Spinal Cord Injury

A systematic review
of current treatment options
and
future medical therapeutic strategies
for the functional repair
of
spinal cord injury

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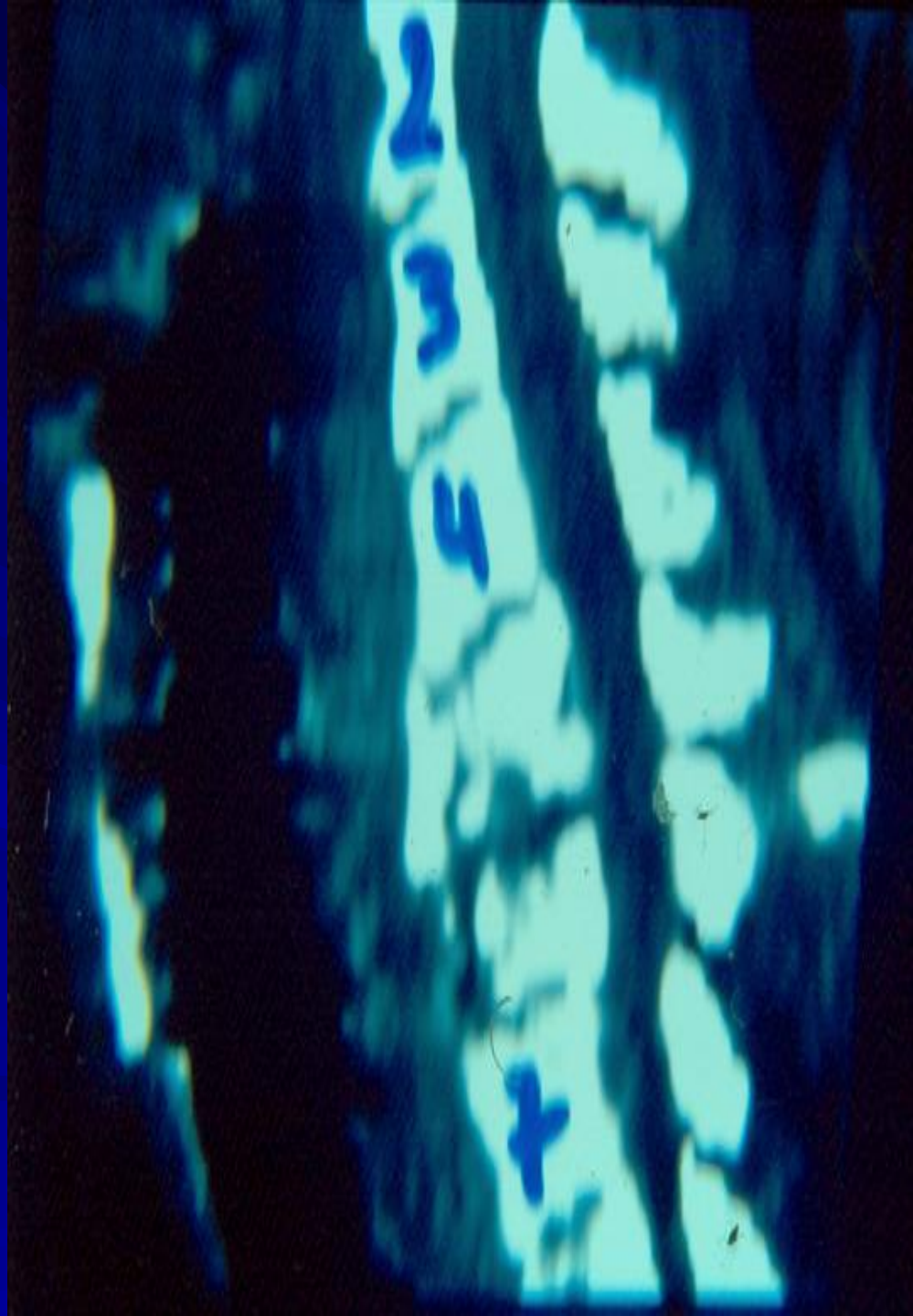
Epidemiology

- The incidence of acute SCI has been reported as 15 to 40 in a million in the world.
- Common causes :
  - Motor vehicle accidents
  - Sport injuries
  - Work related accidents
  - Assaults
  - Falls

- The majority of patients with SCI are young and the economic and societal impact is enormous,
both to the immediate family and to society at large.

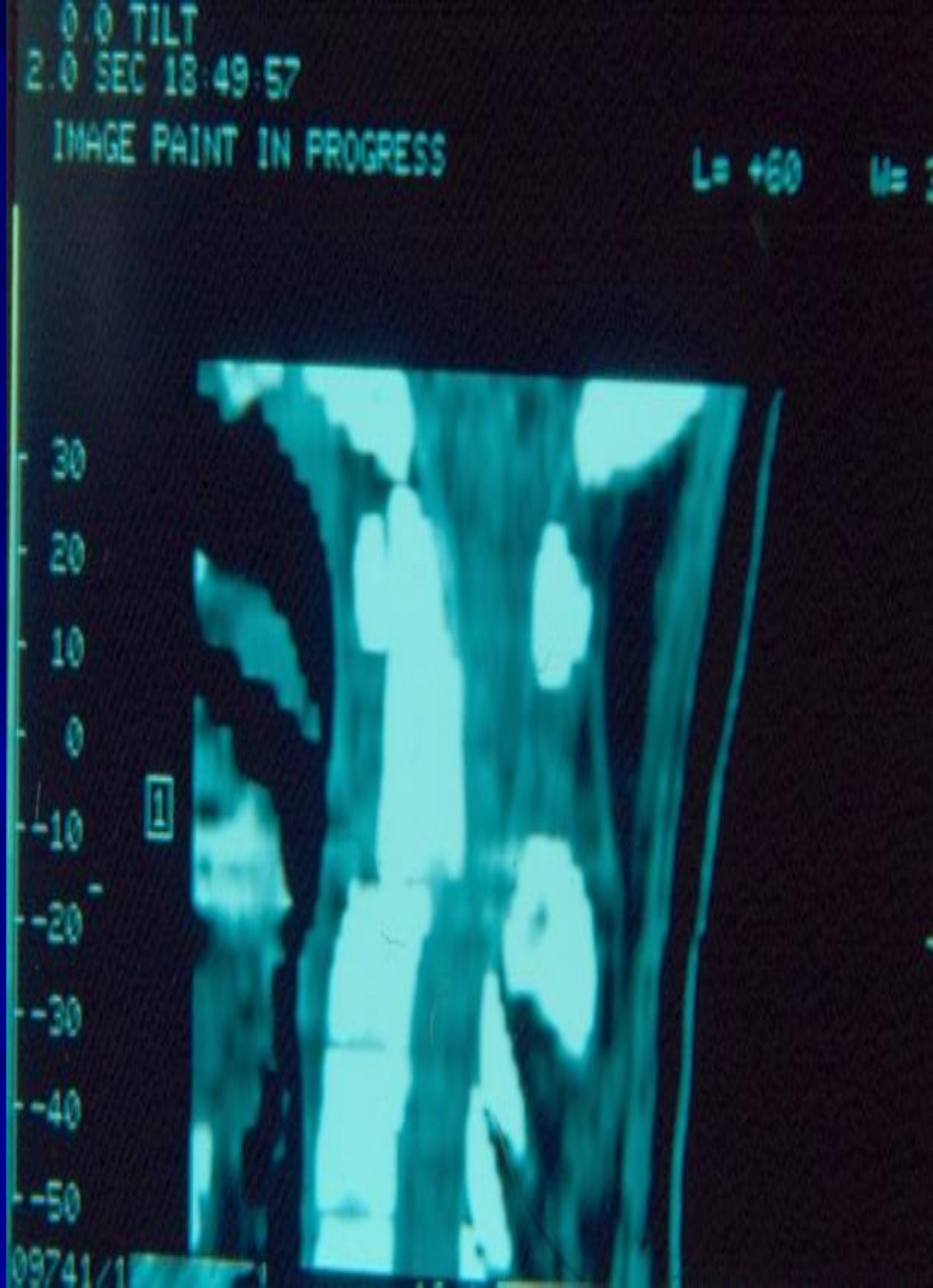
Pathophysiology

- It is now well recognized that acute SCI involves both
  - primary
  - and secondary injury mechanisms.



- The primary mechanism involves the initial mechanical injury due to:
  - local deformation and
  - energy transformation
  - that occurs within the spinal cord at the moment of injury, which is irreversible.

Bunge RP et al 1993
Kakulas BA et al 1984

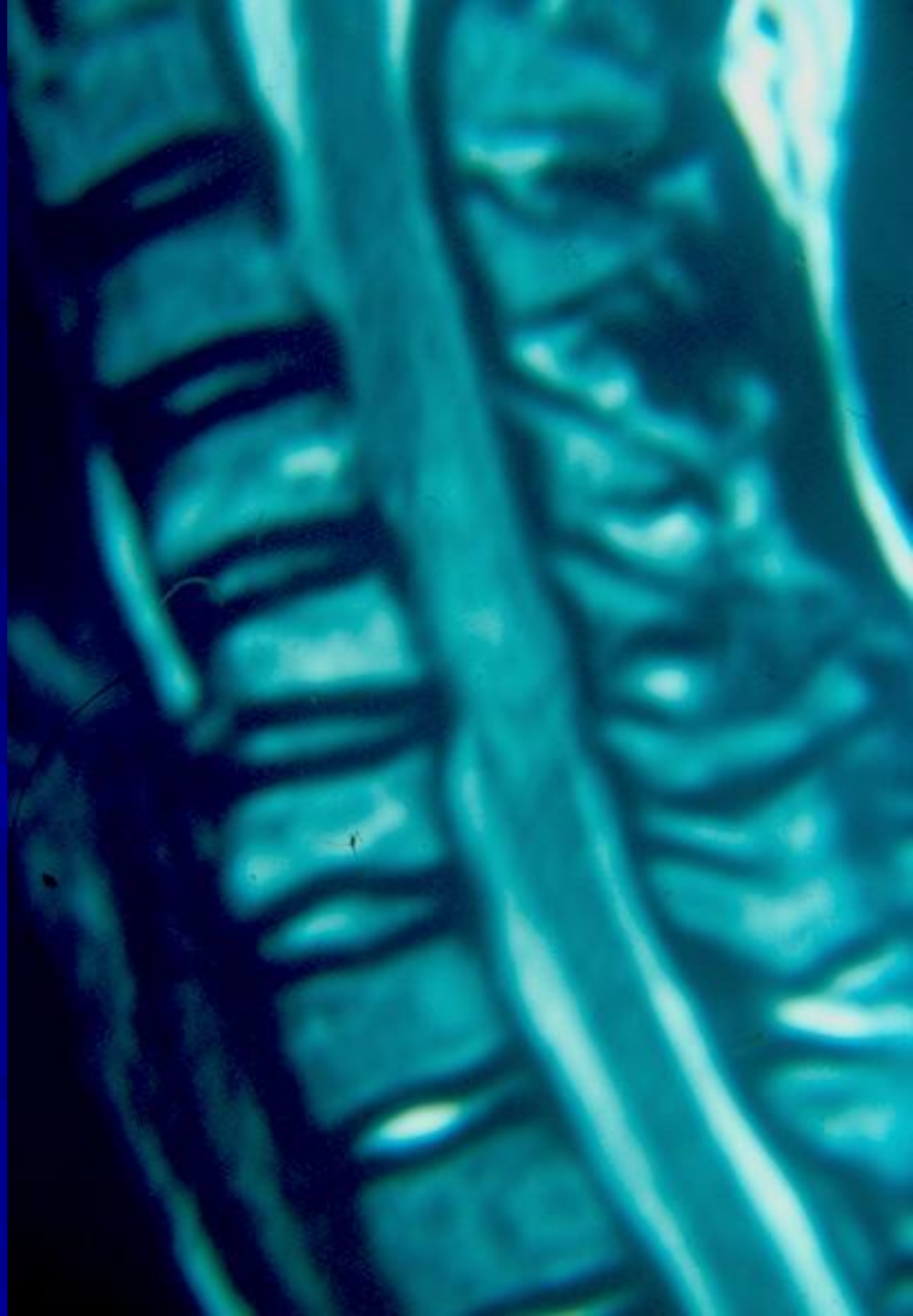


- In the majority of cases, primary SCI is caused by:
  - rapid spinal cord compression due to bone displacement from a fracture dislocation or burst fracture.

