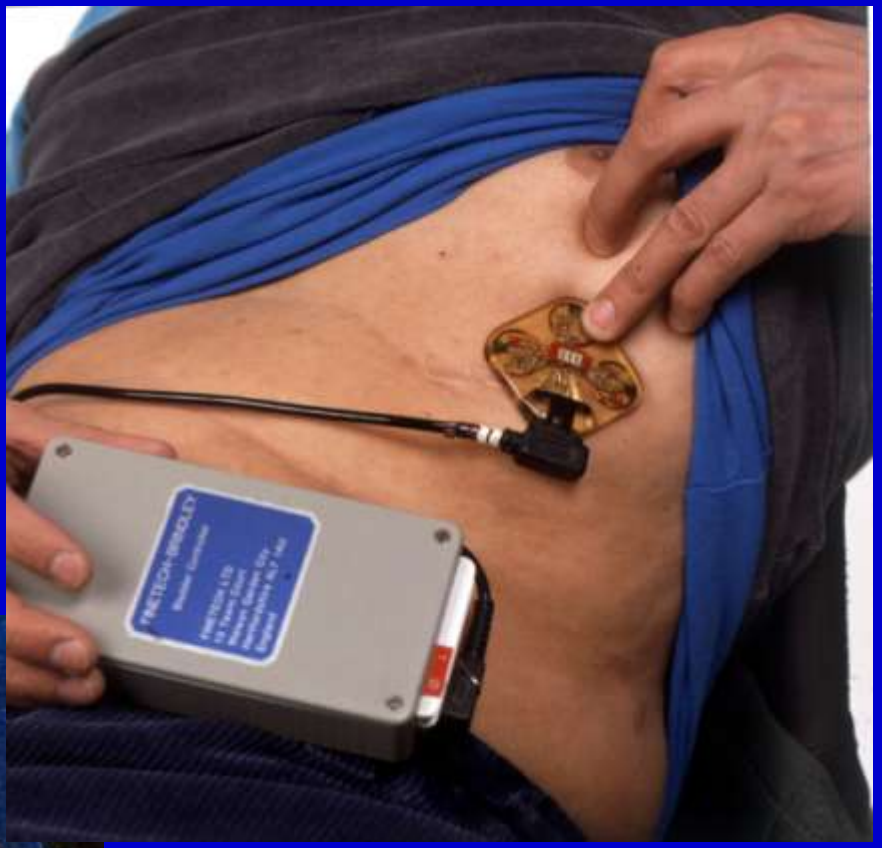
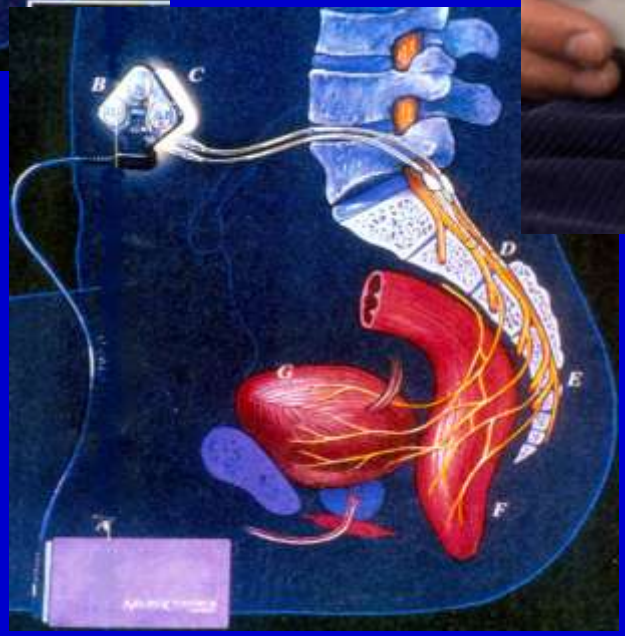


