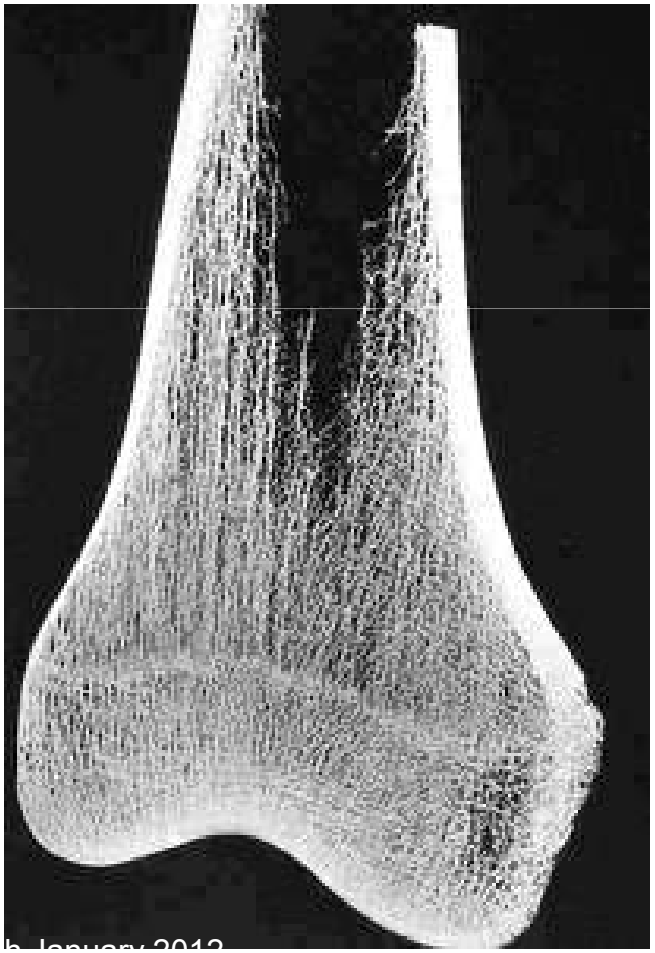
Basic Principles that have changed orthopaedic practise

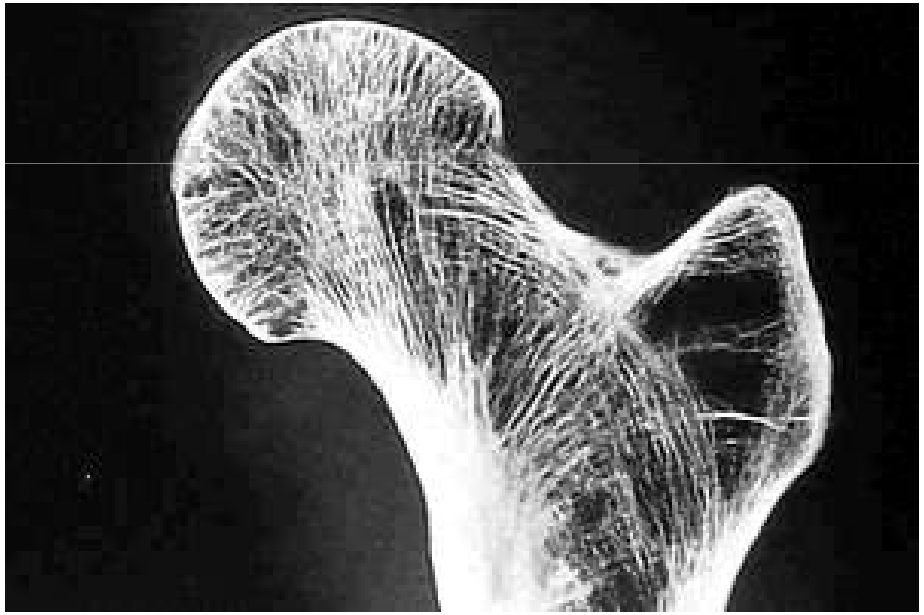
Sean Hughes

Emeritus Professor Orthopaedic Surgery

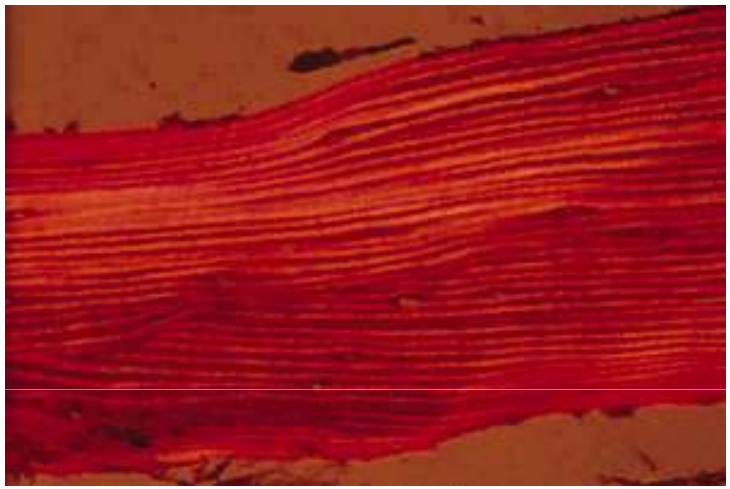
- **Fracture Healing**
- **Joint Replacement**
- **Surgical Management of Low Back Pain**