Bunge RP et al 1993
Kakulas BA et al 1984

- Other potential mechanisms include:
  - Acute spinal cord distraction
  - Acceleration deceleration with shearing
  - Laceration from penetrating injuries

Kraus GF et al, 1975
Dolan EG et al 1980



- The concept of secondary mechanisms injury following primary SCI was first postulated by Allen in 1911.

Allen A. et al, 1911

- There is now considerable evidence that the primary mechanical injury initiates a cascade of secondary injury mechanisms such as:
  - Vascular changes
  - Including ischemia
  - Loss of autoregulation
  - Neurogenic shock
  - Hemorrhage

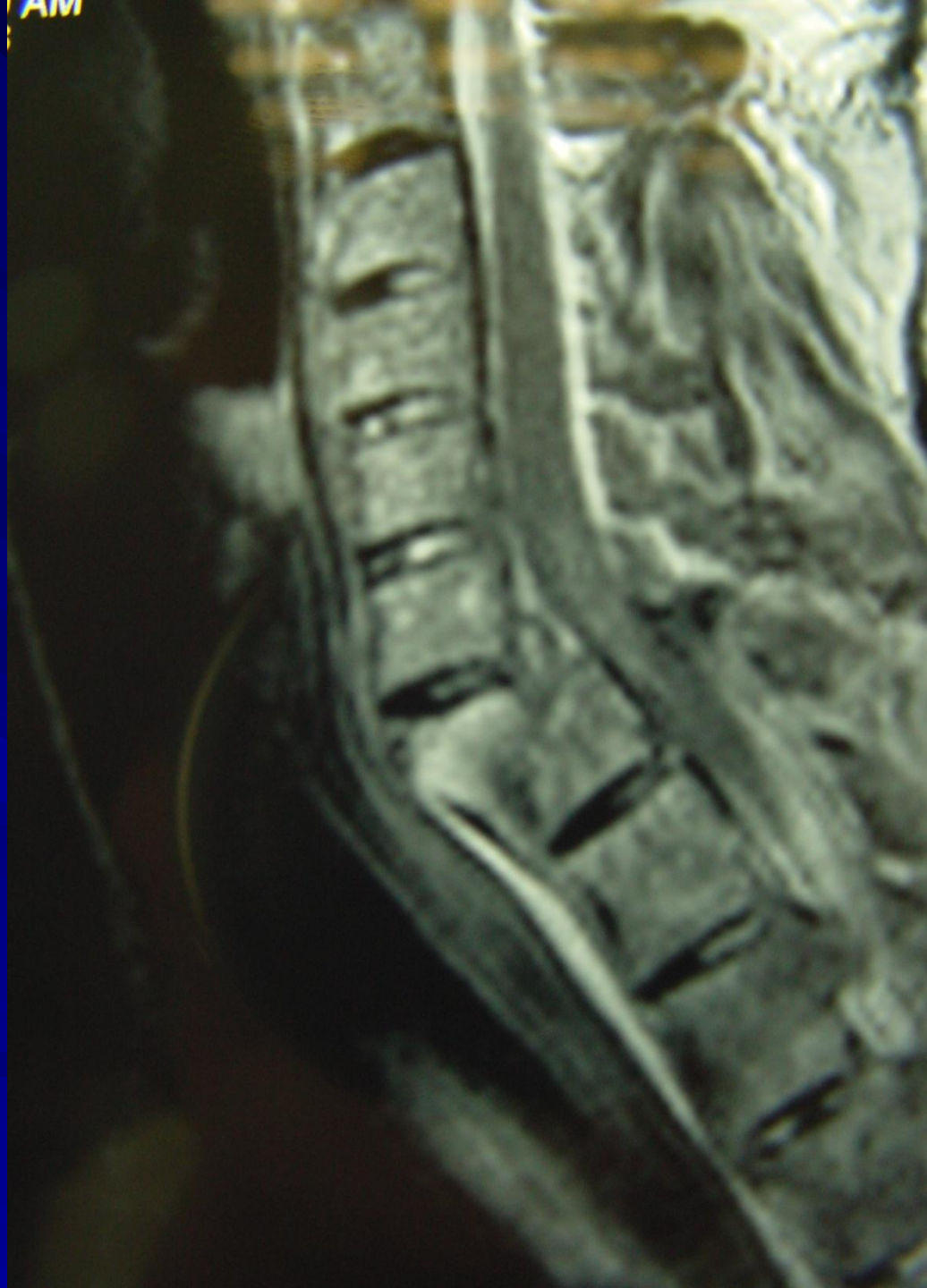
Fehling MG, et al 2000
Tator CH, 1991

Cont…

- Loss of microcirculation
- Vasospasm
- Thrombosis
- Electrolyte derangements
- Increased intracellular calcium
- Increased potassium
- Accumulation of intracellular sodium
- Accumulation of neurotransmitters

Fehling MG, et al 2000
Tator CH, 1991

Cont…



- Seretonin catecholamines
- Extracellular glutamete
- Excitoxicity
- Arachidonic acid release
- Production
  - Eicosanoids
  - Free radicals
- Lipid peroxidation
- Endogenous opioids
- Edema
- Inflamation

Fehling MG, et al 2000
Tator CH, 1991
Young W et al, 1986

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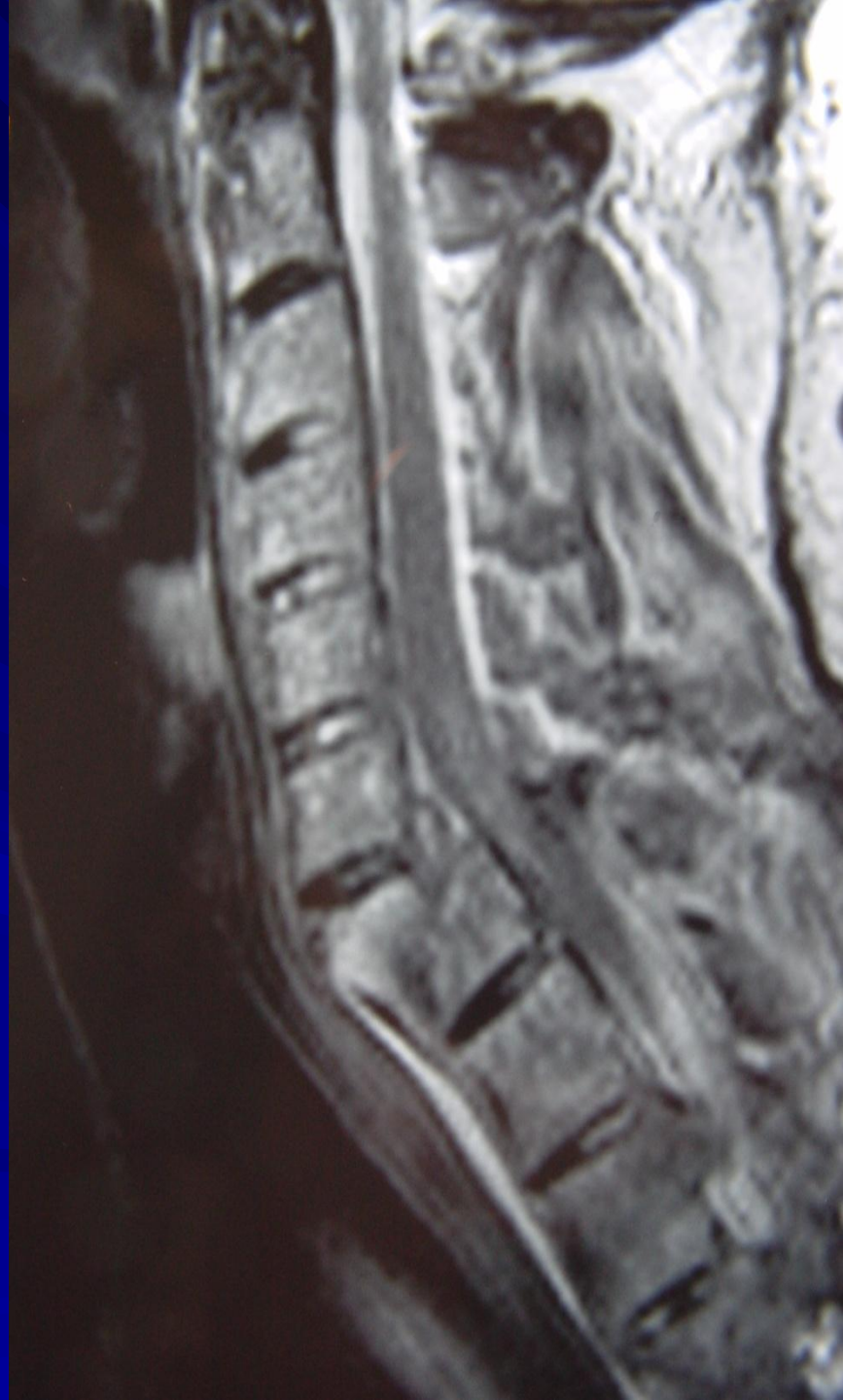
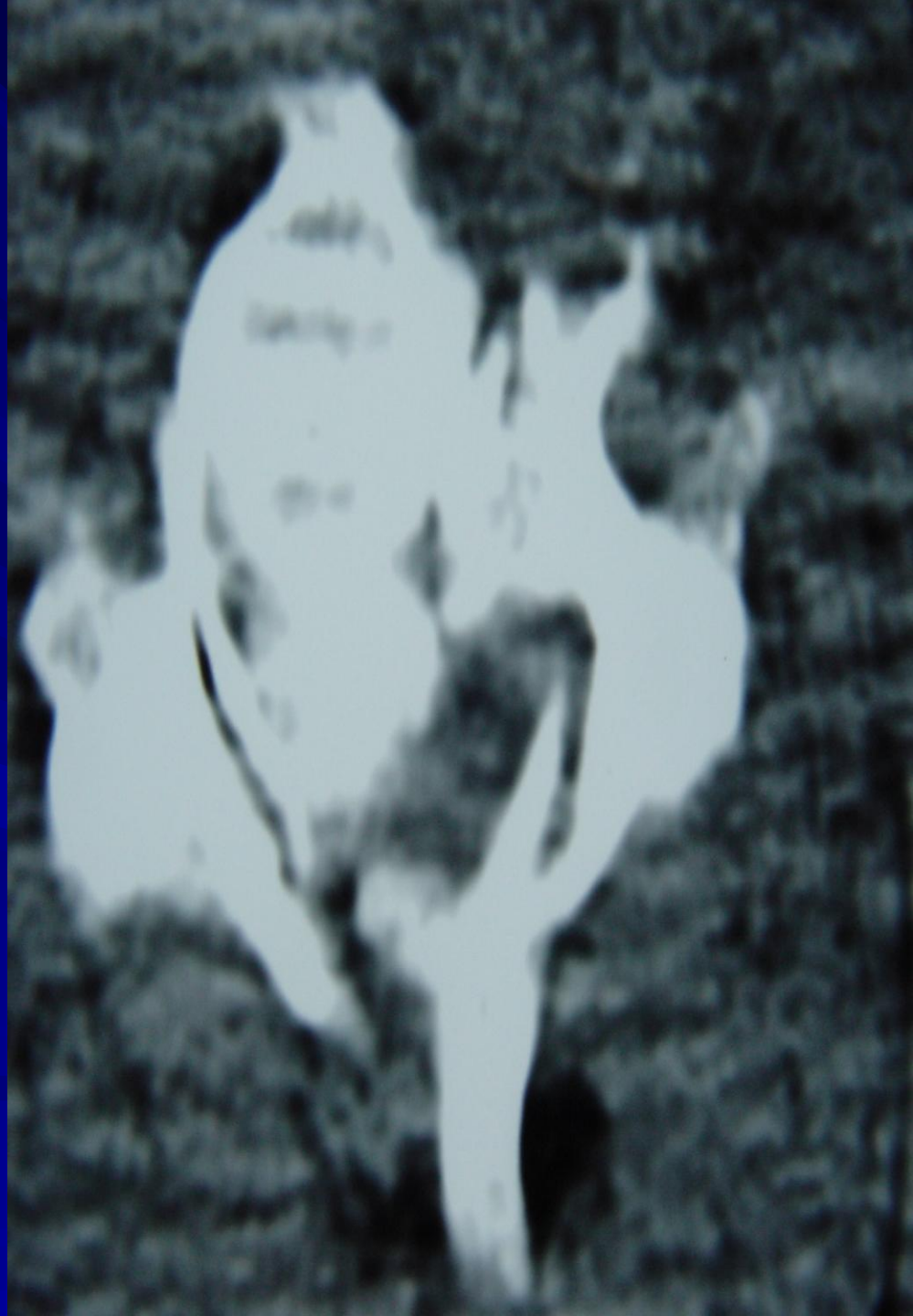