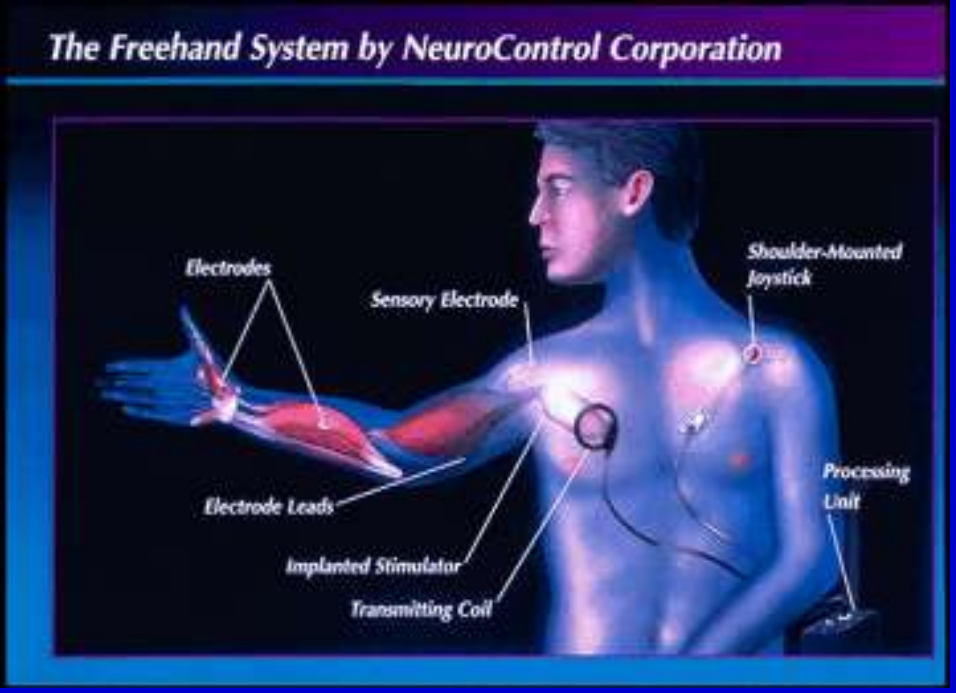




Bladder
Bowel
Impotence

Sacral Anterior Root Stimulator

FreeHand System



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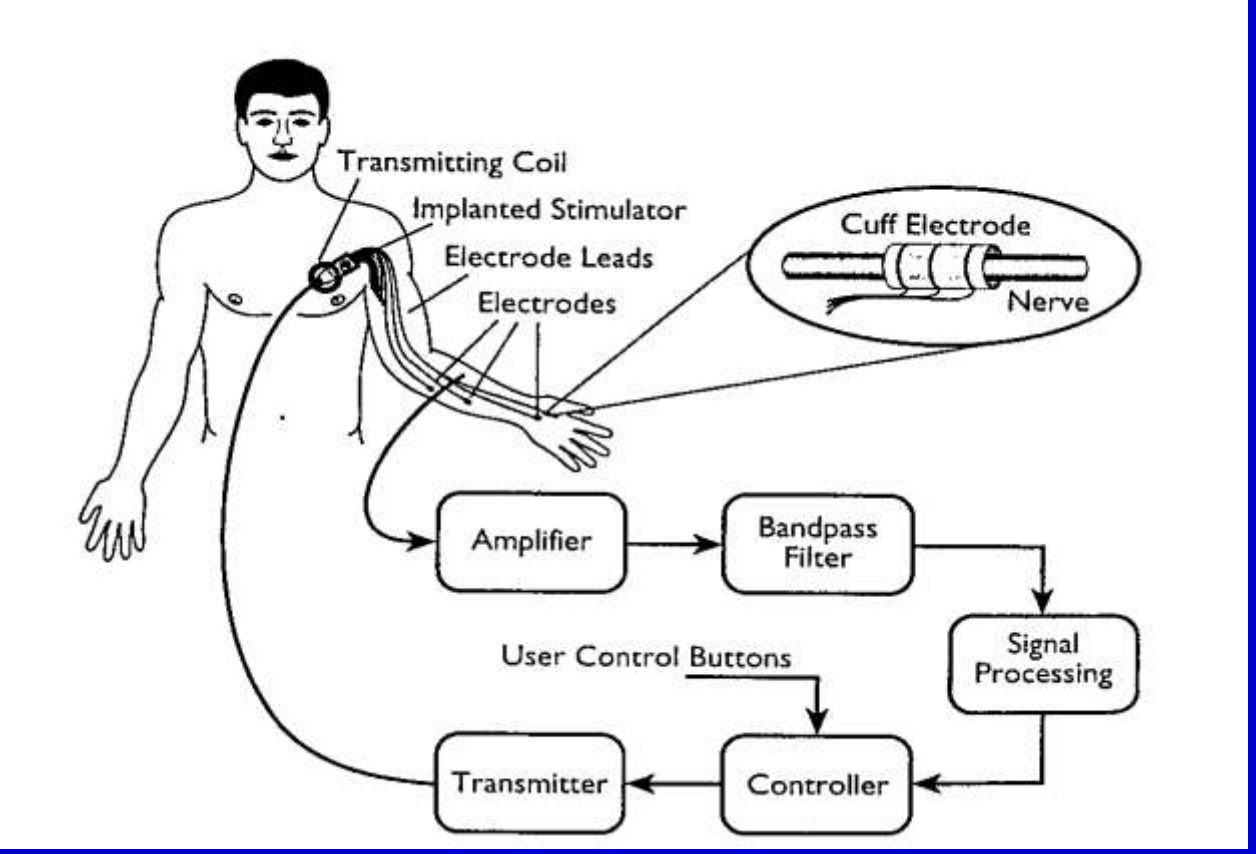