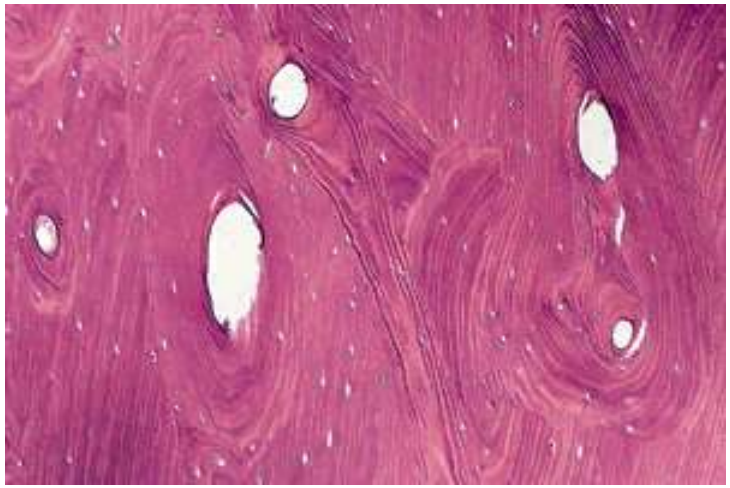
Cortical and Cancellous Bone

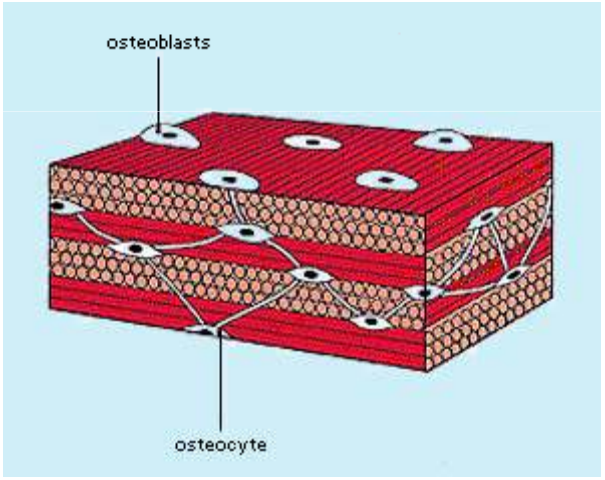




Mature Bone

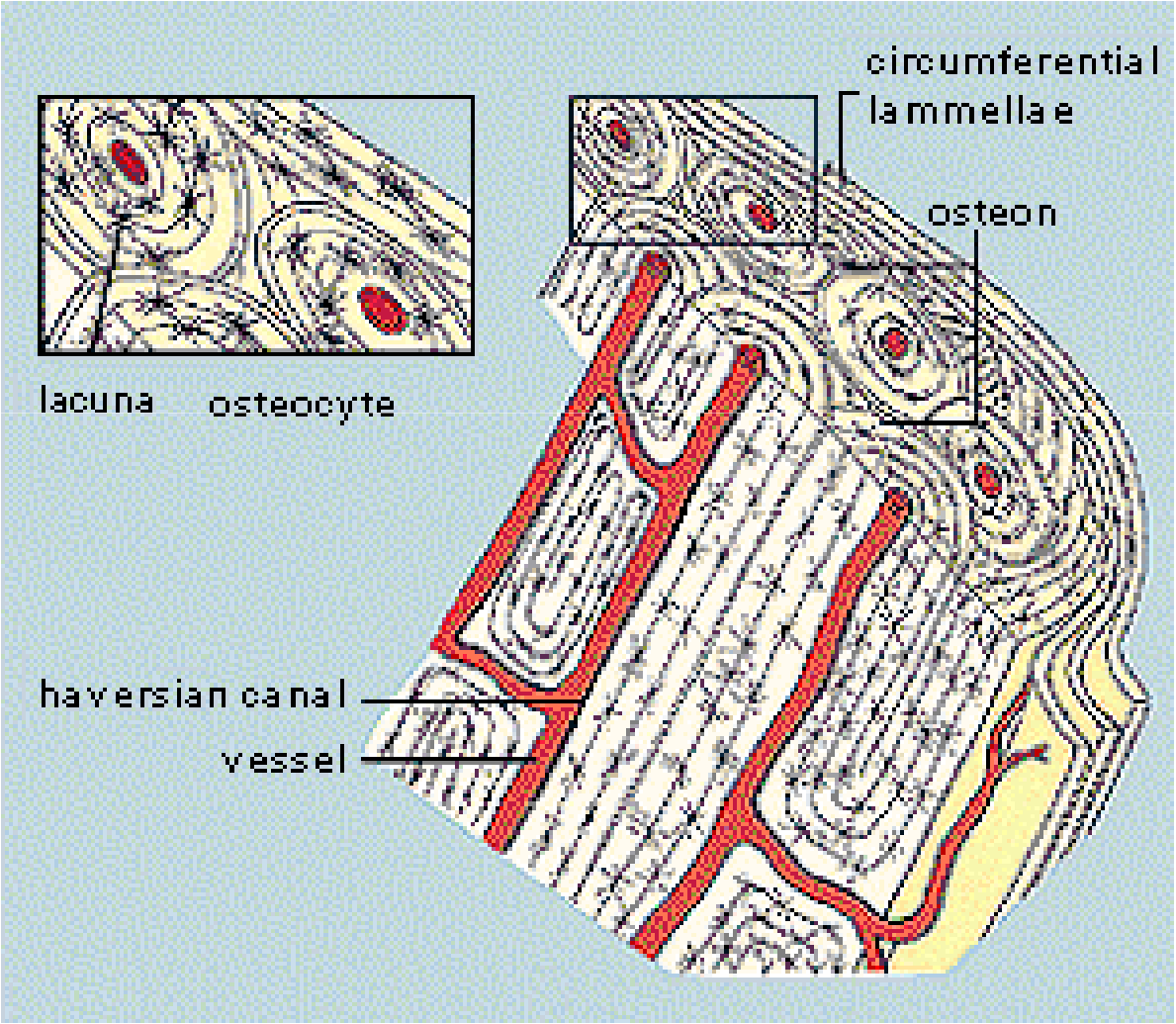




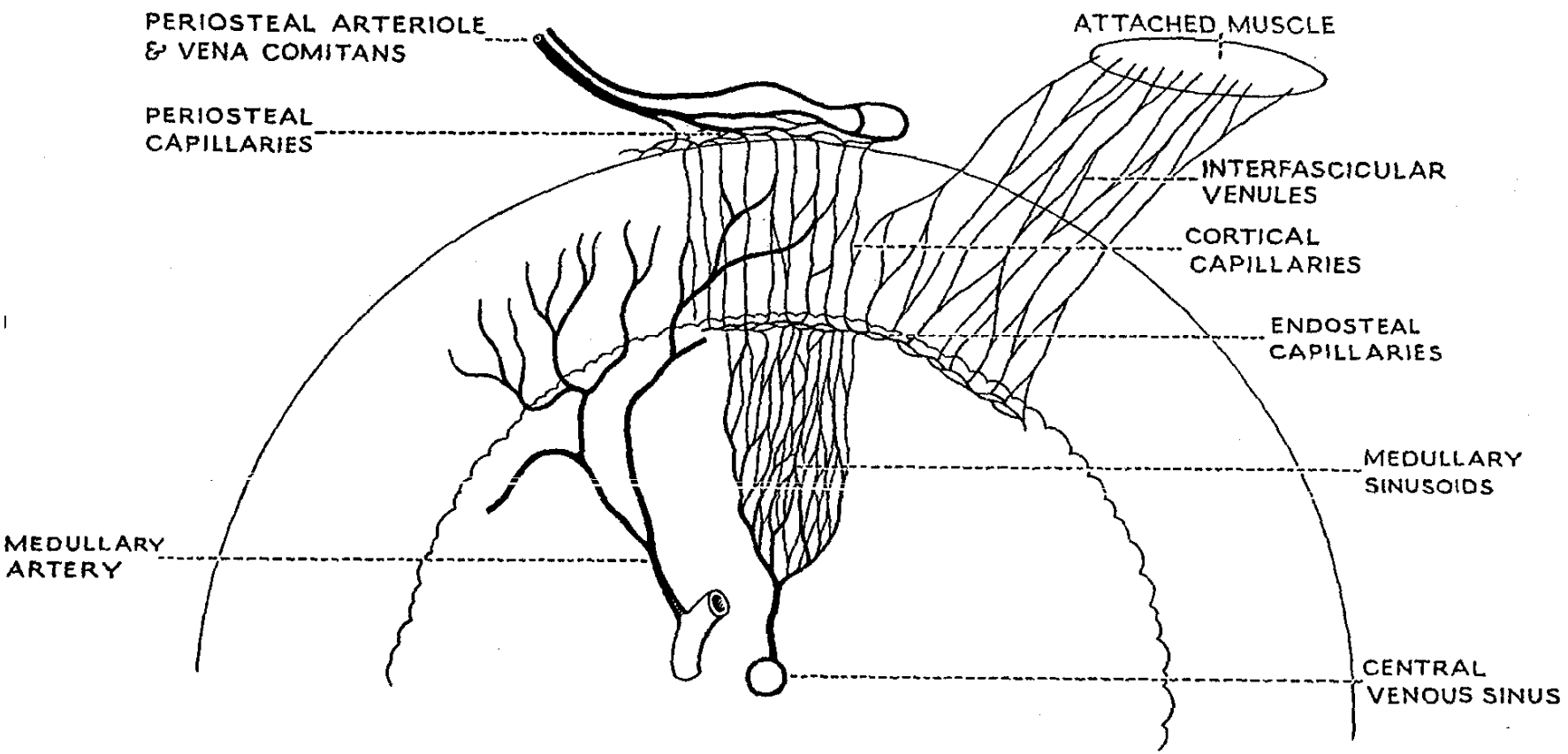


Ham

Osteon And Haversian Canals



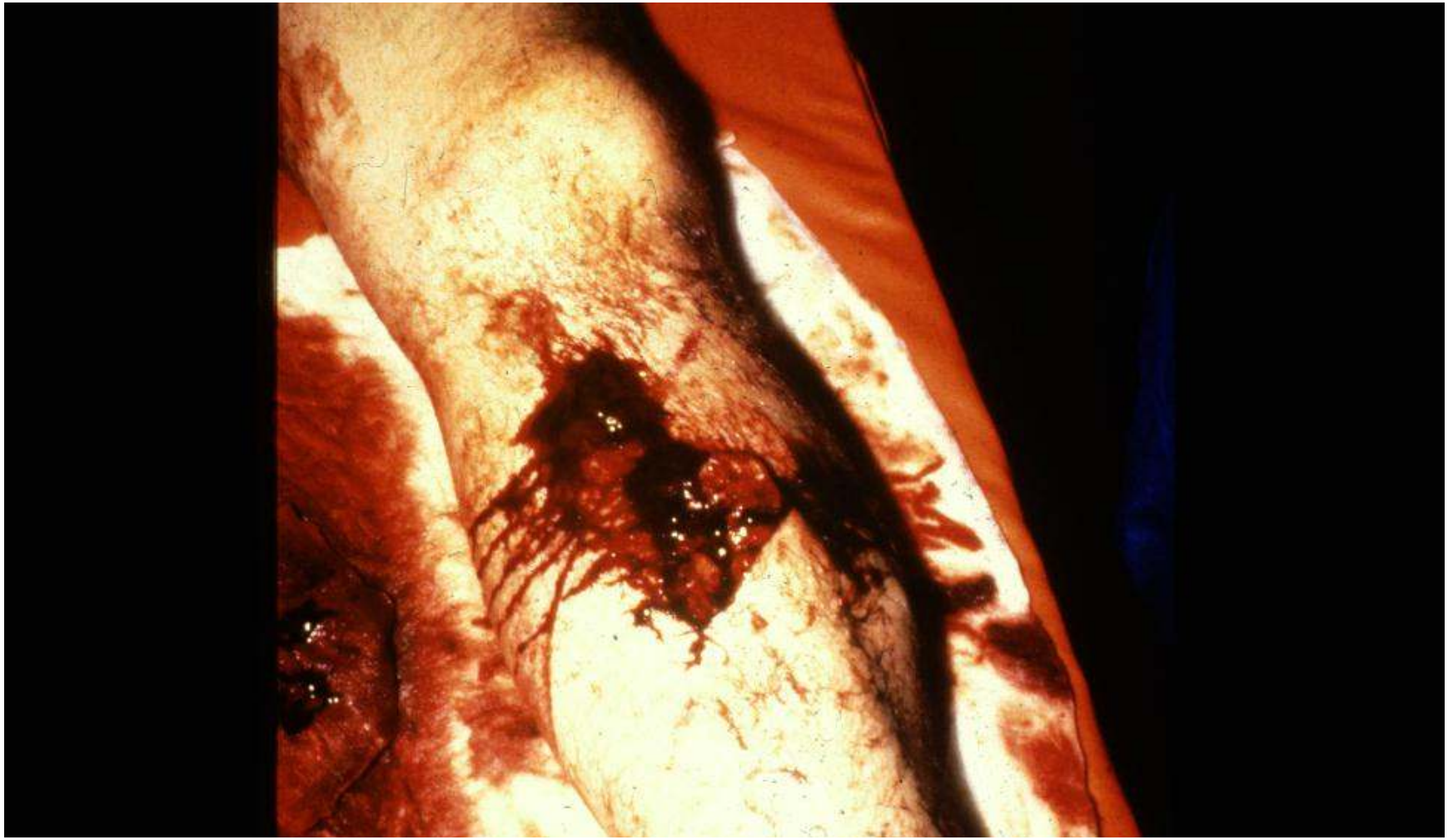
Blood Flow in the Cortical Diaphysis



Murray Brookes

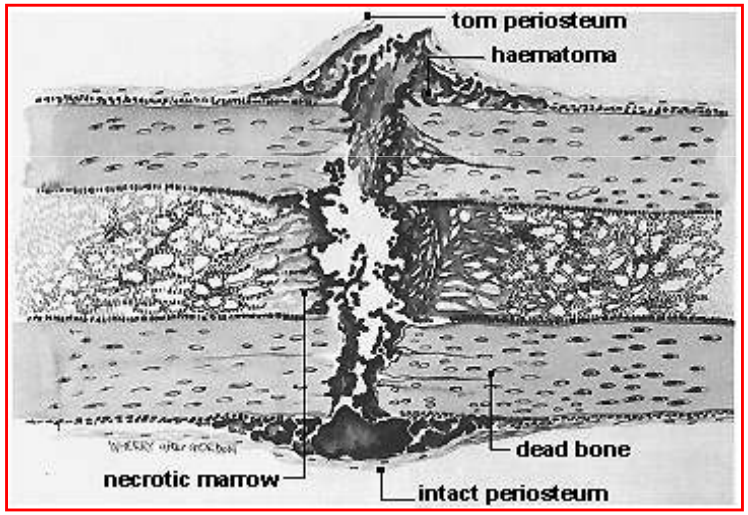