- Loss of energy metabolism
- Including adenosime thriphosphate dependent cellular processes
- Apoptosis

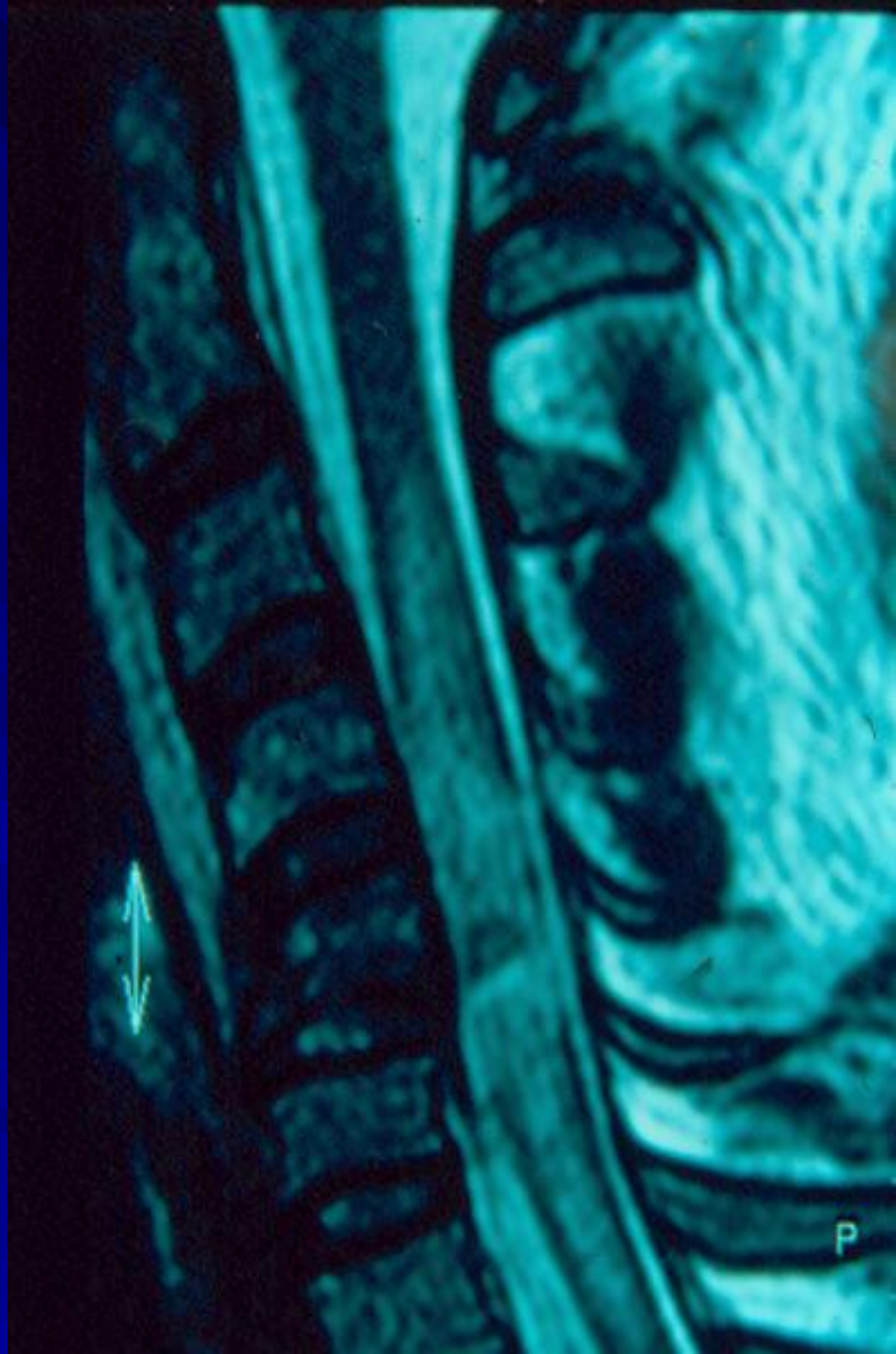
Fehling MG, et al 2000
Tator CH, 1991
Young W et al, 1986

- Secondary injury is preventable, and may be reversible.



- The increased understanding of the pathophysiology of acute SCI has led to clinically relevant neuroprotective therapies to attenuate the effects of the secondary injury.

Fehlings MG et al, 1994



- Currently the management of patients with acute spinal cord injury (SCI) includes :
  I. Pharmacological agents
  II. Cellular therapies
  III. Surgical intervention

Pharmacological treatment

(neuro protecting – neuro regeneration promoting)

- Steroids
- Methyprednisolone
- Ganglioside GM-1
- Opioid receptor antagonists
- Thyrotroping releasing hormone and its analogs
- Nimodipine
- Gaciclidine GK11
- Magnesium

David W. et al Clin. Orthop. 2011
Tevfik Y. et al World J. Orthop. 2015

Cont…

Pharmacological treatment
(neuro protecting – neuro regeneration promoting)

- Hypothermia
- Minocycline
- Erythropoietin
- Progesterone
- Cyclooxygenase inhibitors
- Riluzole
- Atrovastin
- Rho antagonists and other components (Cethrin)

David W. et al Clin. Orthop. 2011
Tevfik Y. et al World J. Orthop. 2015

Methylprednisolone
(neuro protection)

- NASCIS
  (National Acute Spinal Cord Injuries Studies)

  I. NASCIS I for 48 hours
  II. NASCIS II for 24 hours
  III. NASCIC III for 72 hours

- Started within 3 – 8 hours after trauma

- The National Acute Spinal Injury studies (NASCIS II – NASCIS III) have reported a modest beneficial effect of high dose methylprednisolone if given within eight hours of injury in patients with SCI, and suggested that treatment within three hours may be better than treatment initiated 3 – 8 hours after trauma.

Bracken MB et al 1993
Bracken MB et al, 1997

Rizulole

- Is a sodium channel blocking agent
- It is reported to have neuro protecting properties for blocking voltage-sensitve sodium channels whose persistent activation (excitotoxicity) has been demonstrated to have deleterious effects on neural tissue.

RILUTEK - Greece

Rho antagonists (Cethrin)

- Is a protein therapeutic that blocks signaling form myelin debris present at the site of injury in the injured spinal cord.
- Cethrin promotes regeneration of cut axons and remodeling of damaged circuits.
- Cethrin is delivered topically during decompression surgery.

Greece (-)

Cellular Transplantation Therapies

- The rationale for cell transplantation treatments are to provide the injured tissue with :
  - Growth promoting factors
  - Cell replacements
  - Structural elements
  - Myelinating units

Garcia Alias G, J. Neurosci. Res. 2004

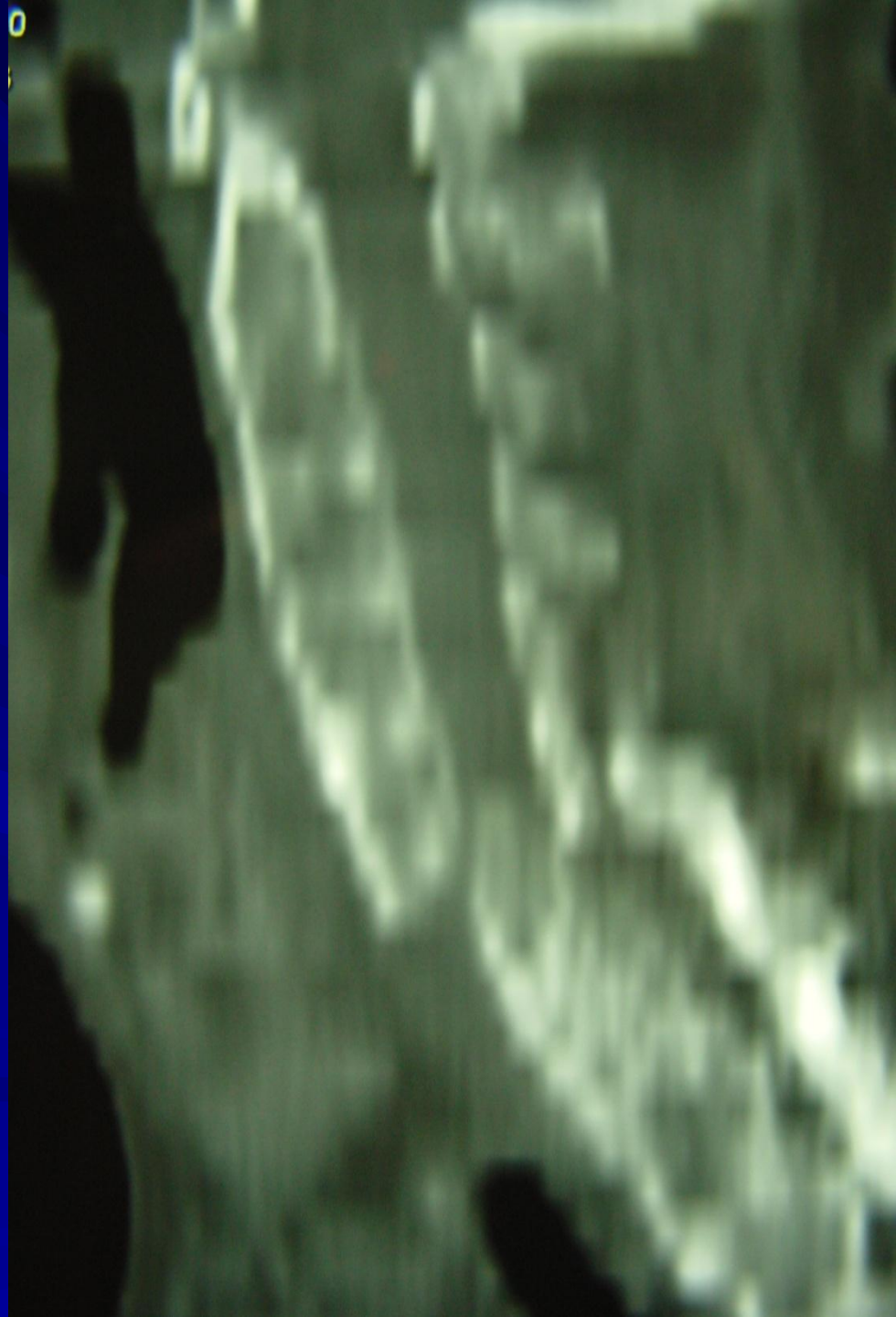
- Reconstructive and regenerative experimental cellular strategies containing:
  - Embryonic or adult stem cells or tissue
  - Genetically modified fibroplasts
  - Olfactory ensheathing cells
  - Bone marrow stromal cells
  - Neural stem cells
  - Activated macrophages
- All of them have been reported with varying degrees of recovery in different models of SCI