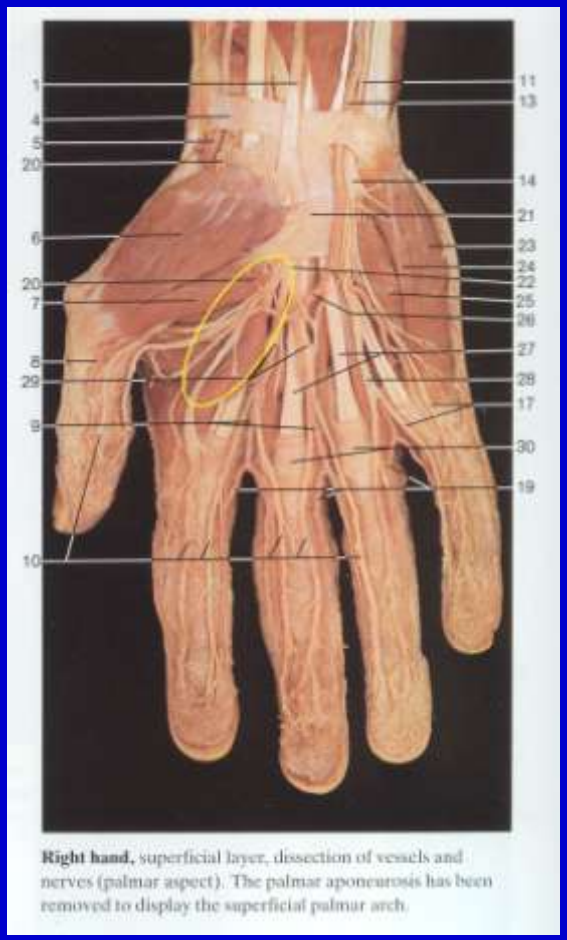

Right hand, superficial layer, dissection of vessels and nerves (palmar aspect). The palmar aponeurosis has been removed to display the superficial palmar arch.

The electrode nerve cuff is 18mm long, the inner diameter is 3mm and the wall is app. 1mm thick.

SMI Ålborg University

Inmann et al. 2001

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Electrical stimulation

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Too many electrodes!

Cure—Not Care®

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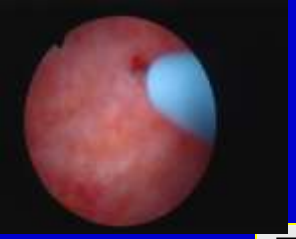
PERSPECTIVES

Technology generally will become an important element to improve the possibilities for individuals with SCI, partly in the development of new treatments, and not least in the development of better aids, which can ease the everyday life.

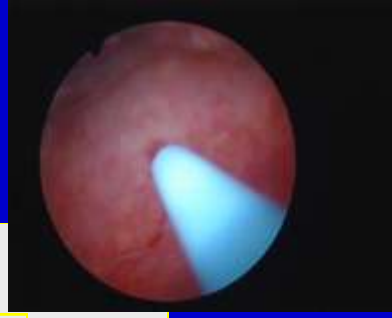
PERSPECTIVES

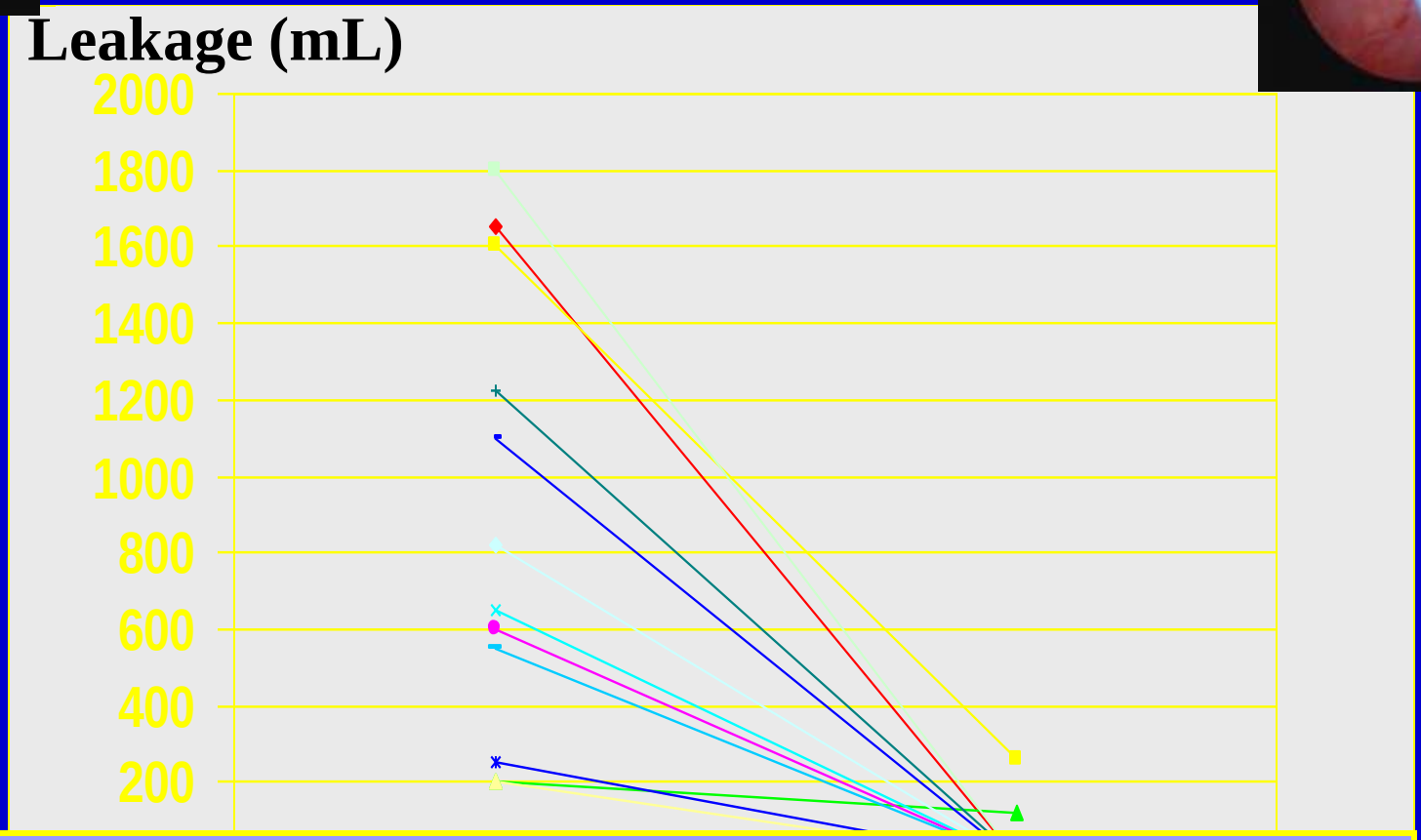
There will continuously be a development in the possibilities within central areas like bladder and bowel management, and likewise there is hope for the challenges related to spasticity and pain treatment, as these are some of the fields of importance to the SCL individuals.