Road Traffic Accident

Tibial Fracture

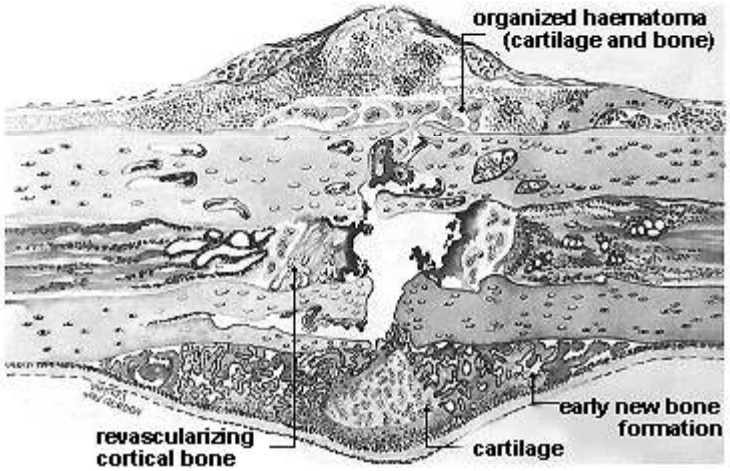


Fracture

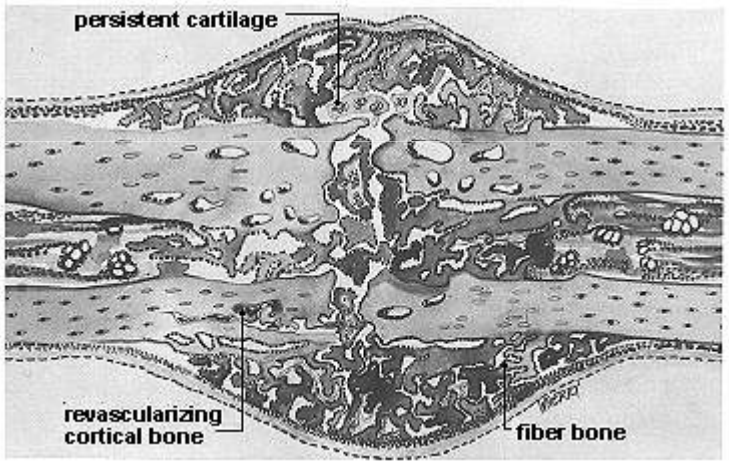
Histology of typical fracture



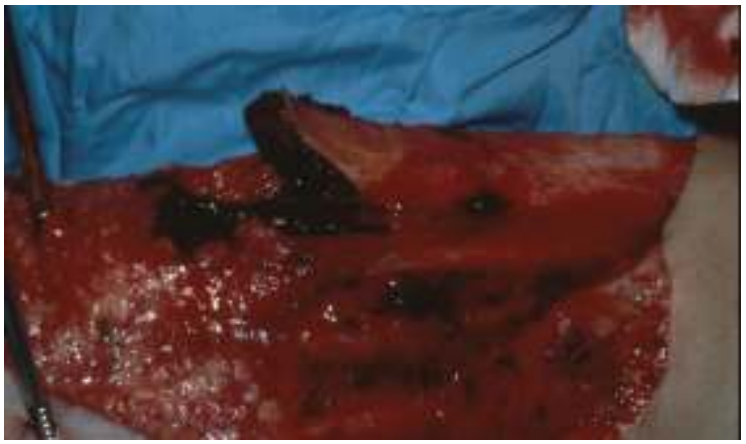
Soft Callus

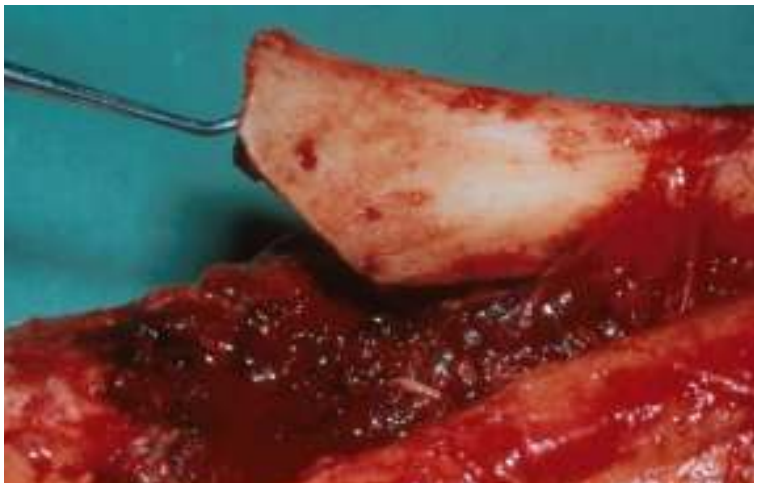

organized haematoma
(cartilage and bone)
early new bone
formation
revascularizing
cortical bone
cartilage