Garcia Alias G, J. Neurosci. Res. 2004
Barakat DJ, et al Cell Transpl. 2005

Surgical intervention

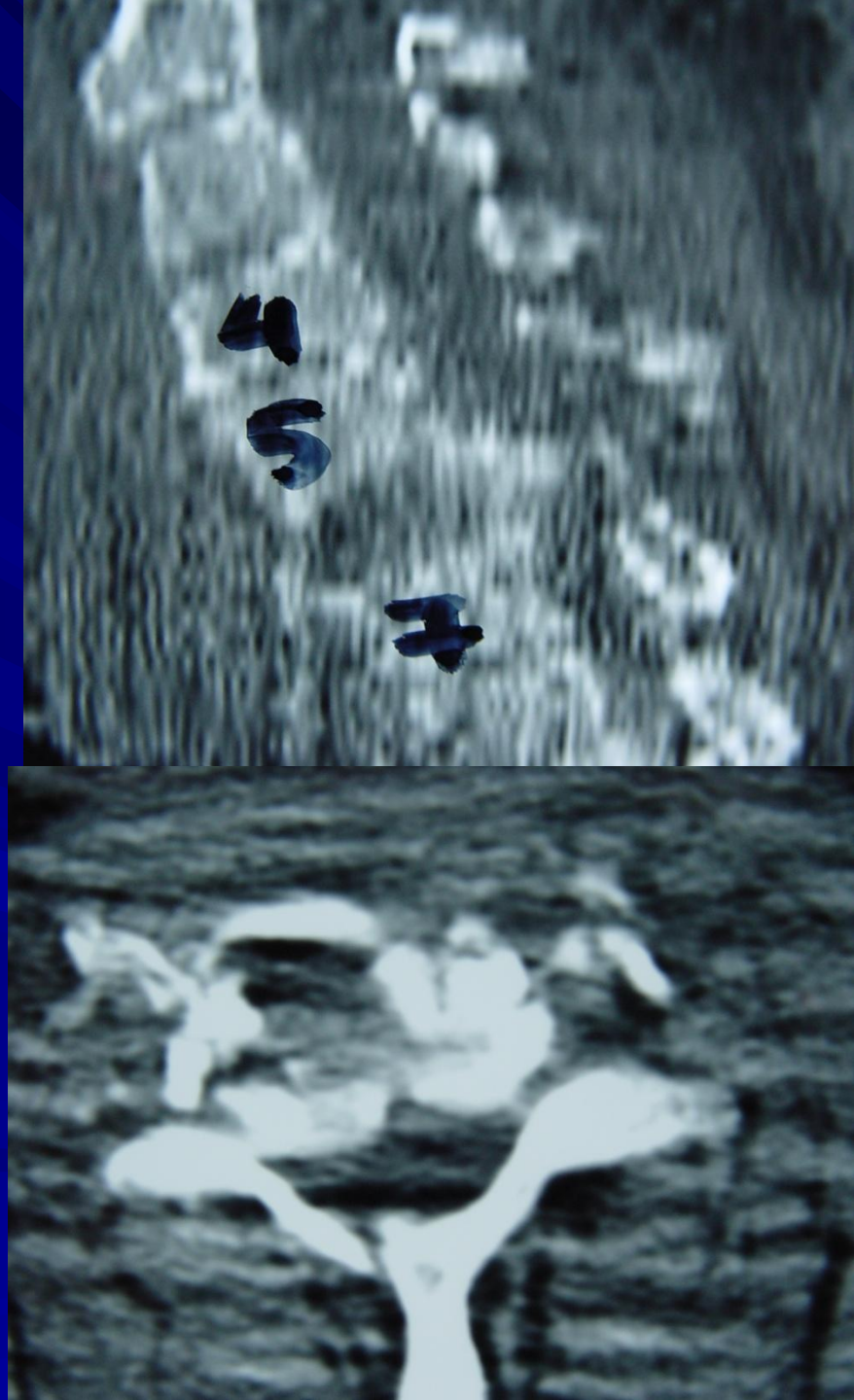
- The role and timing of surgical intervention after an acute spinal cord injury (SCI) remains one of the most controversial topics pertaining to spinal surgery

- Studies support the concept of targeting secondary mechanisms in acute SCI and also the importance of the timing of intervention.

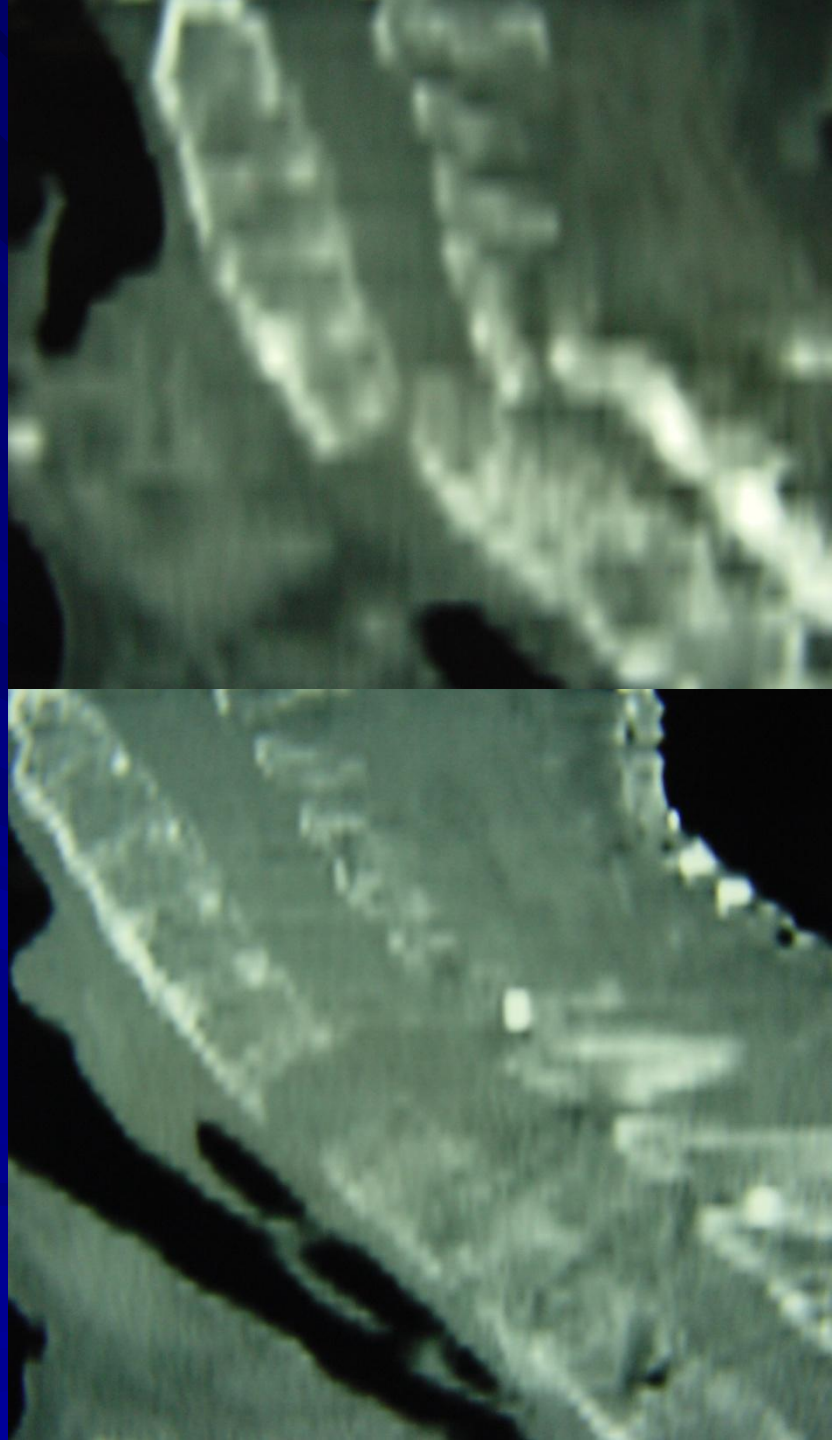


- There is experimental evidence that persistent compression of the spinal cord is a potentially reversible form of secondary injury.

Dolan EJ, et al 1980
Aki T et al, 1984



- The presence and duration of a therapeutic window during which surgical decompression could mitigate the secondary mechanisms of SCI remains unclear

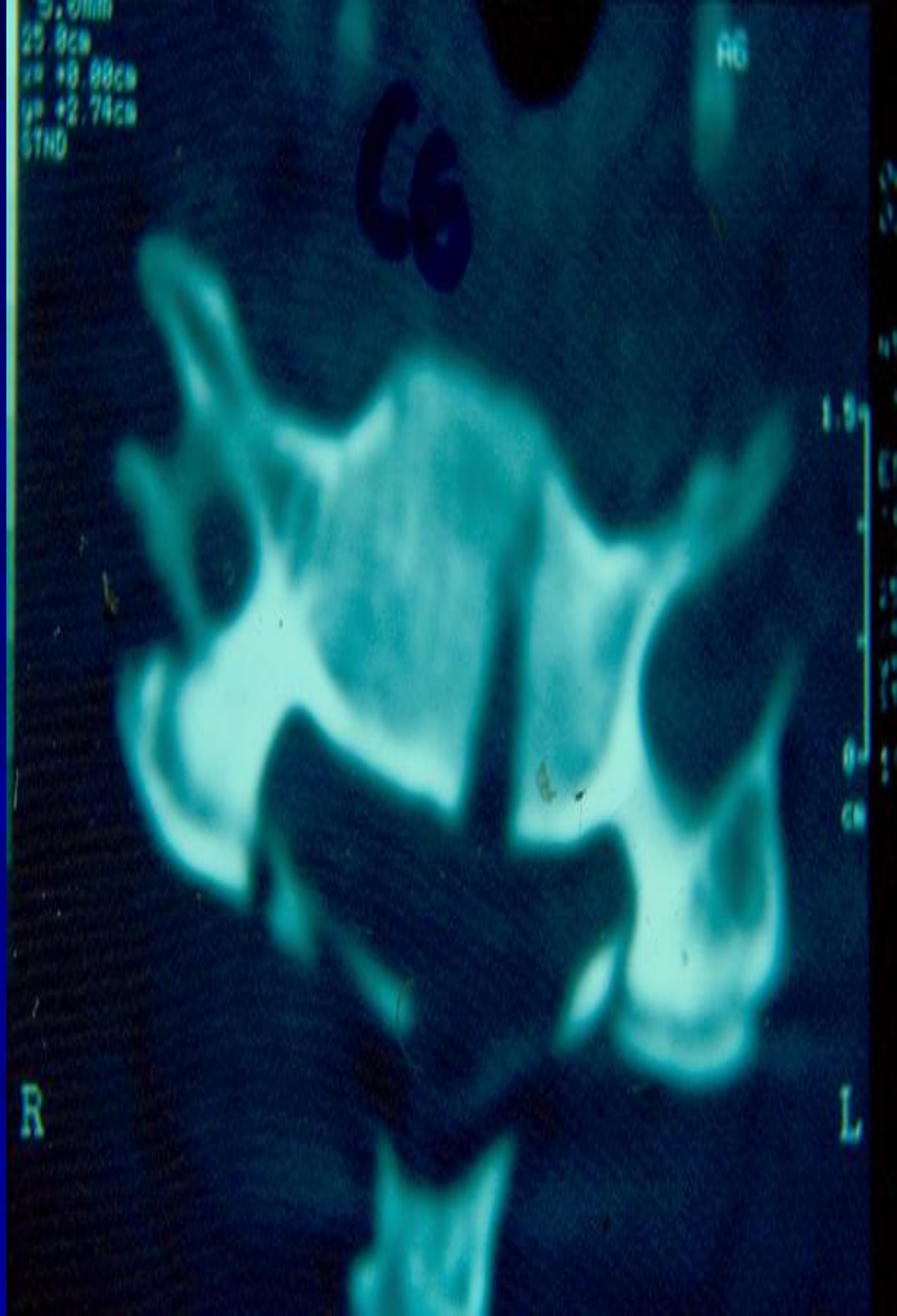


- This lecture will review the experimental and clinical evidence regarding:
  - the value of decompressive surgery in treating patients with acute non-penetrating SCI

    And
  - the role and timing of early decompression for SCI

- This computerized literature review yielded a total of 960 studies, which were then pared down based on relevance to the tissue of SCI management.