BOTULINUM TOXIN

Effect (Leakage (mL))

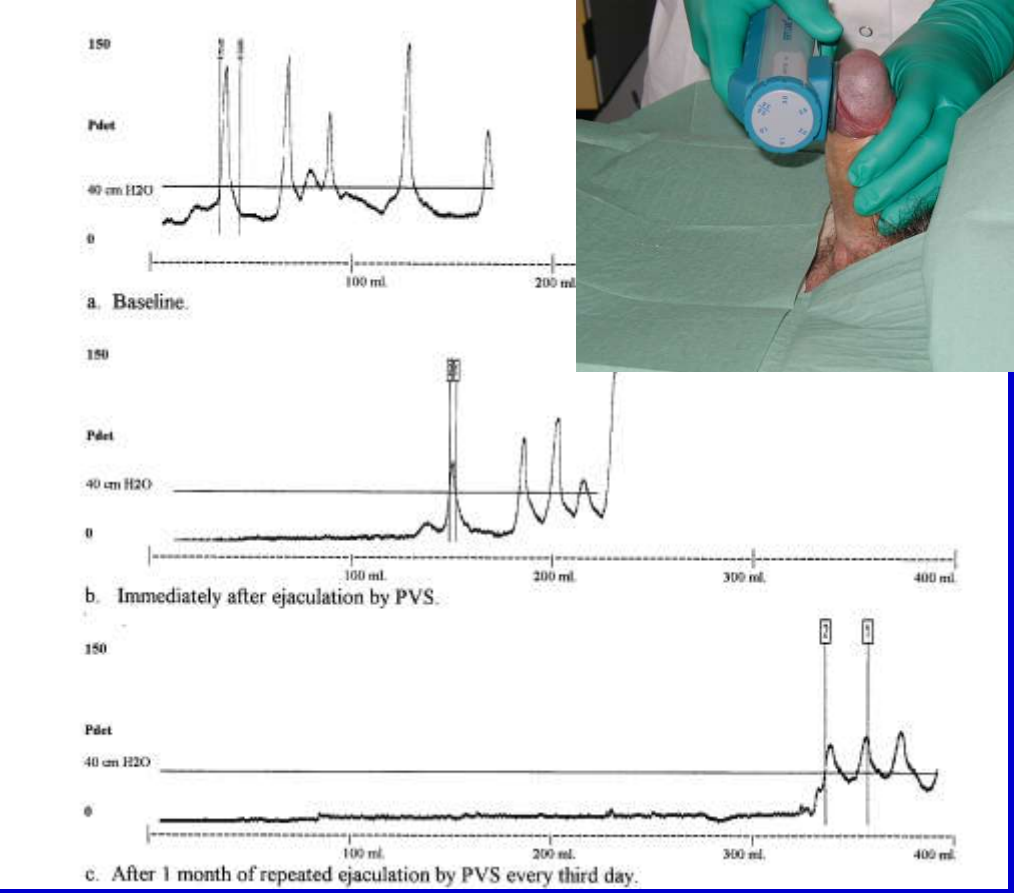




Before Botox (mL)	After Botox (ml)
735 (200-1800)	0 (0-250) ***

***) p<0.0005

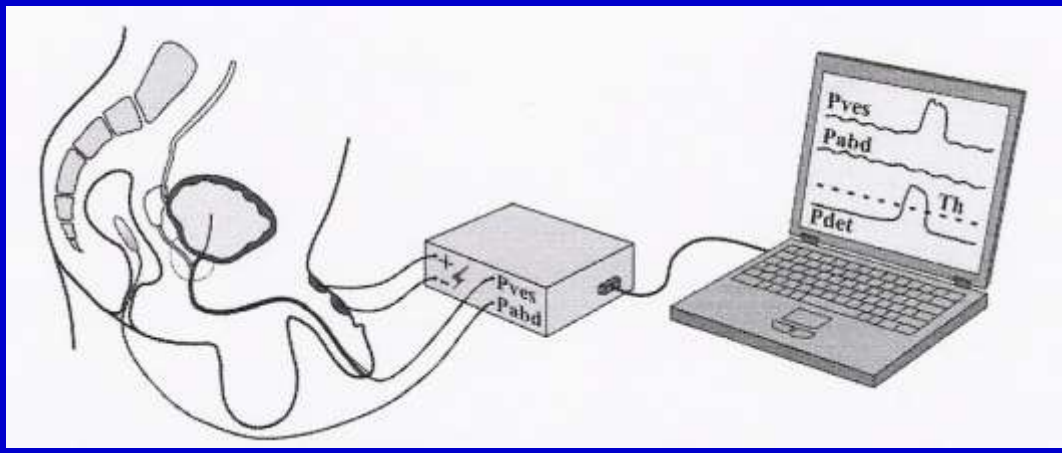
Bagi & Biering-Sørensen 2004



Læssøe et al. Effects of ejaculation by penile vibratory stimulation on bladder reflex activity in a spinal cord injured man. J Urol 2001;166:627.