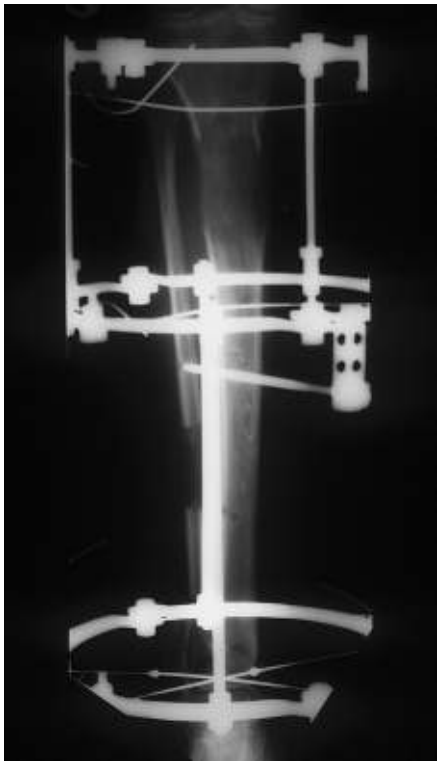
Hard Callus

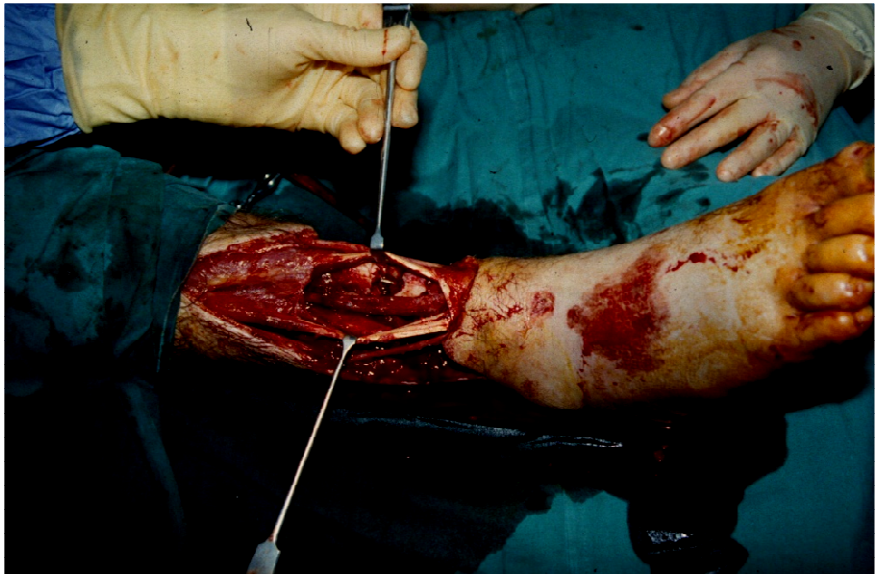

persistent cartilage
revascularizing
cortical bone
fiber bone

Open Fractures





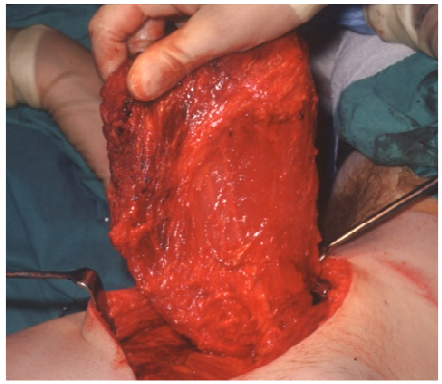




Open Fractures

Muscle Flaps

Latissimus dorsi



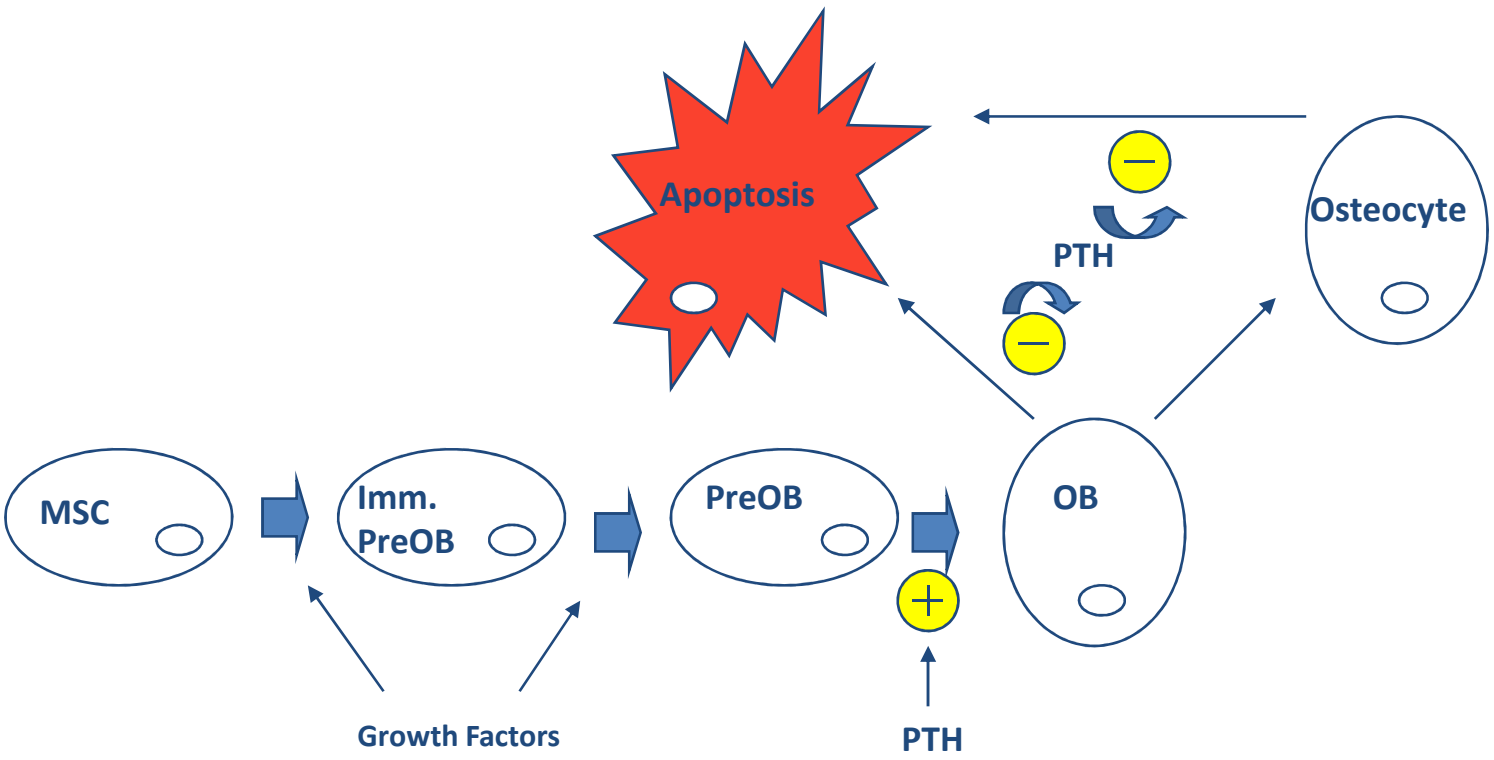
Rectus abdominus

Stem Cells

Stem Cells and Haematopoiesis

- Embryonic Stem Cells
- Adult derived Stem Cells
  - Mesenchymal
  - Haematopoietic
- Umbilical cord blood stem cells

Mesenchymal Stem Cells



-VEGF

-FGF-2

-IGF-1

-TGF-βs

-BMPs

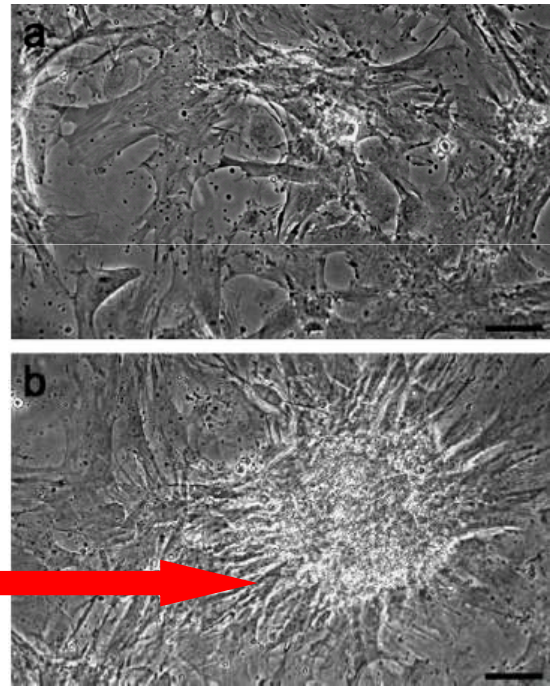
from Lane et al 2003

Mesenchymal Stem Cells

Bone

a. MSCs treated with control medium, 7 day after induction

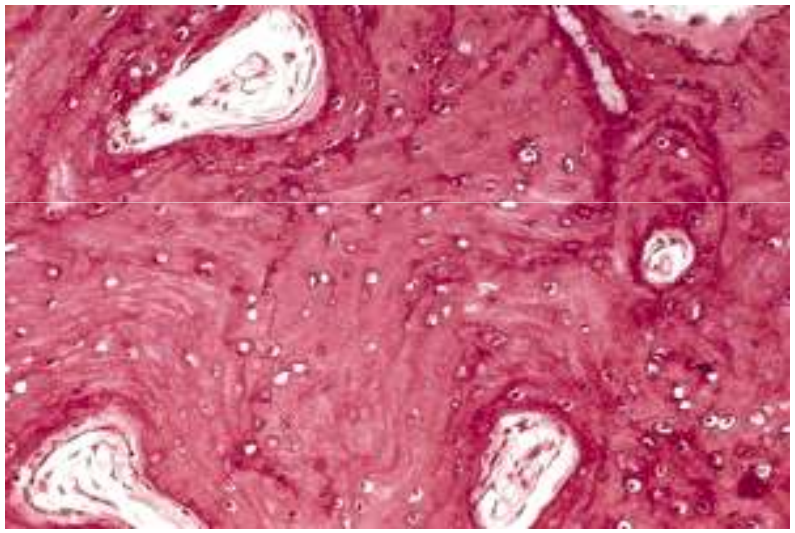
b. MSCs treated with osteocyte culture medium, 7 days after induction

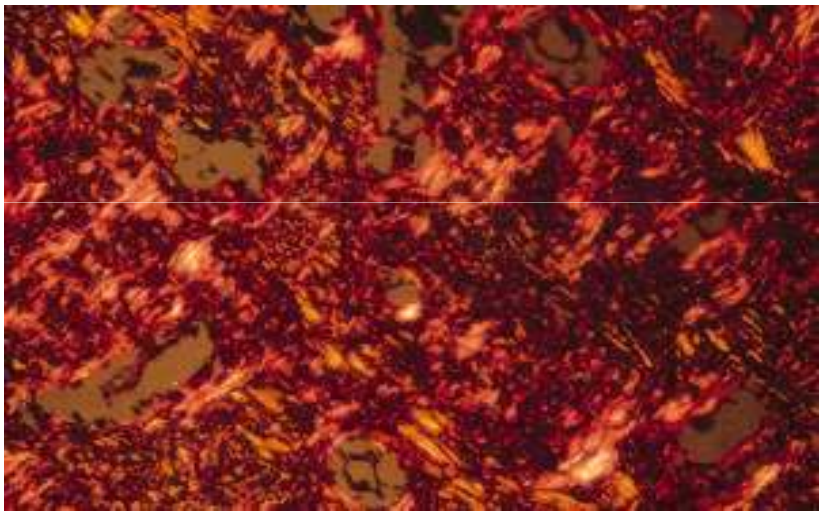


Clear bone aggregates are beginning to form in the cultures of cells treated with OS medium.

Donzelli et al 2007 (Archives of Oral Biology)