M. G. Fehlings , R.G. Perin, Injury, 2005

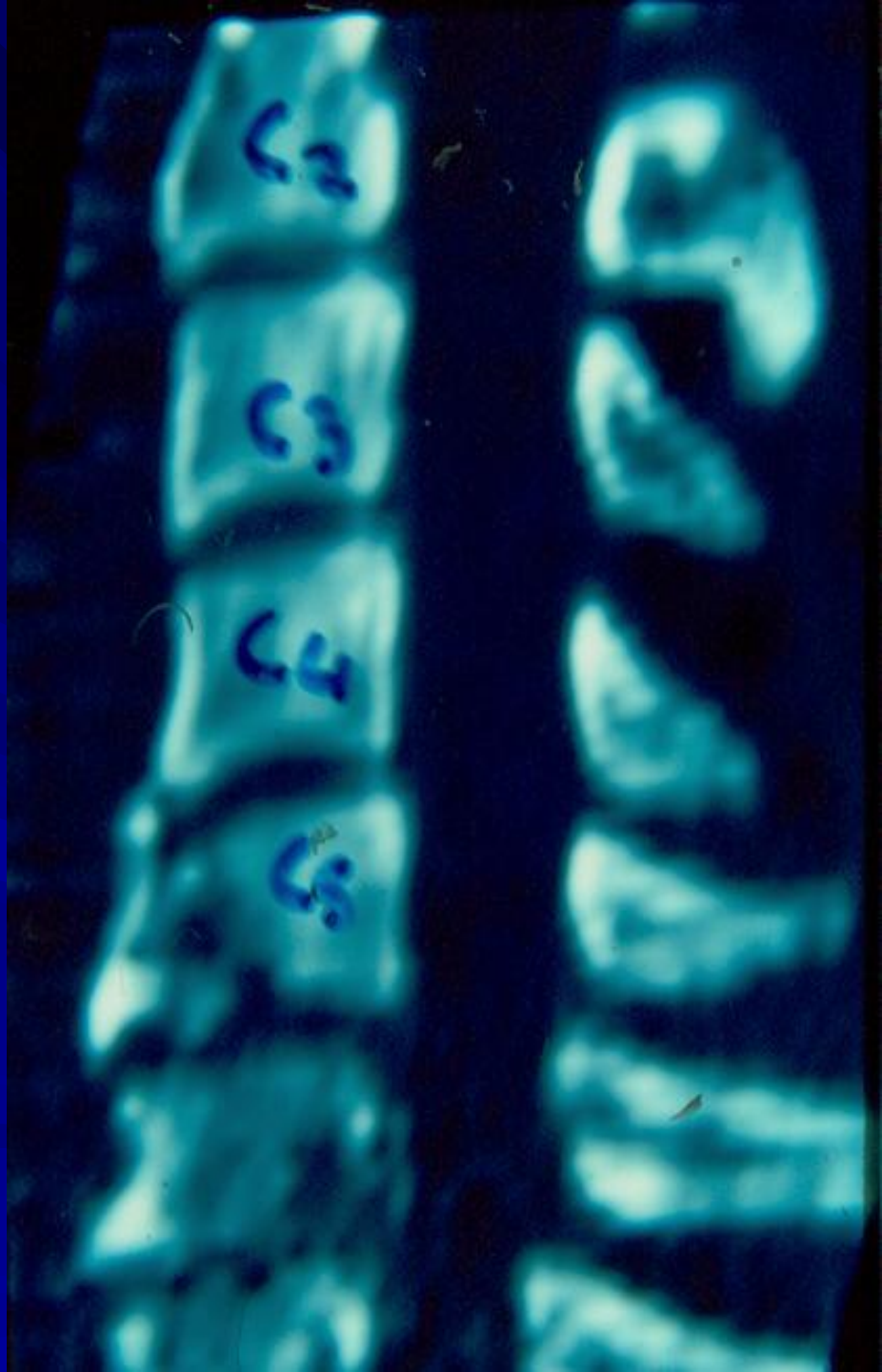


Study Design	Class of evidence
well designed and well conducted randomized controlled trials	I
prospective cohort studies or controlled studies with well defined comparison groups	II
case series; retrospective reviews and expert opinion	III

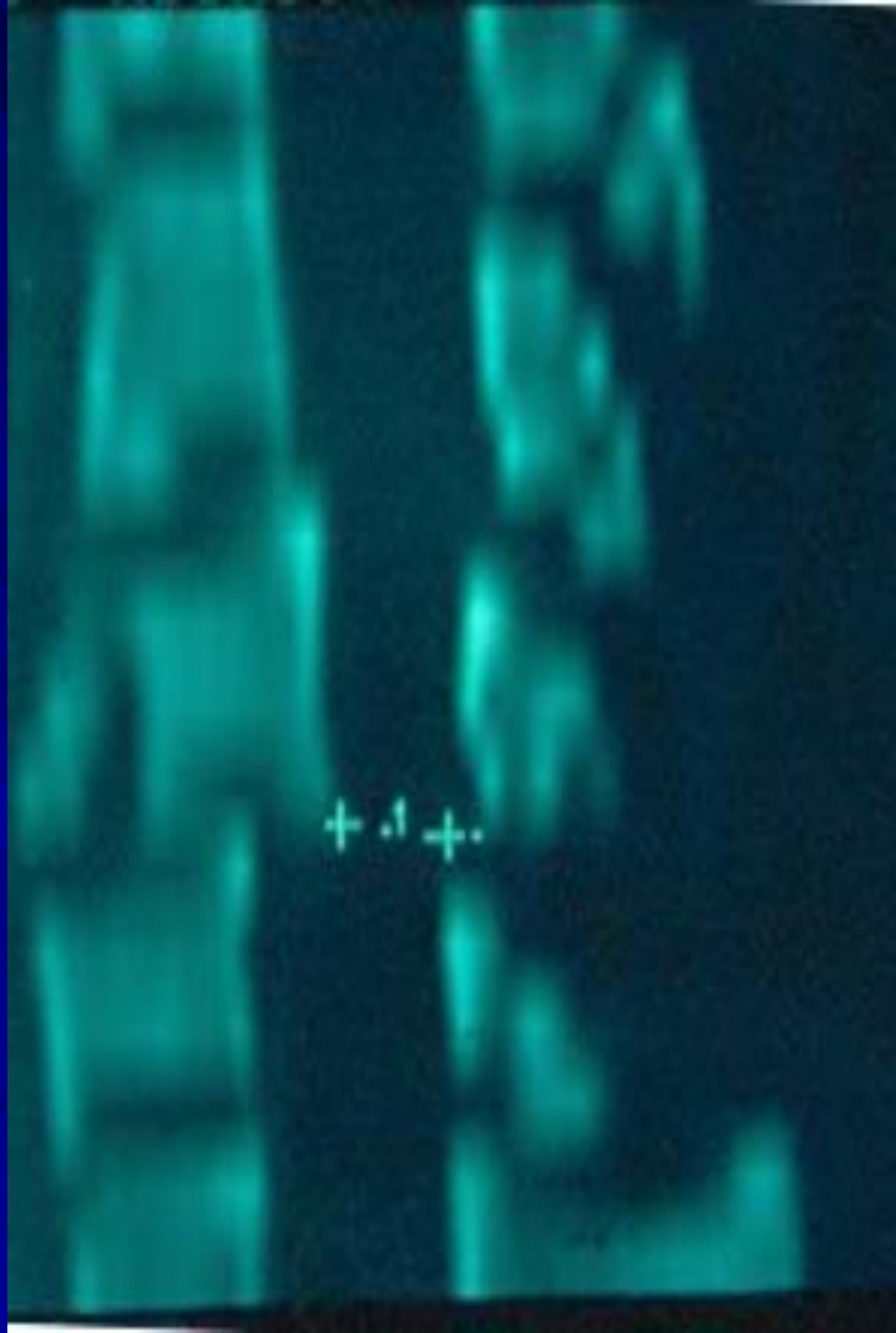
Results

- A total of 65 articles
  - 19 experimental studies in animal models
  - 46 clinical studies

  were selected for detailed analysis.



- Of the clinical articles:
  - 9 dealt with non operative management
  - 31 with the role of early (< 4 weeks) surgical intervention
  - 12 with the effect of closed reduction
  - 7 with the role of delayed decompression

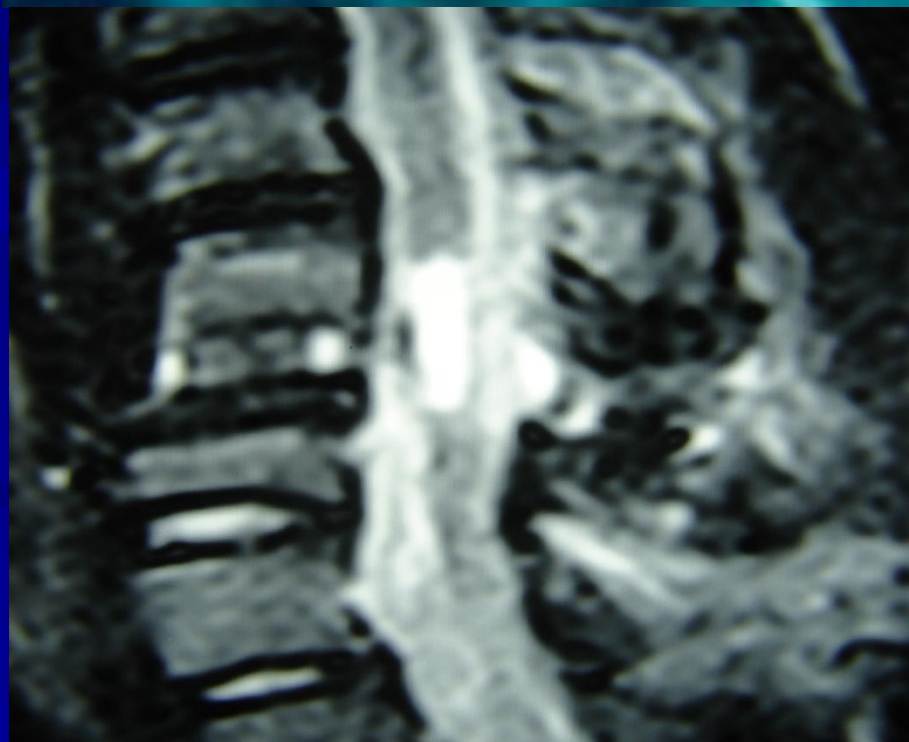


- Based on this analysis, evidence based recommendations regarding the role of acute decompression in SCI was suggested.