Læssøe et al. Effects of ejaculation by penile vibratory stimulation on bladder capacity in men with spinal cord lesions. J Urol 2003;169:2216-9.

Hansen et al. Treatment of neurogenic detrusor overactivity in spinal cord injured patients by conditional electrical stimulation. J Urol 2005;173:2035-9.



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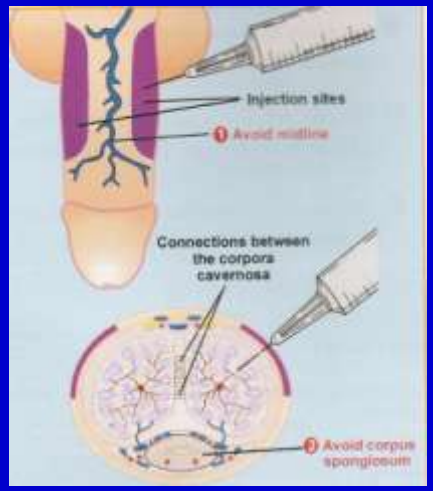
TREATMENT OF IMPOTENCE

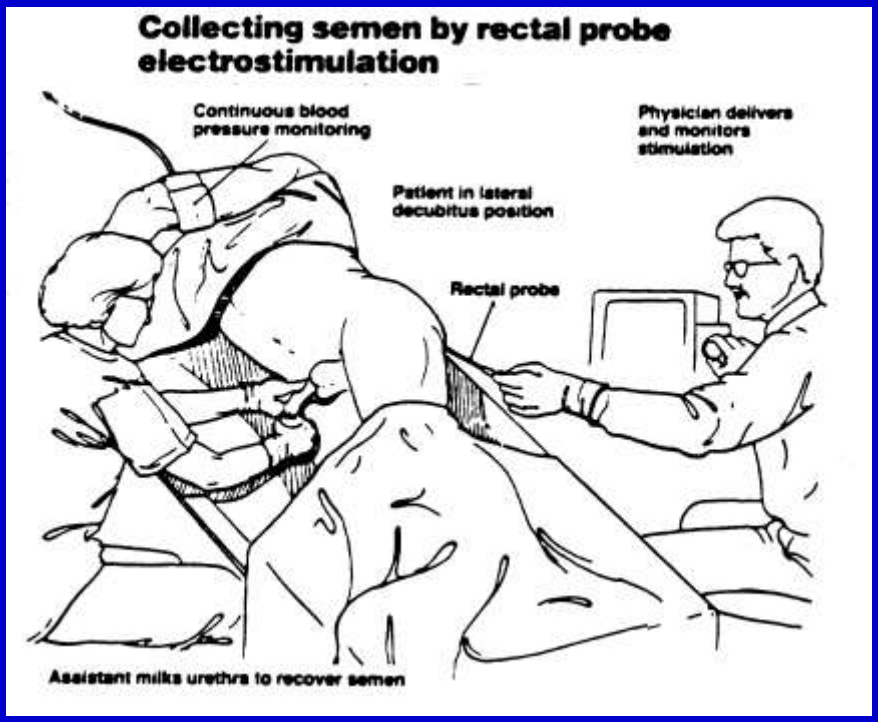
- Venous constriction band
- Viagra (Sildenafil) and others