Immature Bone



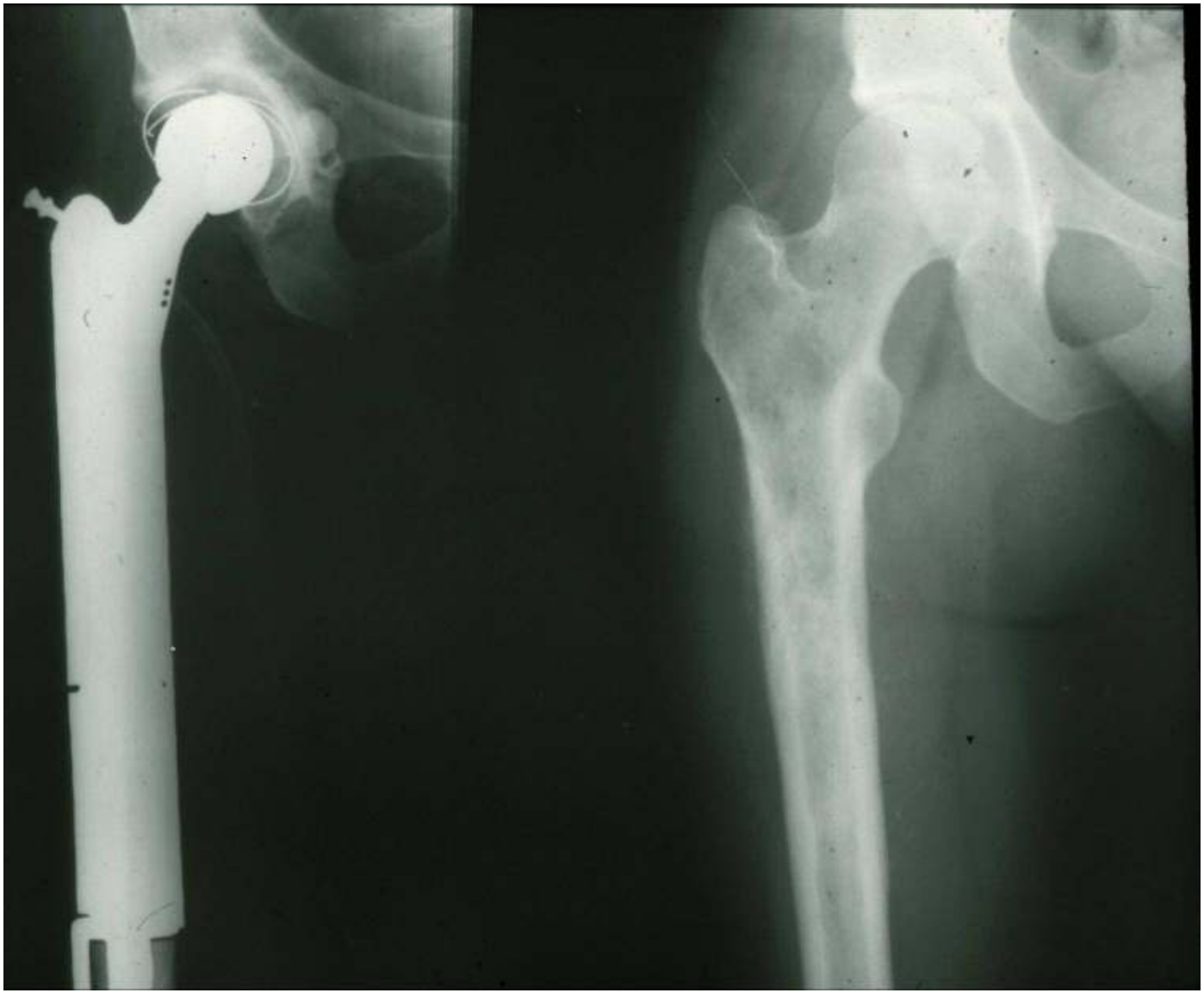


Total Joint Replacement

Osteoarthritis of Hip

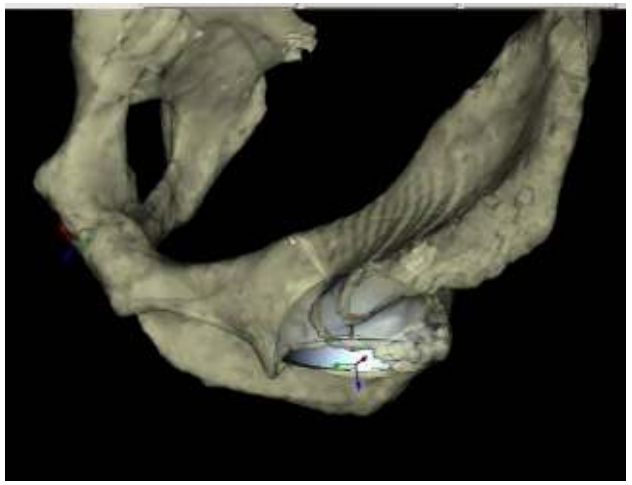
Sir John Charnley
FRS

Cemented Exeter



Surface Replacement

Future



- Virtual Surgery pre op
- Computerised Assistants
  - active robots
    - For complex tasks
  - passive navigators
    - For simple ones
- Postop Measuring
    - Implant position

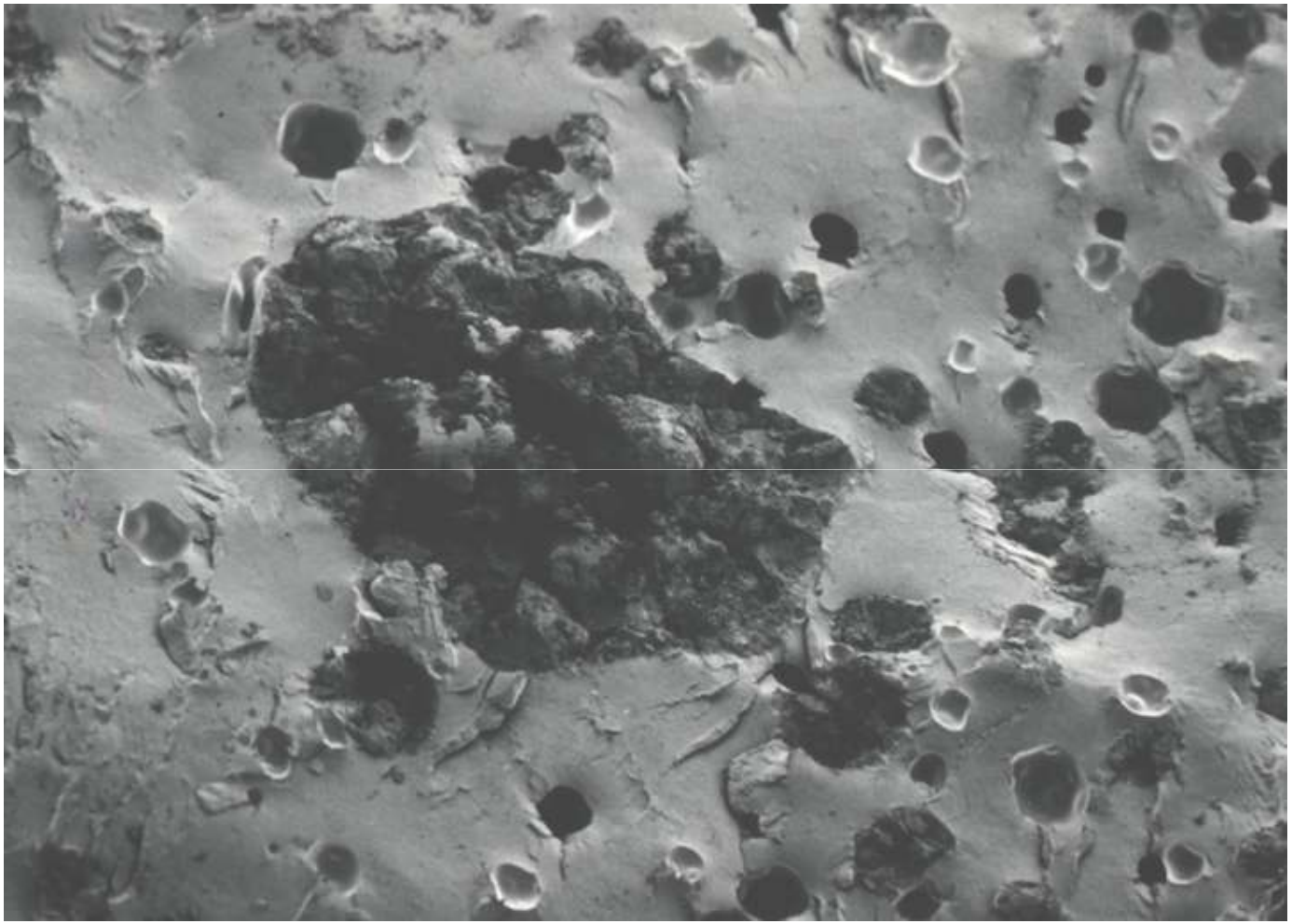
Infection following Total Joint Replacement

Clean Air Systems

- Charnley introduced Howarth clean air systems
- 300 changes per hour
- Reduce level of particle contamination in operating site
- Horizontal or vertical;
- Infection reduced from 3-5% to <1%