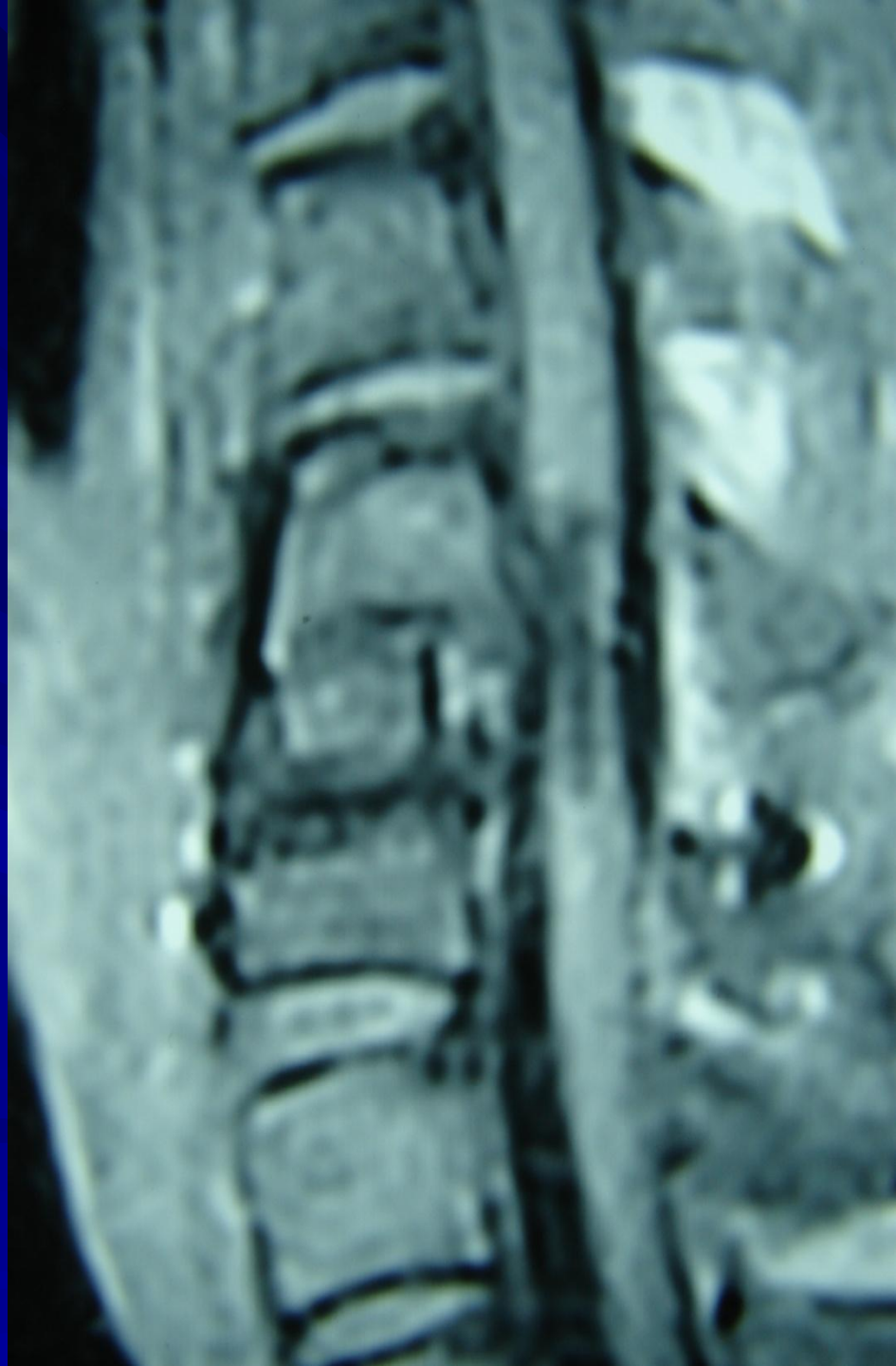
- The severity of SCI in animal models is related to:
  - The force of compression
  - Duration of compression
  - Displacement
  - Impulse
  - Kinetic energy
- Numerous exeprimental studies of decompression after SCI have been performed in various animal models including:
  - Primates
  - Dogs
  - Cats
  - Rodents

- These studies have consistently shown that neurological recovery is enhanced by early decompression
- The most convincing experimental evidence that spinal cord decompression after SCI is beneficial was provided by Dimar et al 1999.

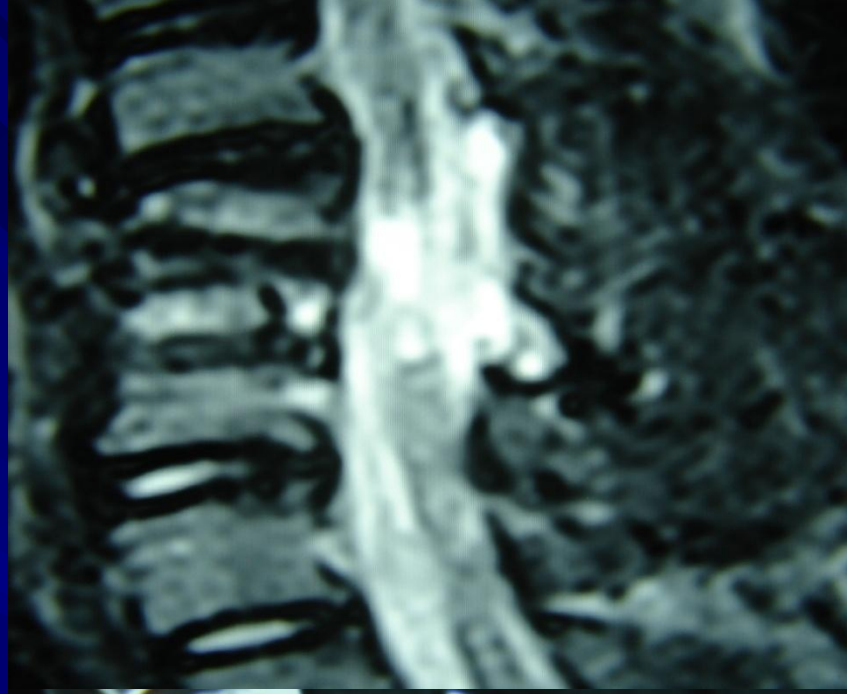
- The effect of decompression at 0, 2, 6, 24 and 72 hours after SCI was then assessed by quantitative analysis of:
  - Locomotor recovery
  - Lesion volume
  - Electrophysiology

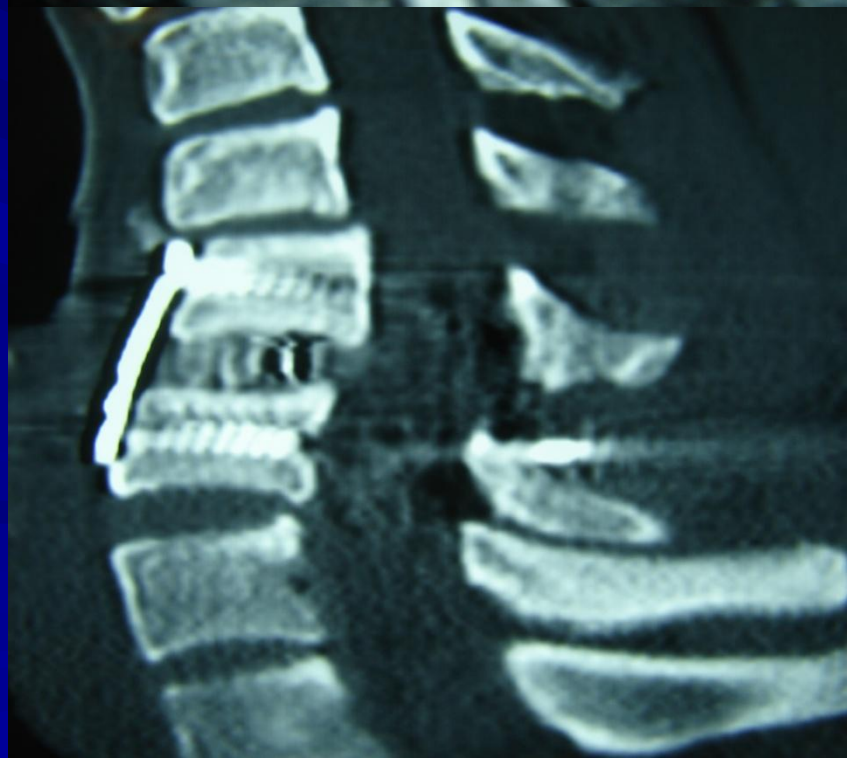


- Neurological recovery was inversely related to the duration of compression with statistically significant differences seen in all experimental groups.
- Functional recovery was significantly better, and lesion volume was significantly smaller in those animals undergoing early decompression



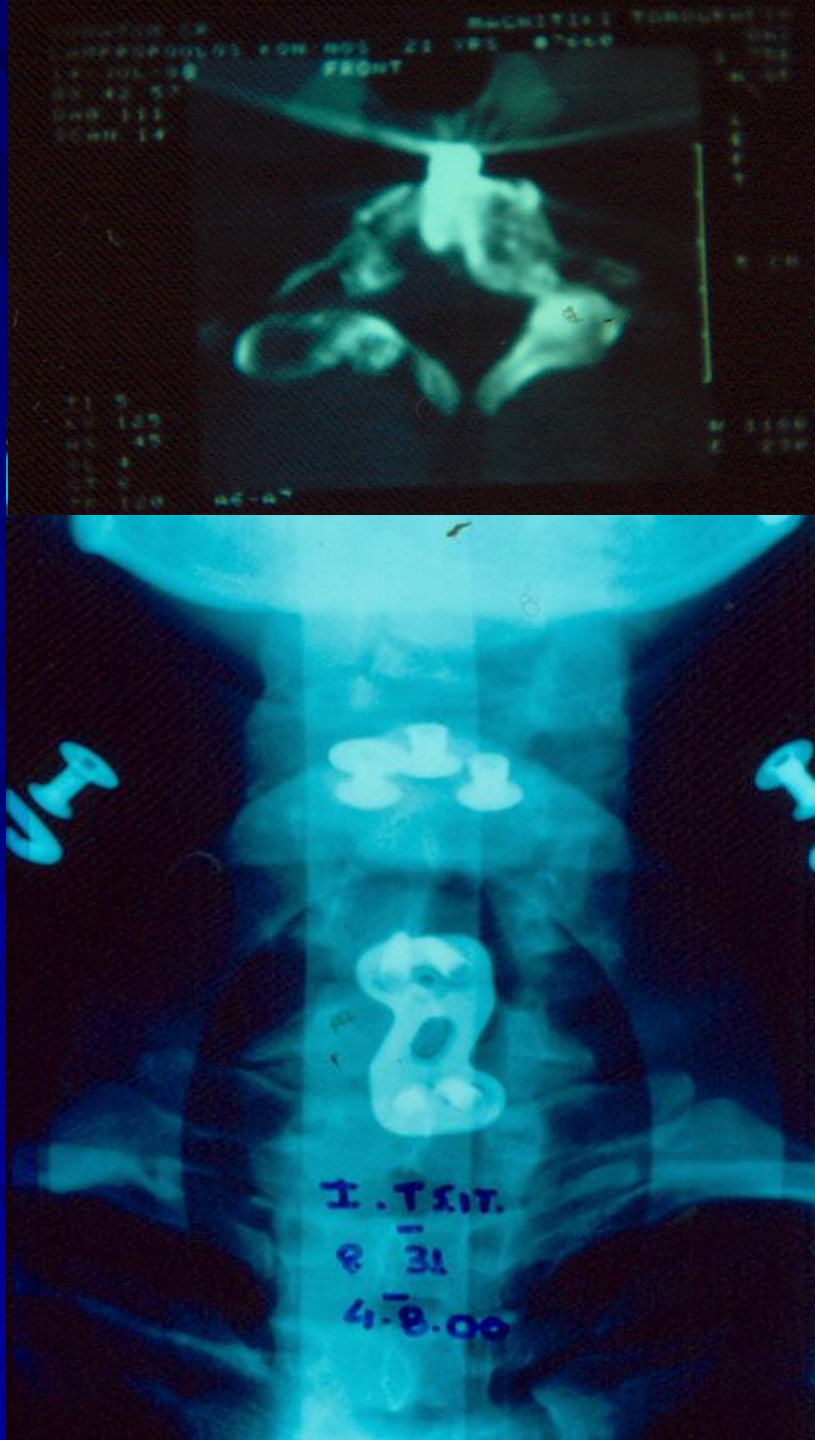
- In contrast the prospective studies by:
  - Vale et al, 1999
  - Vaccaro et al, 1997
  - Waters et al ,1996
- were unable to document a beneficial effect of surgical decompression.
- It is noteworthy, however, that all patients underwent delayed operative management.
- “Early surgery” was defined as being within 72 hours after SCI.