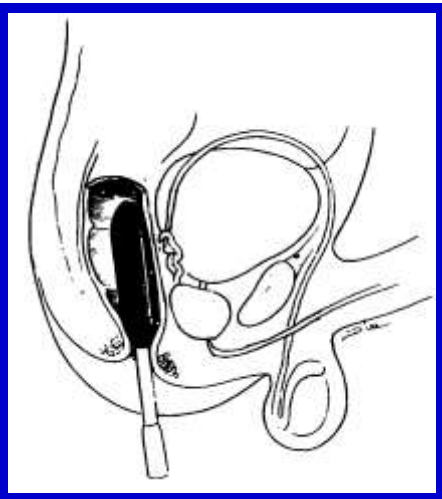
CAVE Nitrate drugs

- Intracavernous prostaglandin E_1



EJACULATION





Elec-tro-ejacu-lation

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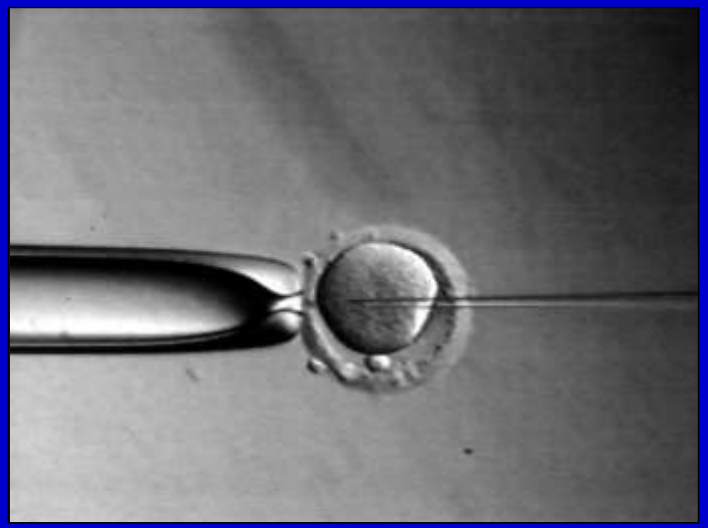
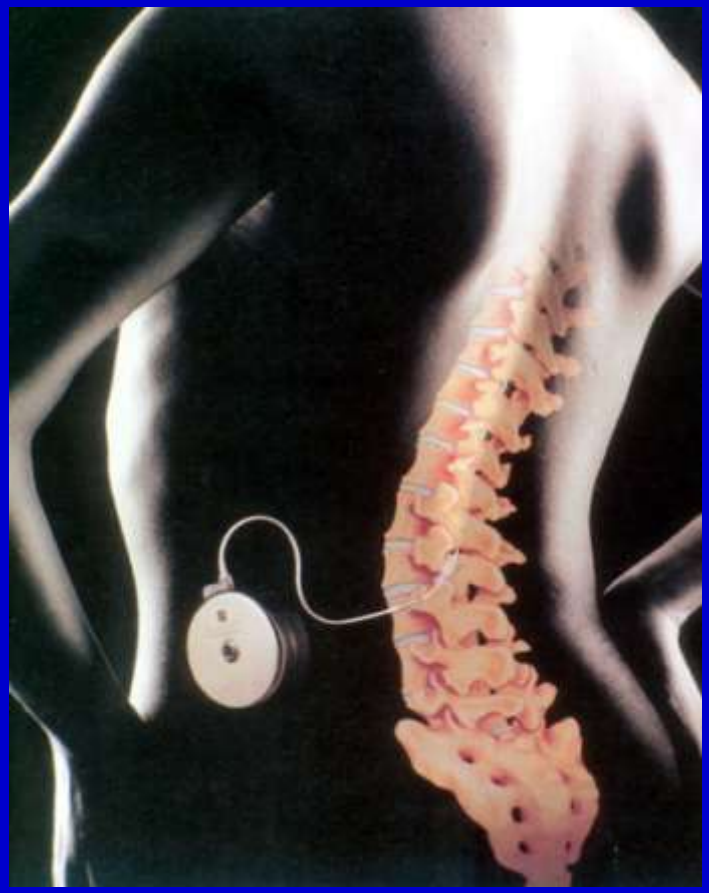
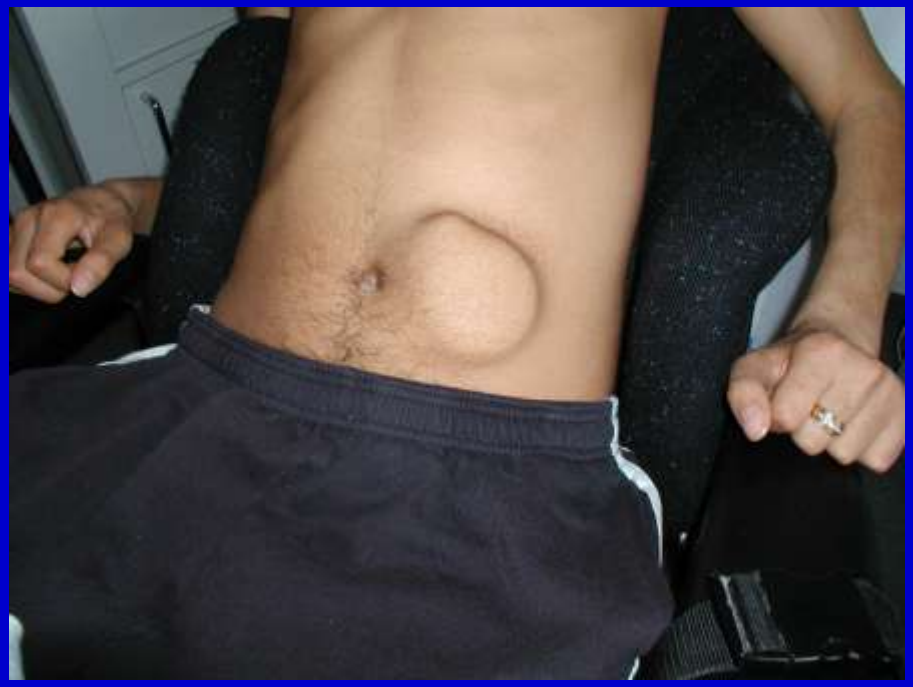
ASSISTIVE REPRODUCTIVE TECHNIQUES:

- Vaginal insemination (IVI) with PVS at home
- Intrauterine insemination (IUI)
- In vitro fertilisation (IVF)
- Intra cytoplasmic sperm injection (ICSI)



Baclofen -pump





INDICATION:

1) Not sufficient effect of, or unacceptable sideeffects of peroral medication, etc.
2) Severe inhibition of ADL due to the spasticity
3) Effect of test-dose with intrathecal baclofen

Taricco et al. Pharmacological interventions for spasticity following spinal cord injury: results of a Cochrane systematic review. Eura Medicophys. 2006 Mar;42(1):5-15.