Antibiotic Prophylaxis

Bone Cement

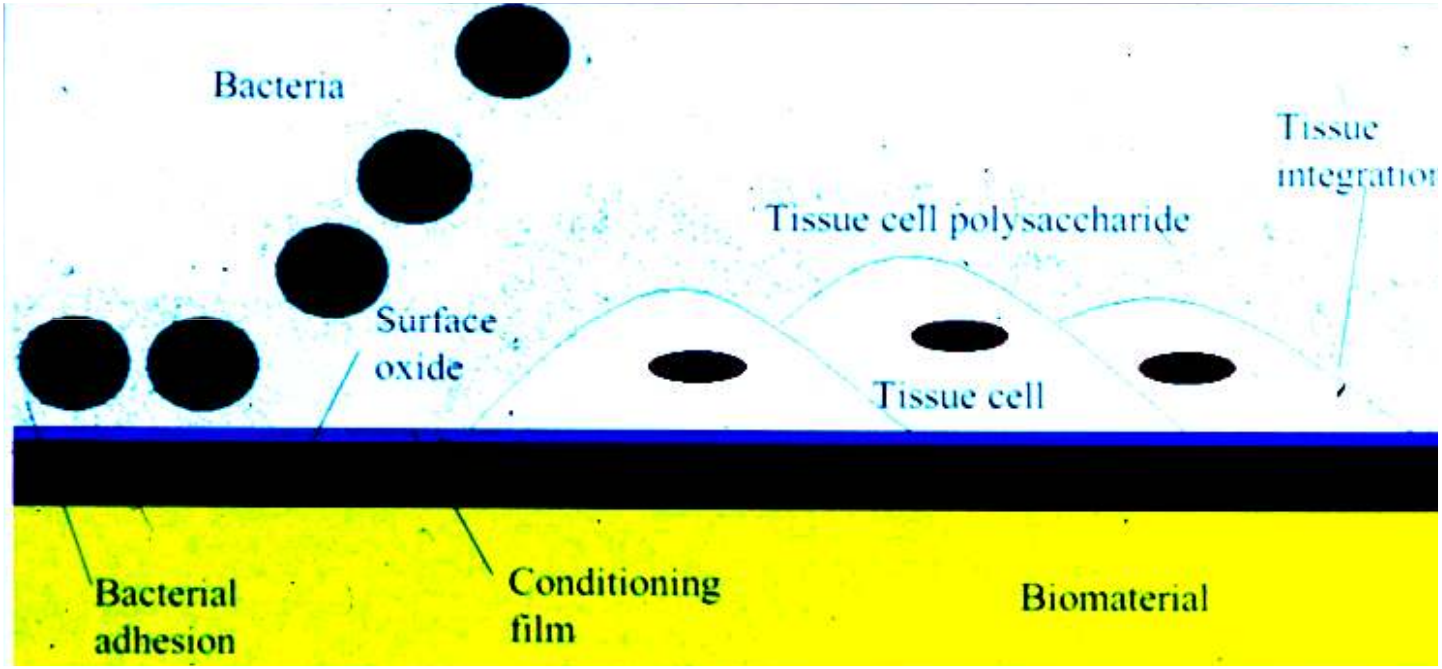


Race for the Surface

Gristina Science 237; 1588; 1987

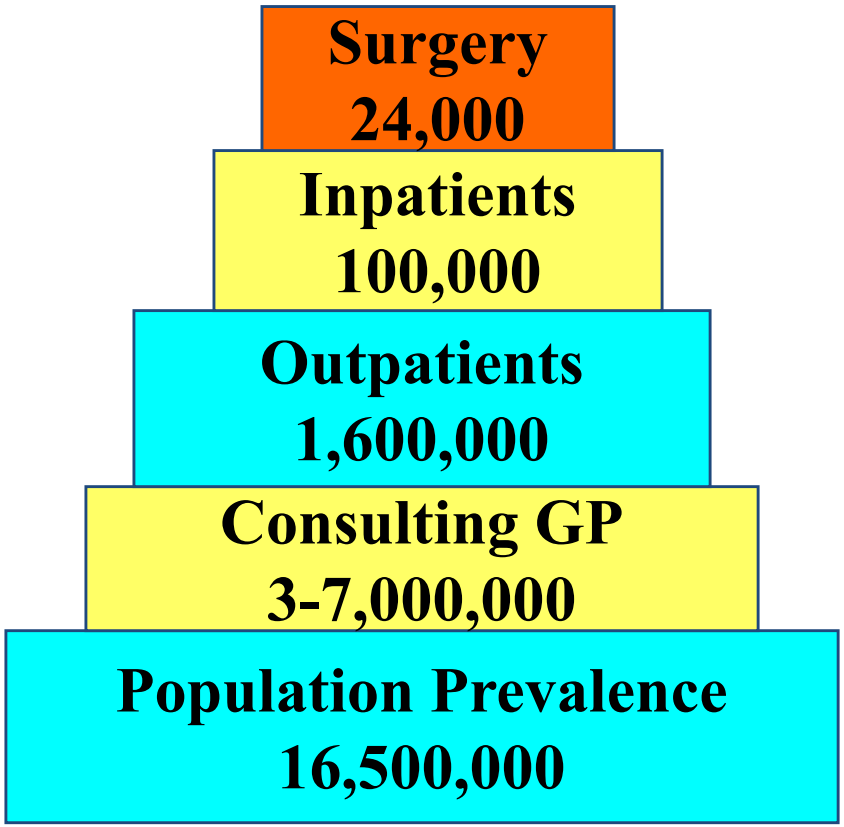
RACE FOR THE SURFACE

Gristina

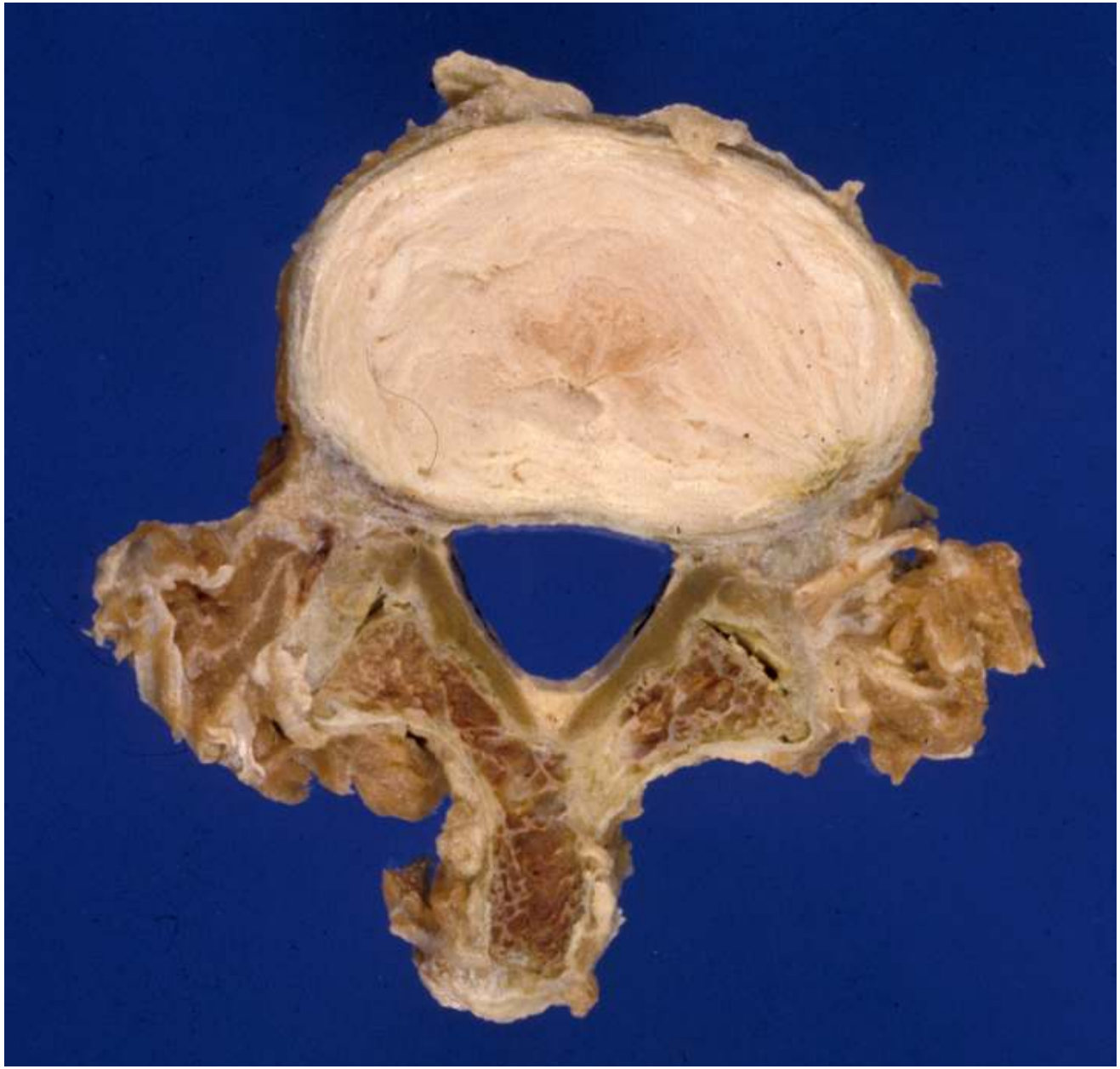


Low Back Pain

Low Back Pain



www.Jr2ox.ac.uk



Disc Nutrition

- Small molecules…….Passive diffusion
- Large molecules…….Fluid flow

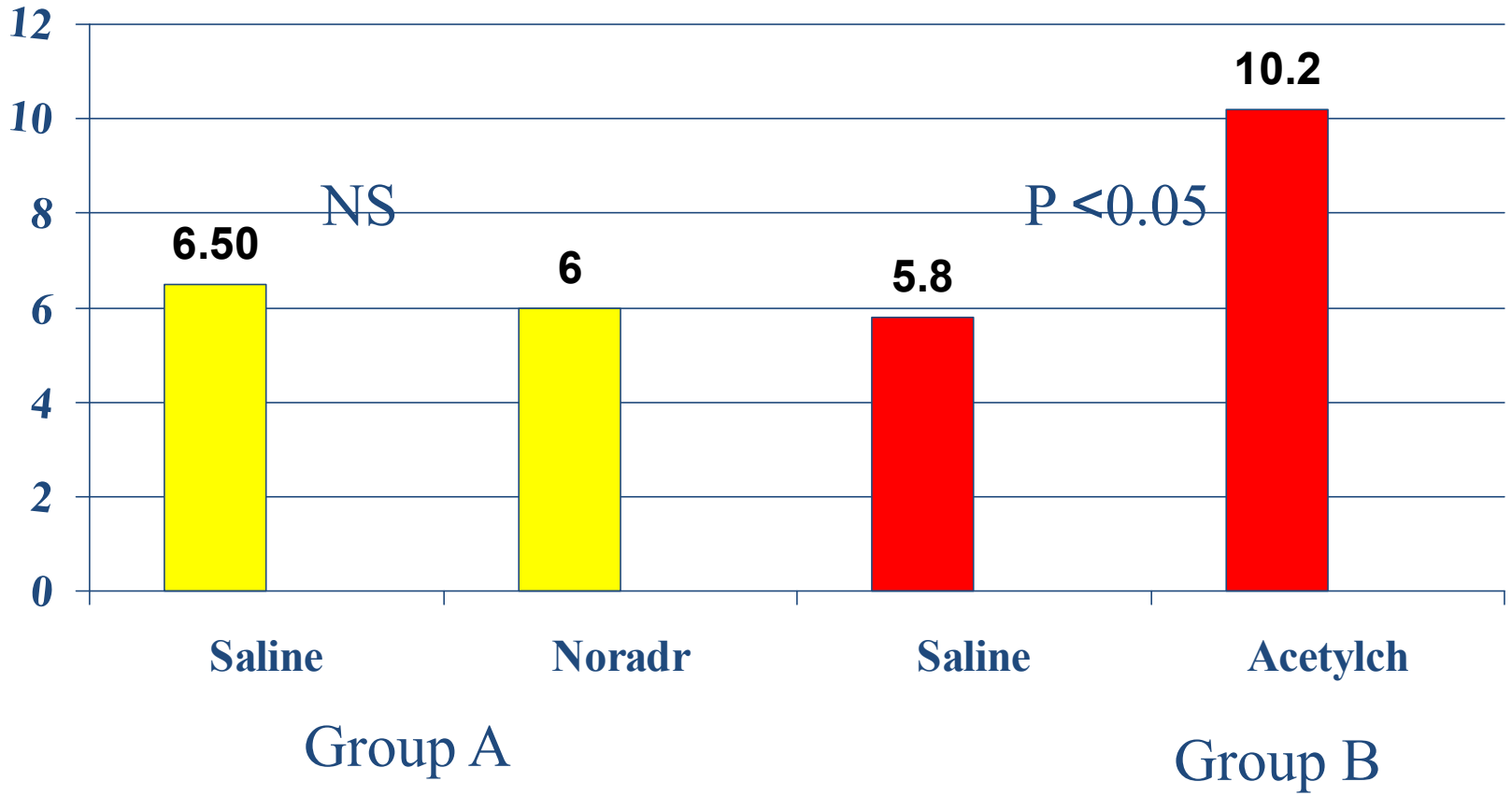
Urban et al. Bioreheology **15**,203,(1978)