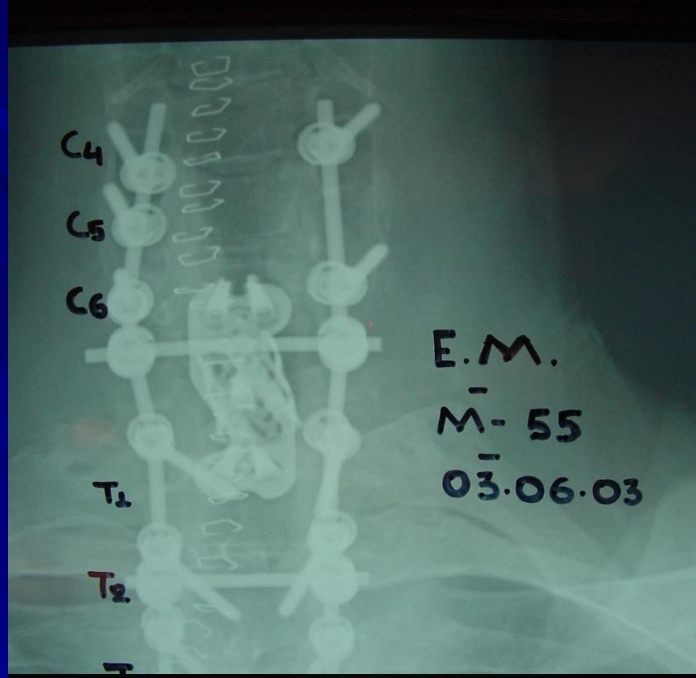


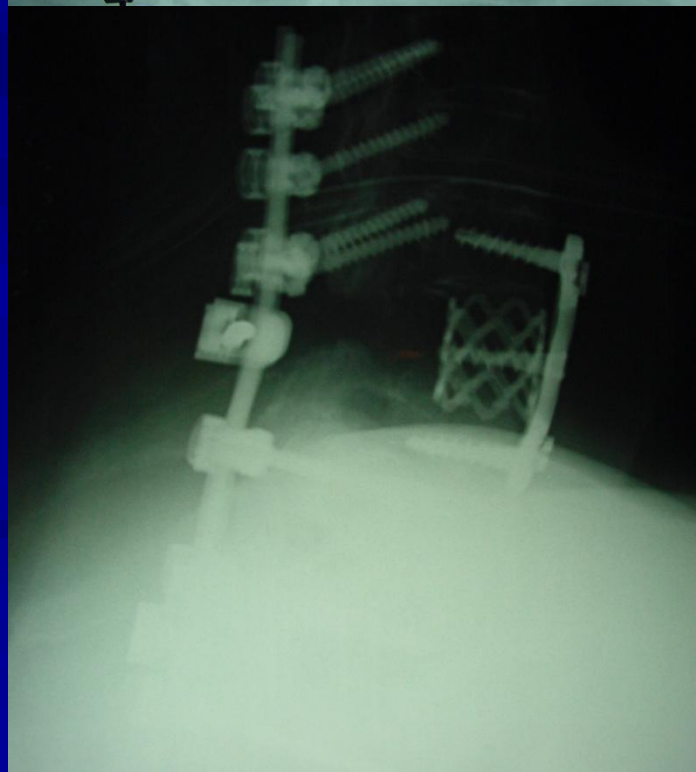
- Aebi et al undertook a retrospective review of 100 patients with cervical spine injuries and attempted to find an association between neurological recovery and the timing of fracture reduction by closed or open techniques.

Aebi M. et al , 1986



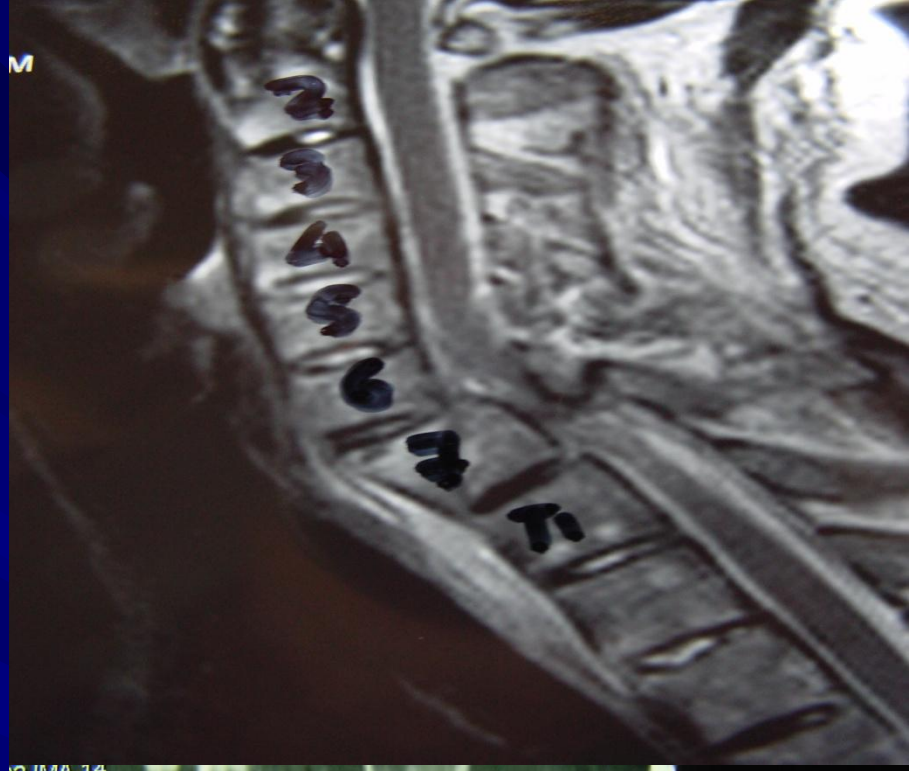
- Overall
  31% of the 100 patients
  recovered
  and
  75% of the recoveries
  were in patients
  reduced
  within the
  first six hours.

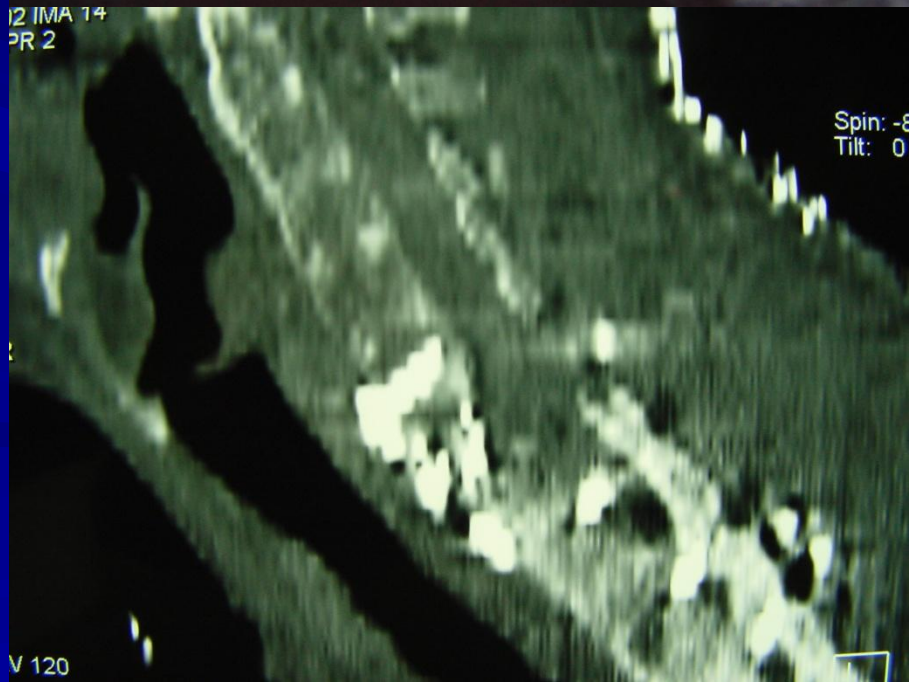




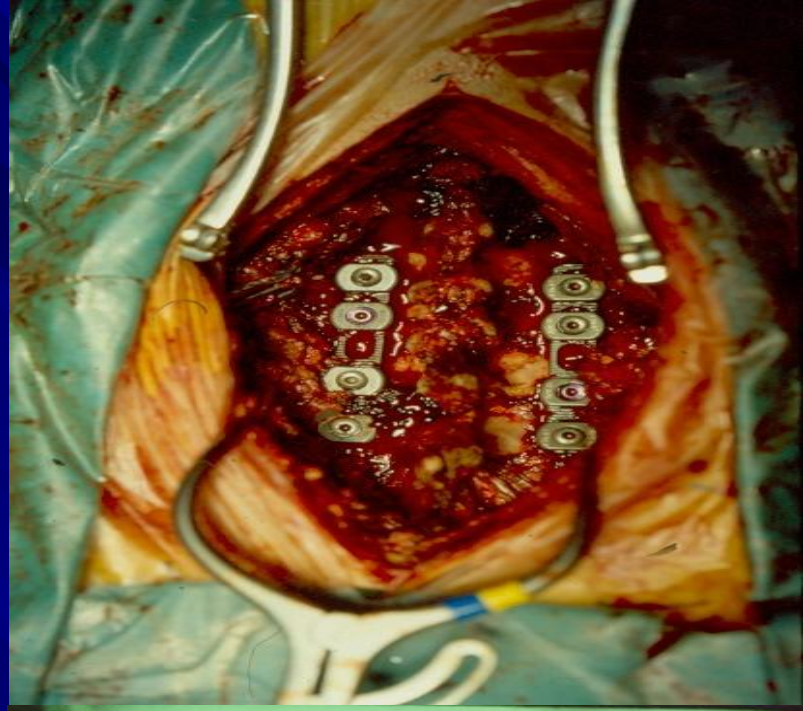
- In contrast to the aforementioned studies of early decompression. Larson et al, advocated operating a week or more after SCI to allow medical and neurological stabilization of the injured patient

Larson et al, 1976





- This approach remains the practice in many institutions, particularly in light of early reports suggesting an increased rate of medical complications with early surgery (< 5 days after SCI)



- Interestingly a number of authors have documented recovery of neurological function after delayed decompression of the spinal cord (months to years) after the injury

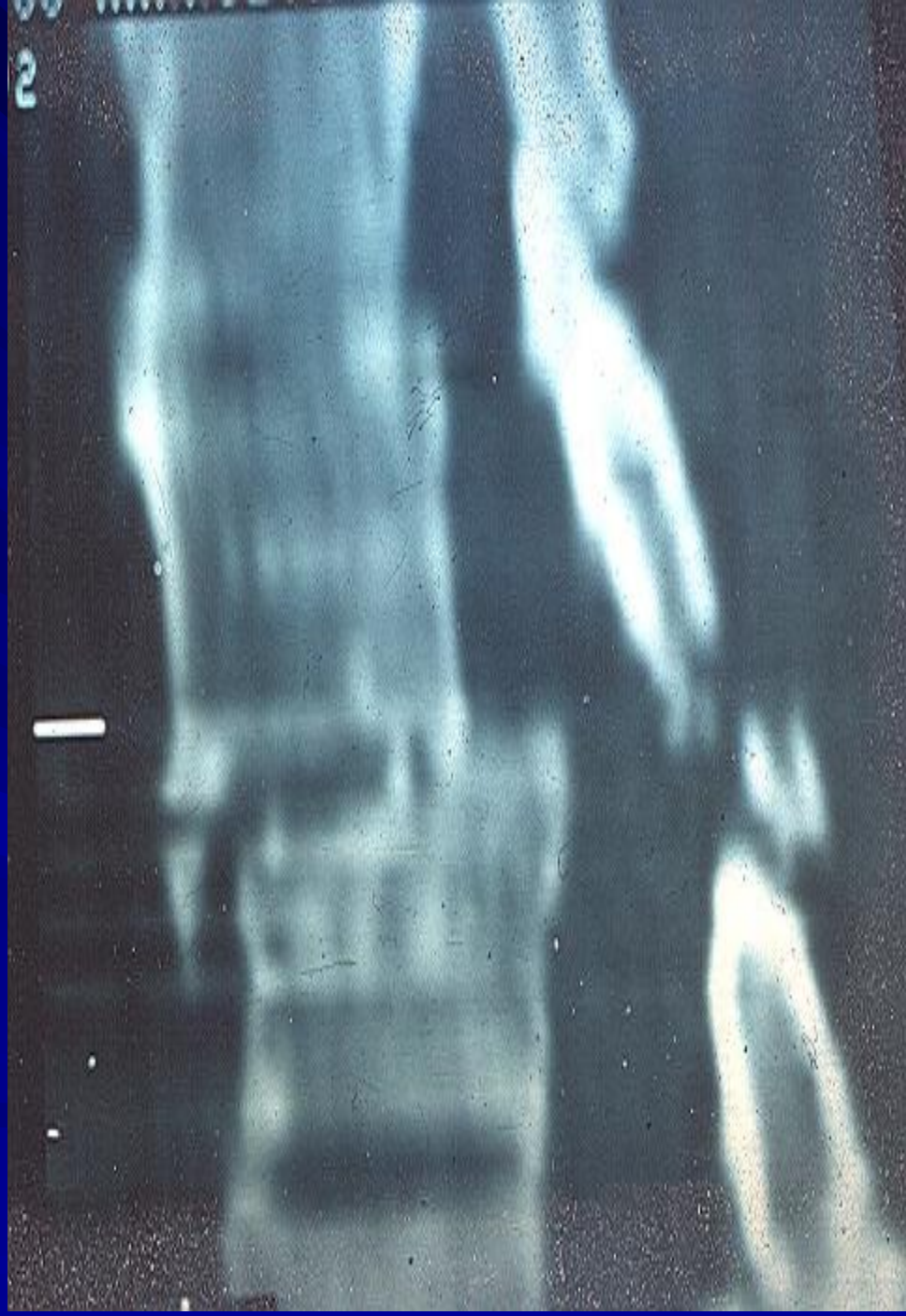
Larson SJ, et al 1976
Anderson PA et al, 1992
Bohlman HH et al, 1992

- Although these studies are retrospective in design (Class III evidence)
  the improvement in neurological function with delayed decompression
  in patients with cervical or thoracolumbar SCI who have plateaud in their recovery is noteworthy and suggests that compression of the cord is an important contributing cause of neurological dysfunction.