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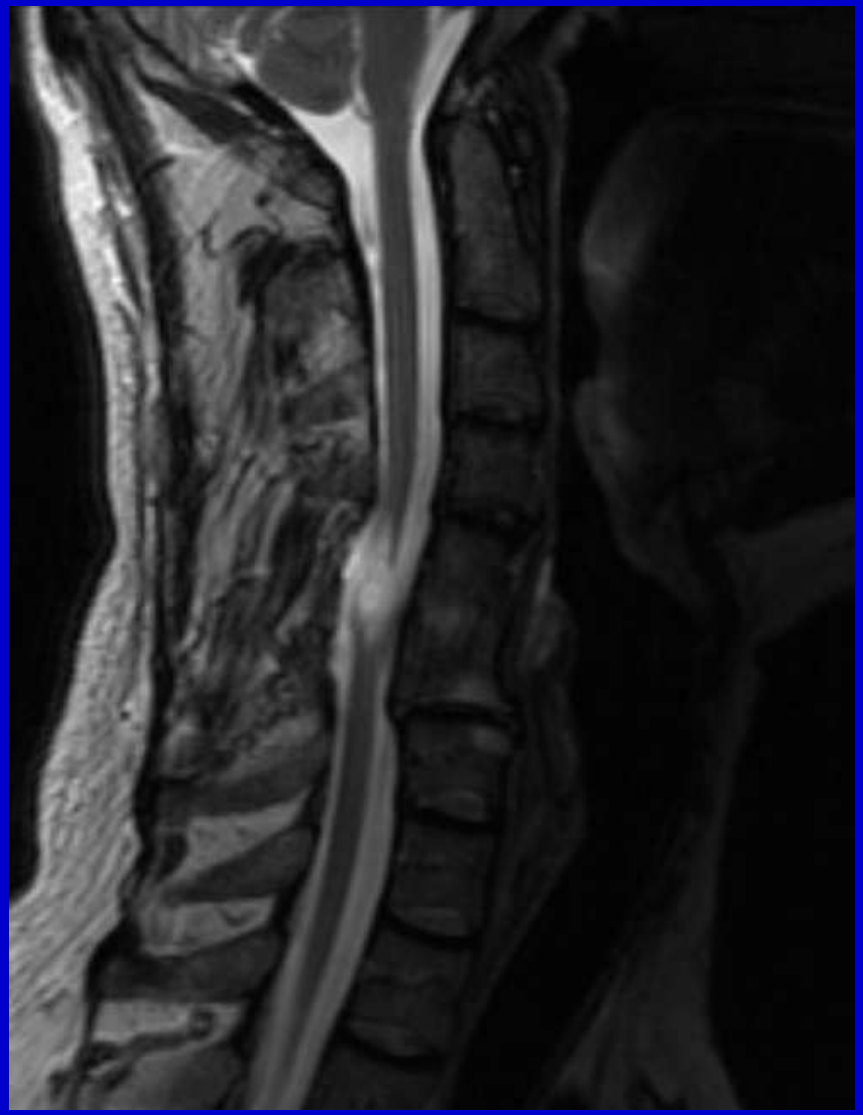
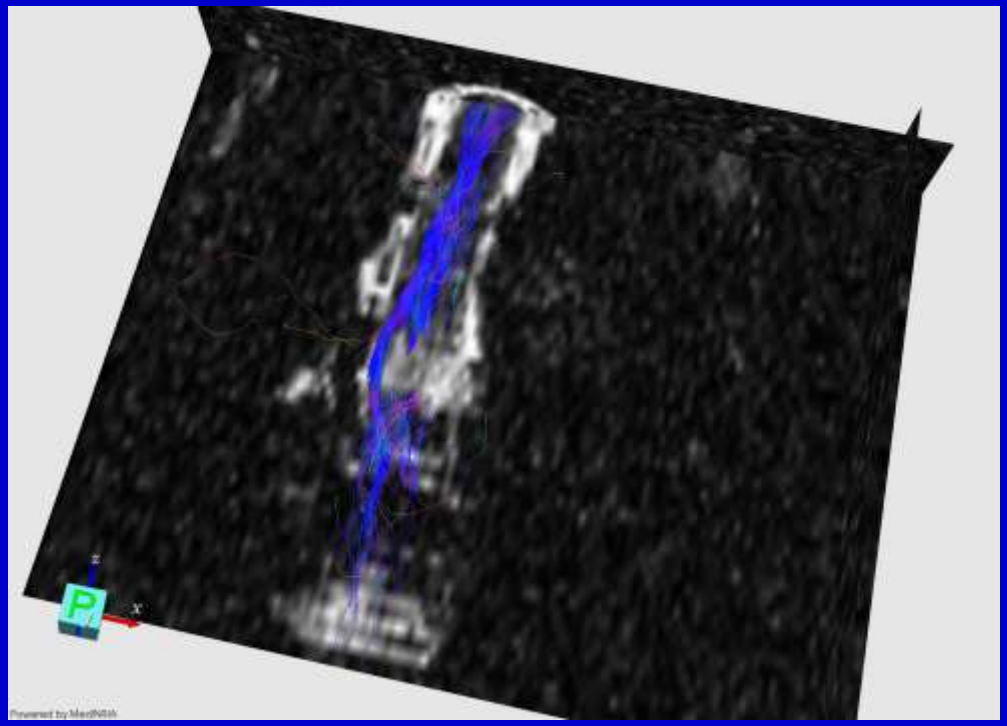
Traumatic C5-lesion imaged with conventional MRI and dti-tractografy