Blood Supply

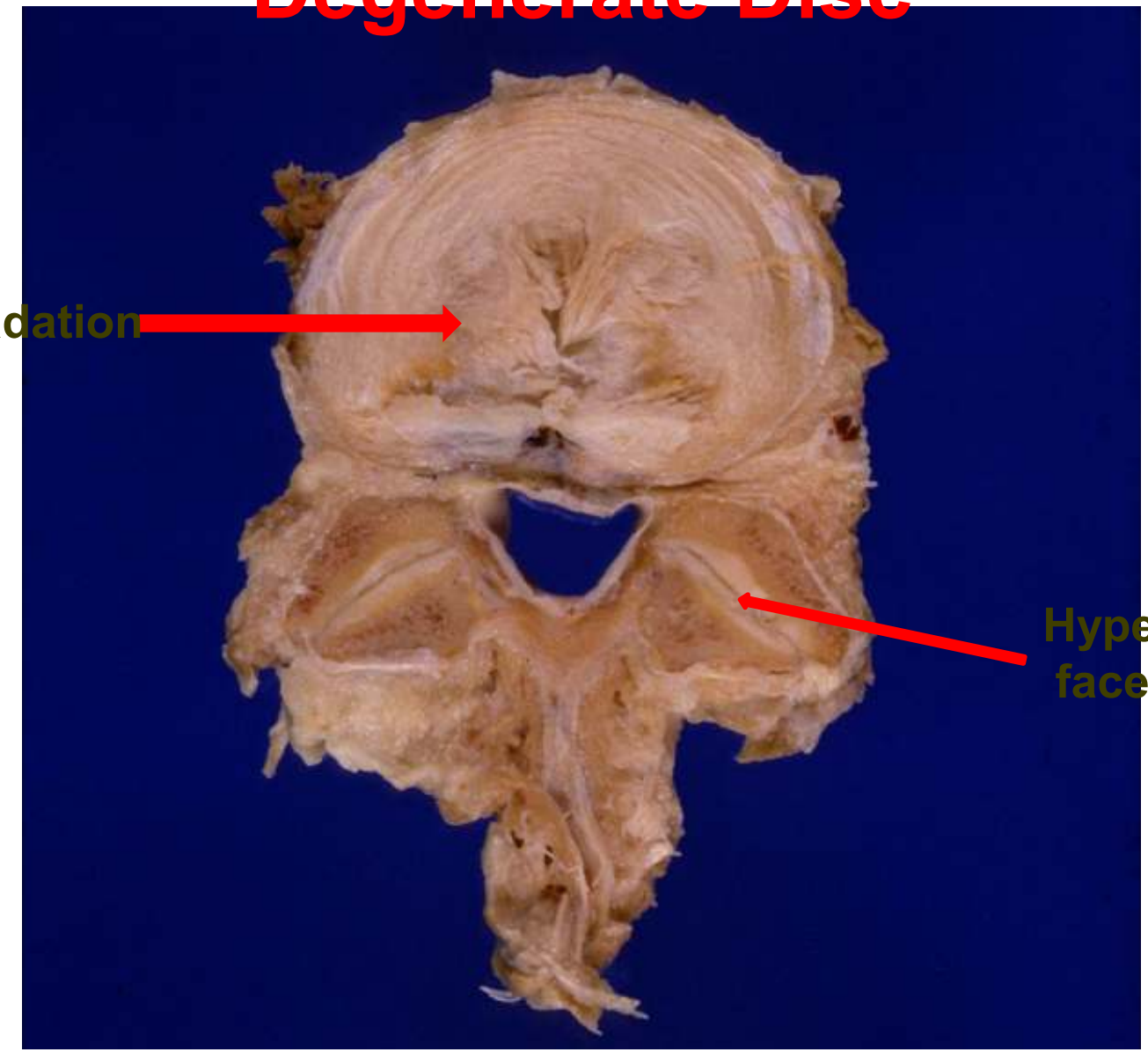
Crock

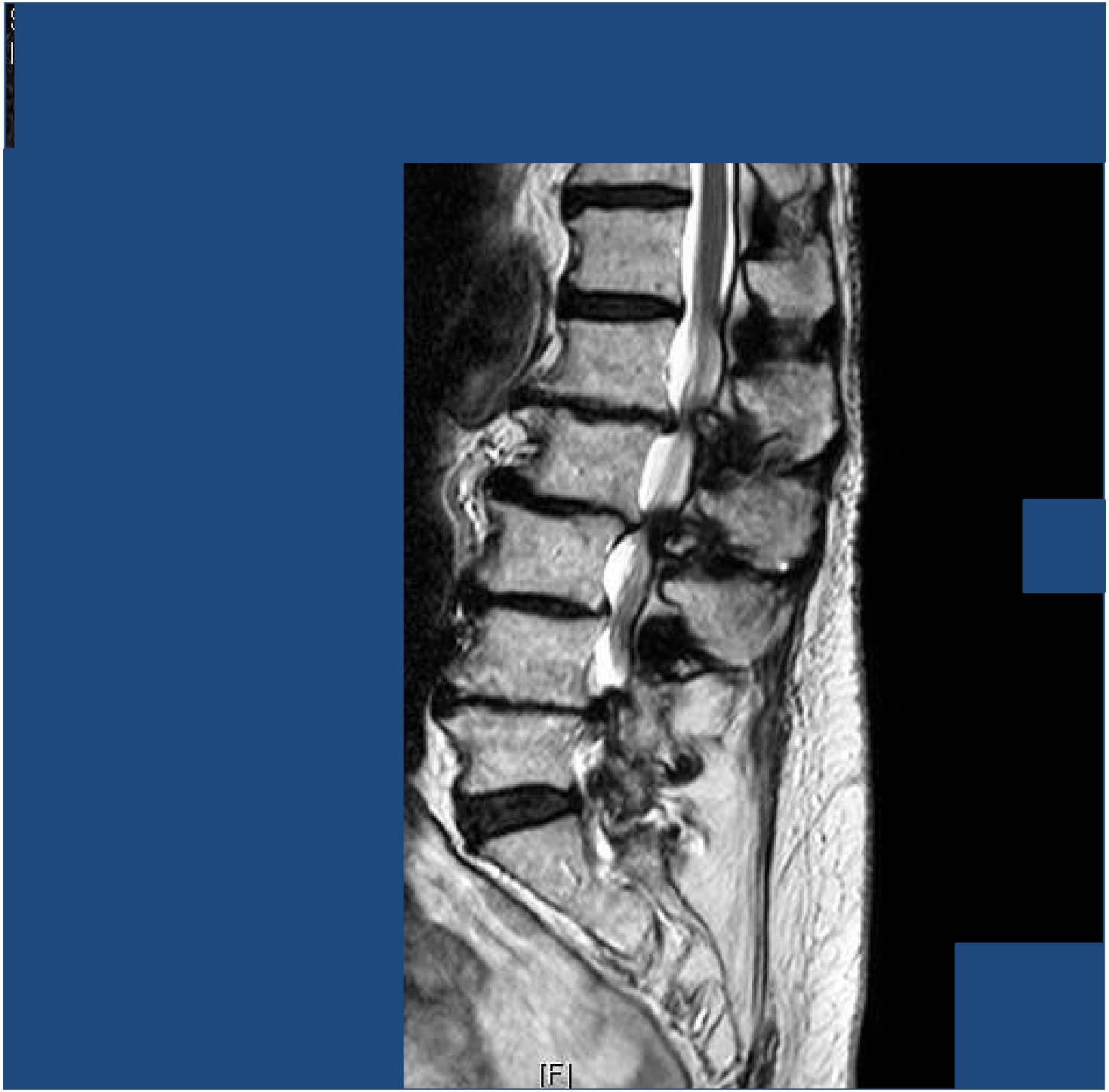
End Plate Blood Flow

Wallace et al Spine 1994

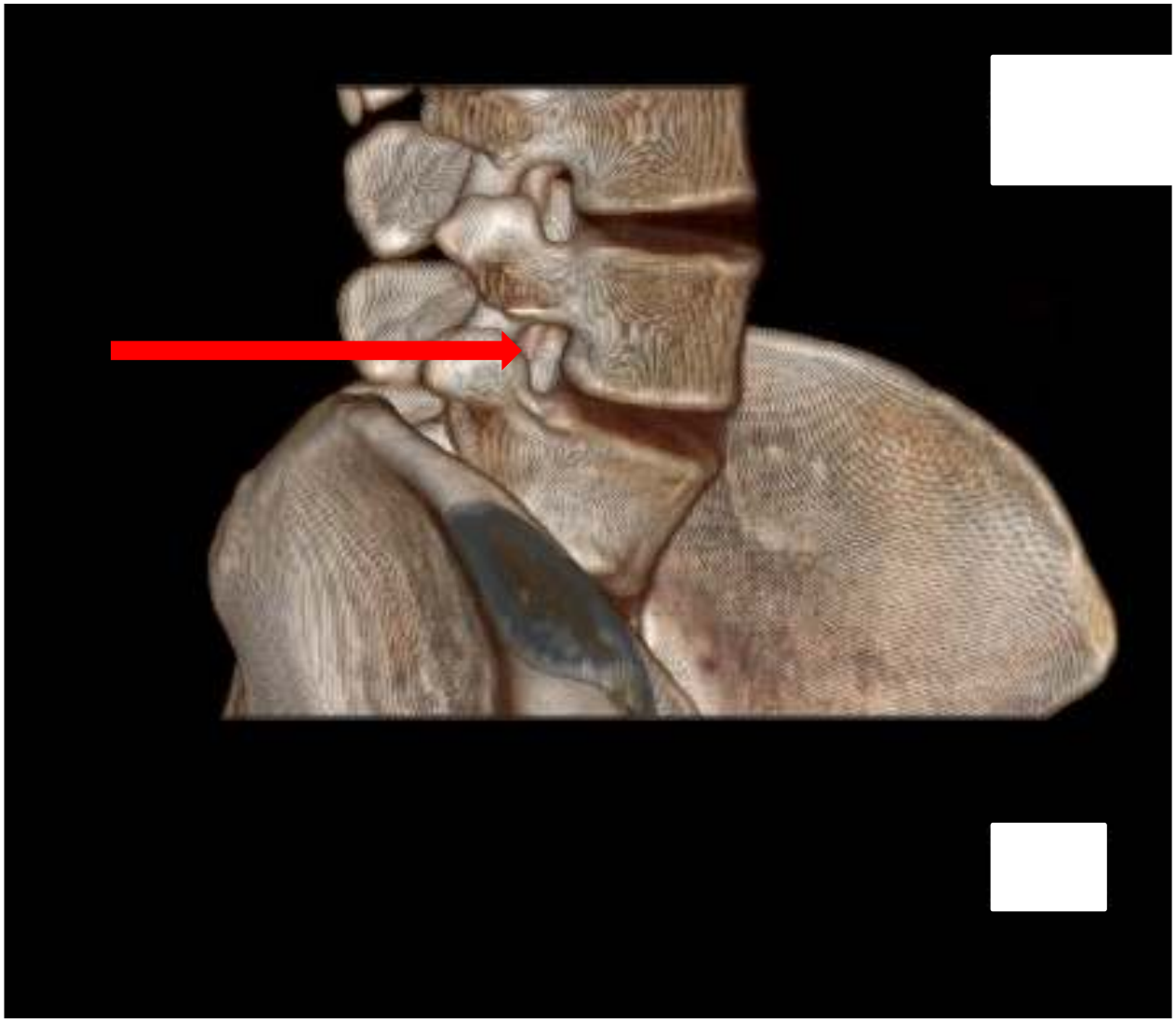