Effect of surgery on complications and length of stay after SCI

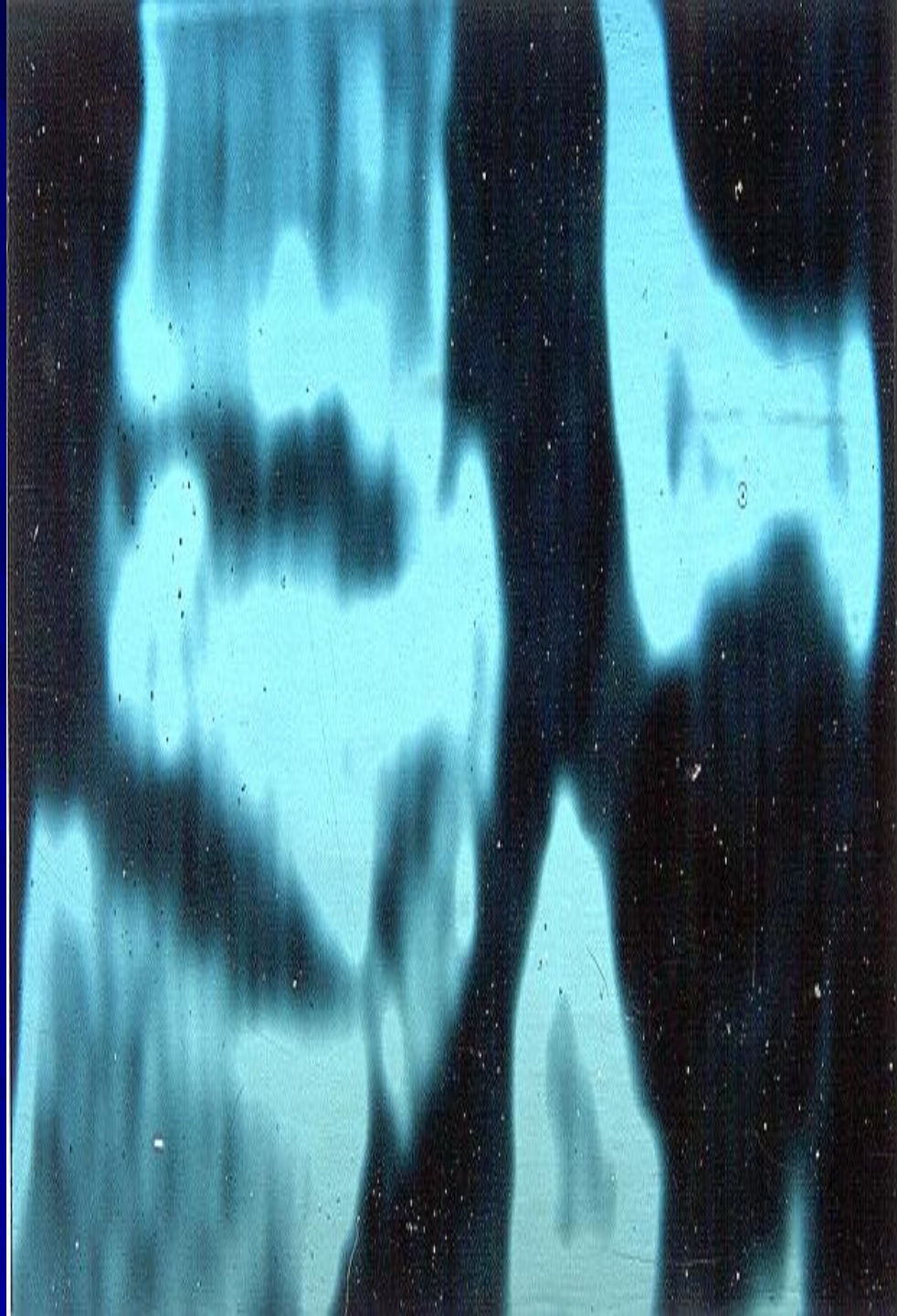
- The issue of whether surgery, especially early surgery, increases the rate of complications in patients with SCI has been one that has generated considerable controversy and debate.

- Many authors have argued against surgery, especially early intervention in these critically ill patients.
  Gutman L, 1976
  Wilmot CB et al., 1986
- However, modern techniques of spine surgery as well as advances in critical care and neuroanesthesia have allowed these patients to undergo surgery with minimal differences in complication rates between operative and non operative cases.
  Benzel EC et al, 1986
  Vale FL et al, 1997



- Duh showed that those operated on in the first 24 hours had a lower rate of complications than those undergoing operative intervention at a later time.

Duh et al, 1994



- Waters et al in a prospective study of 2.204 cases found that there was no difference in the complication rates of cases managed by non operative or surgical techniques.

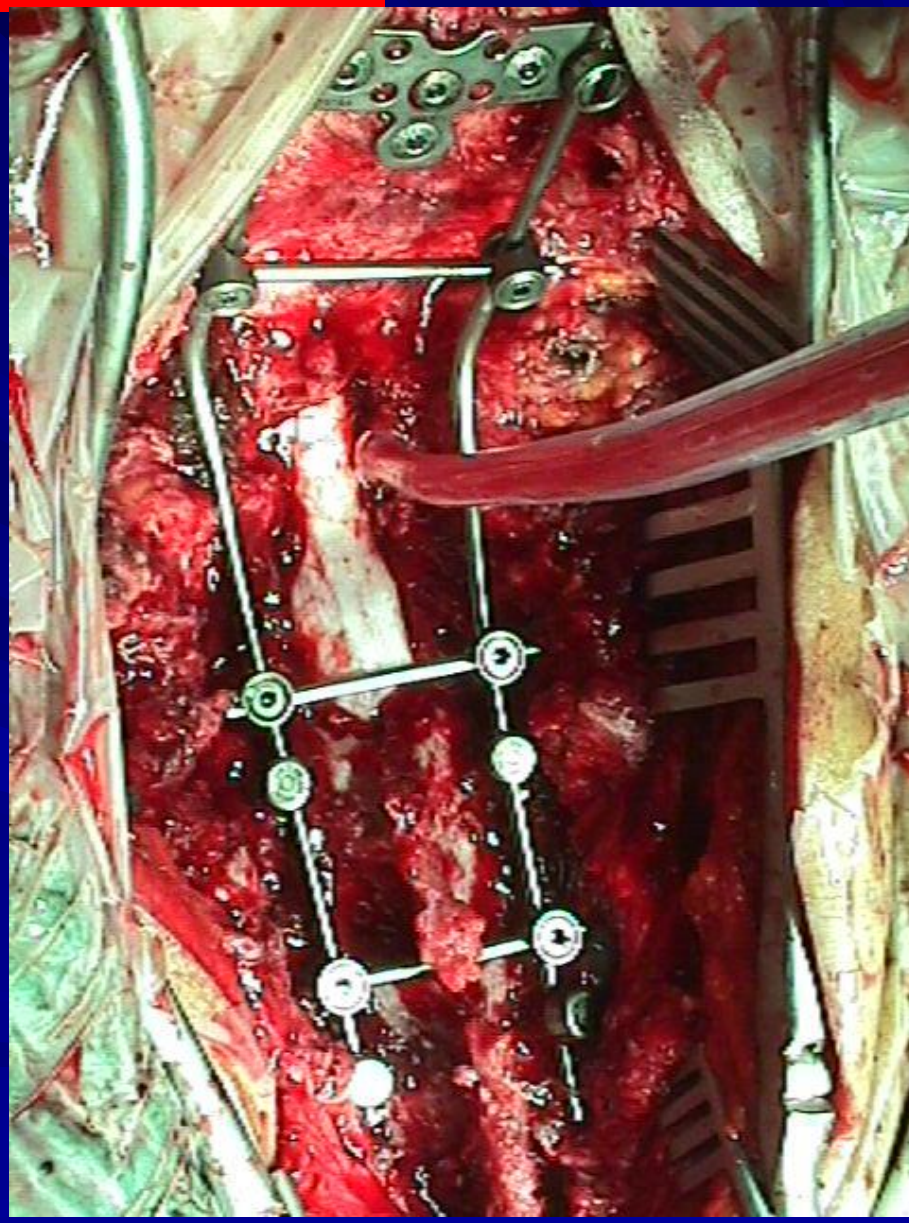
Waters et al, 1999

- Accordingly, there is Class I evidence to support the safety of surgery, including operative treatment within the first 24 hours.

Mirza SK et al, 1999

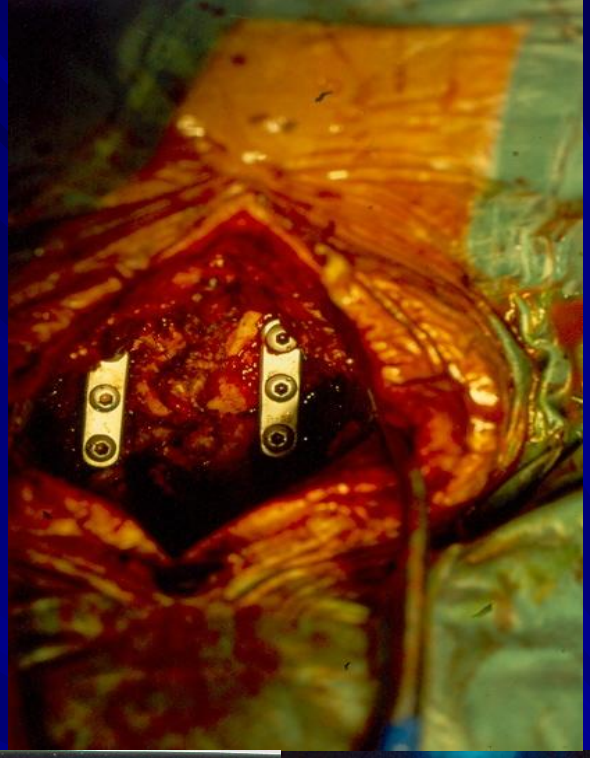
Conclusions

- There is strong experimental evidence from animal models that decompression of the spinal cord improves recovery after SCI.
- It is difficult to determine a time window for the effective application of decompression in the clinical setting from these animal models.



- Studies of secondary injury mechanisms including:
  - ischemia,
  - free radical mediated
  - lipid peroxidation
  - and calcium mediated cytoxicity,
- suggest that early intervention within hours of SCI is critical to obtain a neuroprotective effect.

- There is Class II evidence suggesting that early surgical intervention is safe and effective and even delayed decompression may convey a neurological benefit.



- Clearly, what is needed to definitely answer the question regarding the timing of surgery following SCI is a well designed prospective, randomized controlled, multicenter producing Class I evidence data.
- This can often be done within 24 hours of admission.

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