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Virtual reality - Treadmill training

Robotic-training

Home training

CONCLUSION

- SCI research has progressed from hopelessness to abundance of promise in a relatively short period
- Still no proven path for successful translation of promising strategies to clinical success

Kleitman N. J Spinal Cord Med 2004;27:311-8

CONCLUSION

- Each potential treatment needs to be assessed relative to the risk involved in its use and the intended target of the intervention.
- To date, the most impressive recoveries after SCI have been obtained in people with incomplete injuries undergoing active rehabilitation regimens

Steeves et al. Spinal Cord 2004;42:591-7

ALSO REMEMBER

TODAY MORE NON-TRAUMATIC THAN TRAUMATIC SCL

PRAGMATIC AND HONEST

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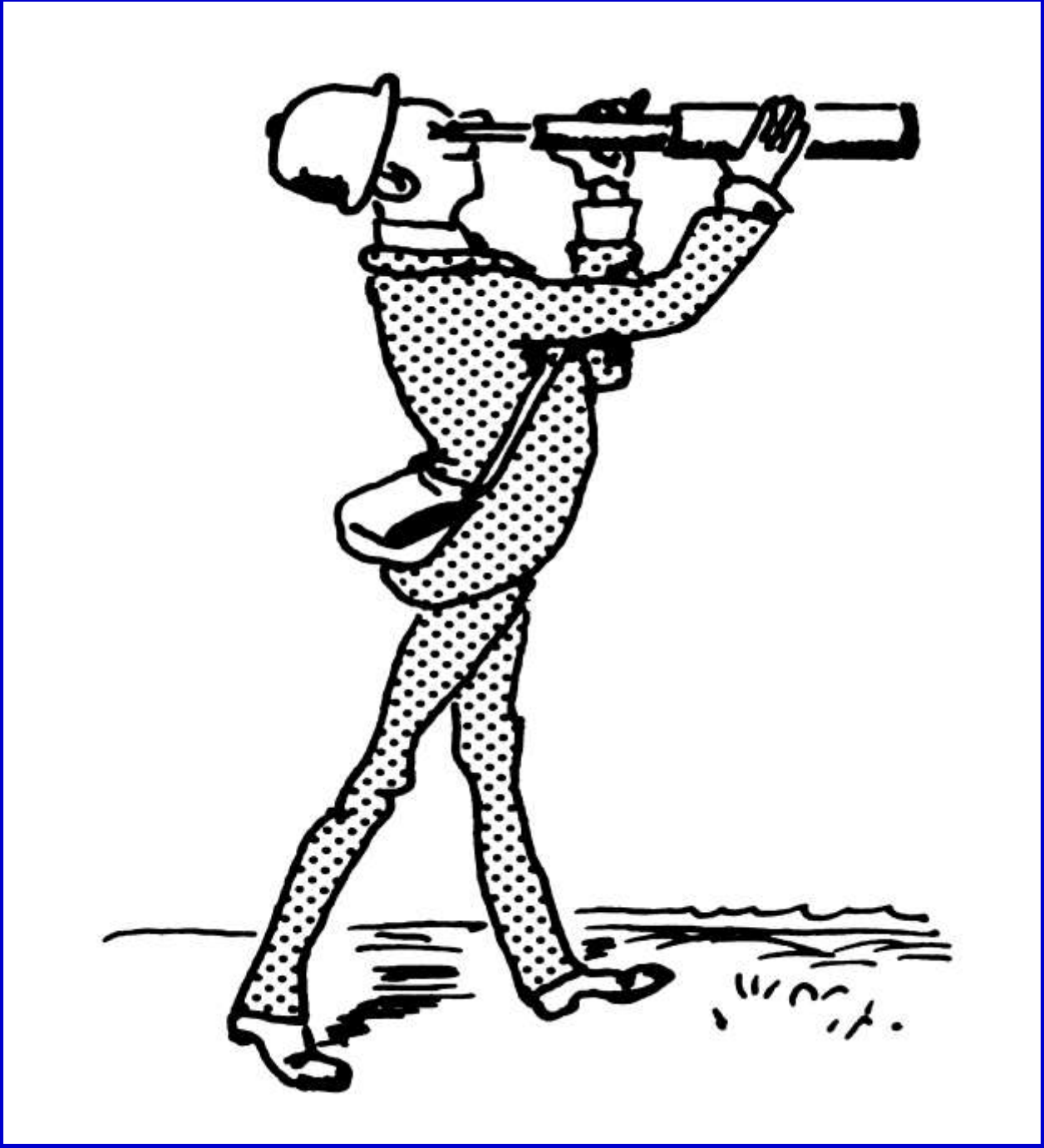


HAVE
A NICE DAY
JIM DAVIS