Degenerate Disc

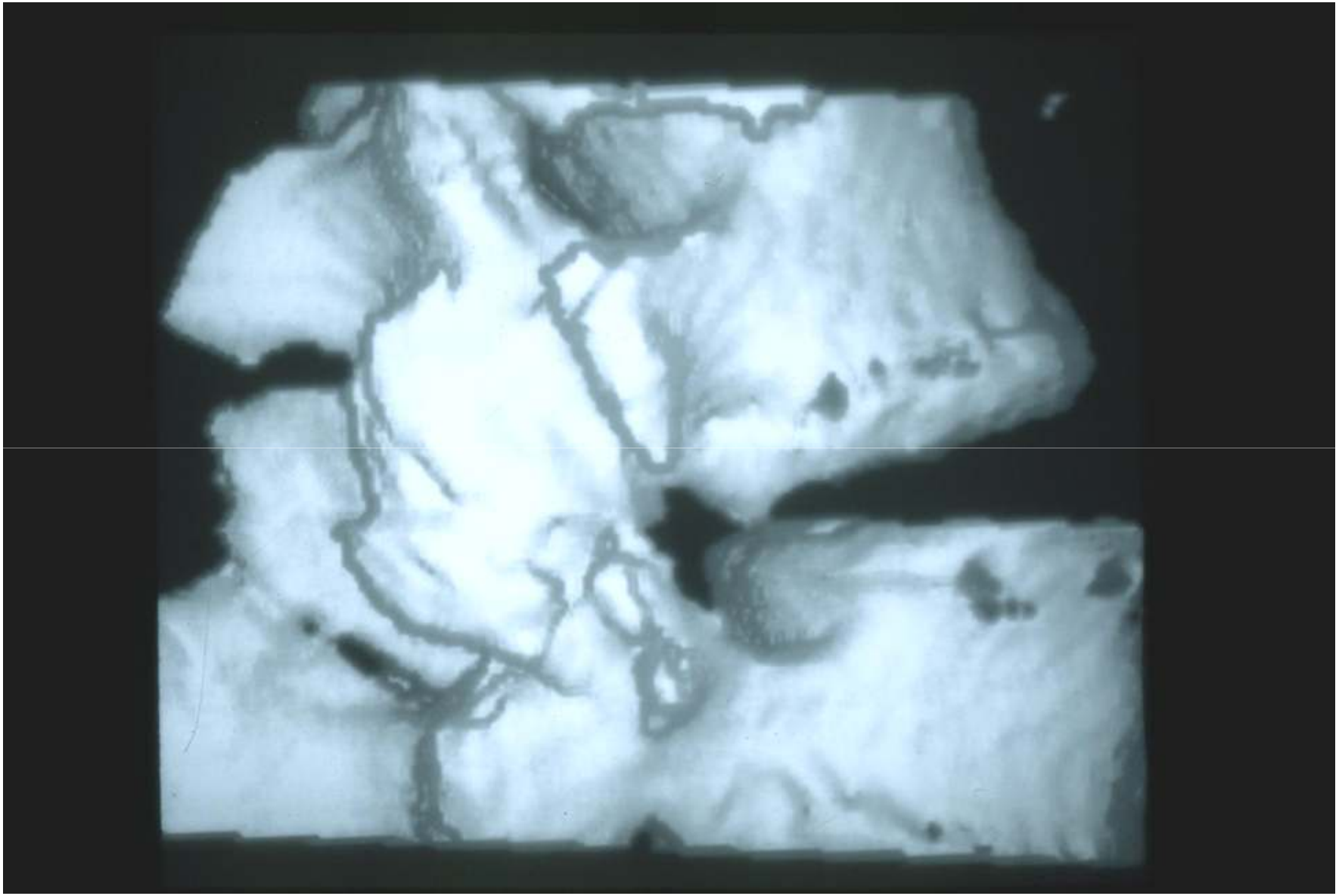



[F]

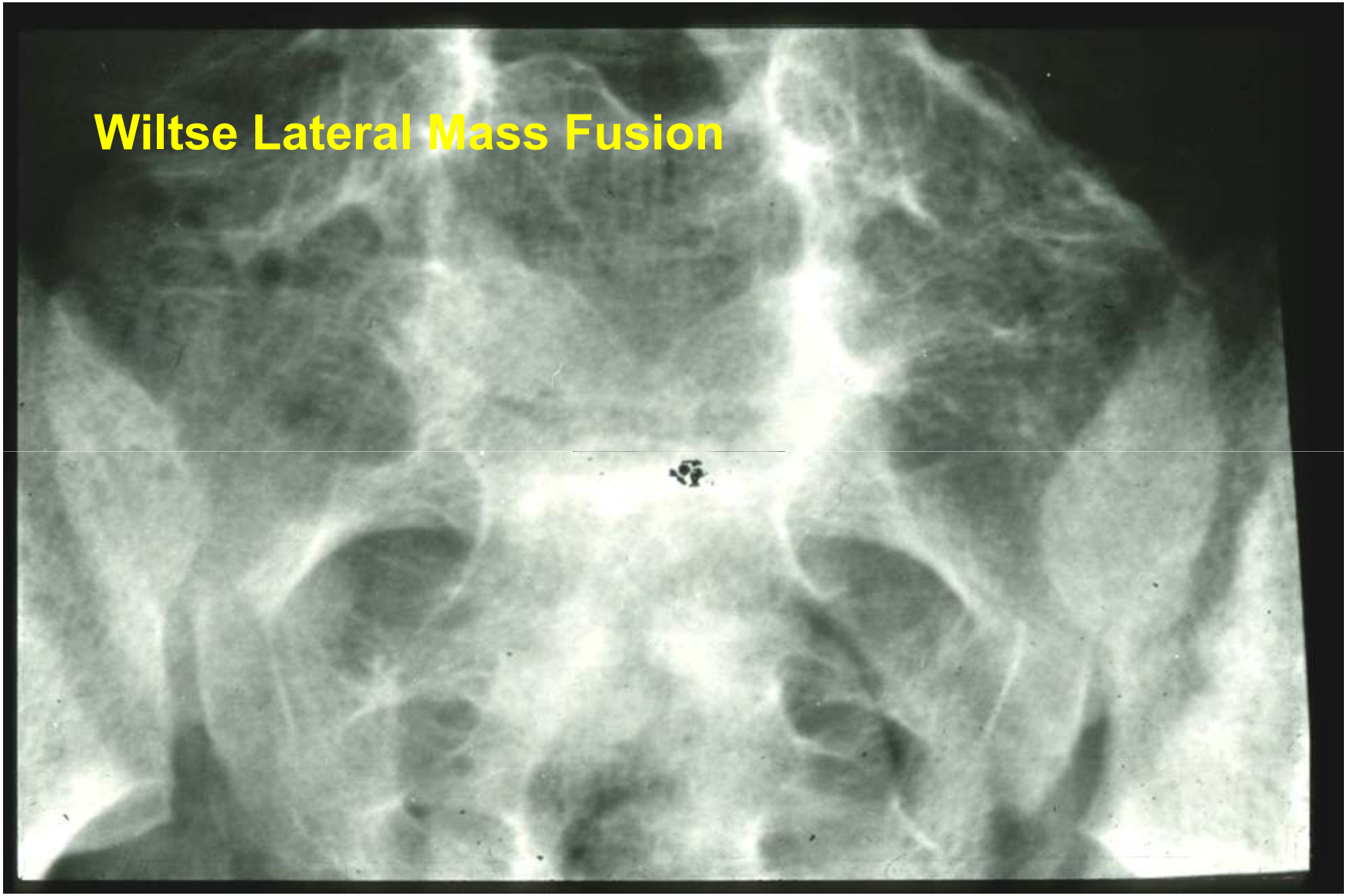
Nerve Roots



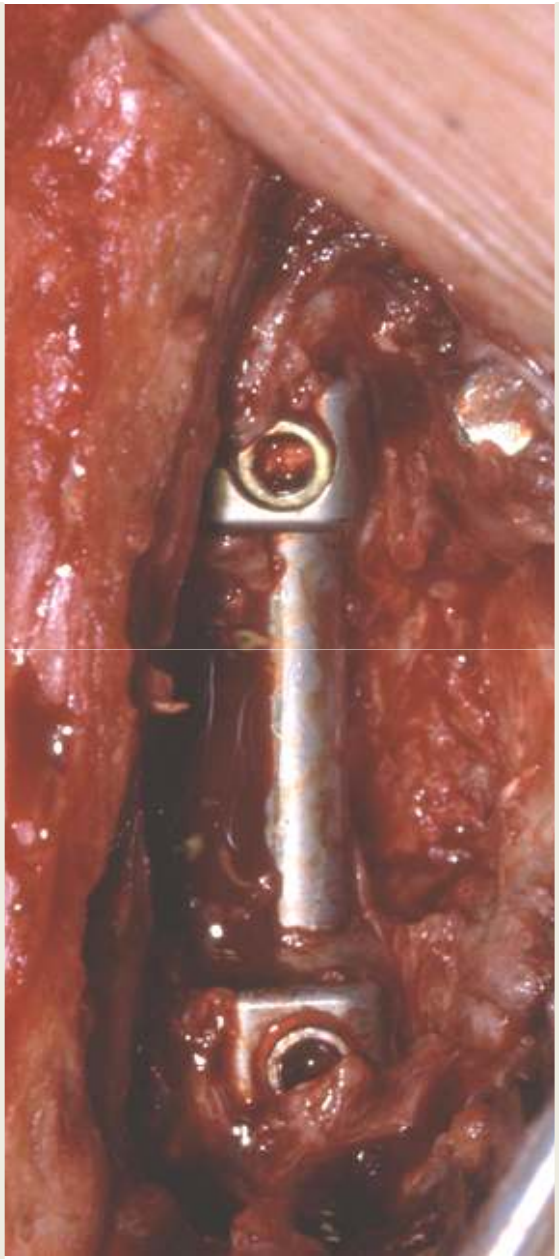
Instability




Spin: 178
Tilt: -0
P

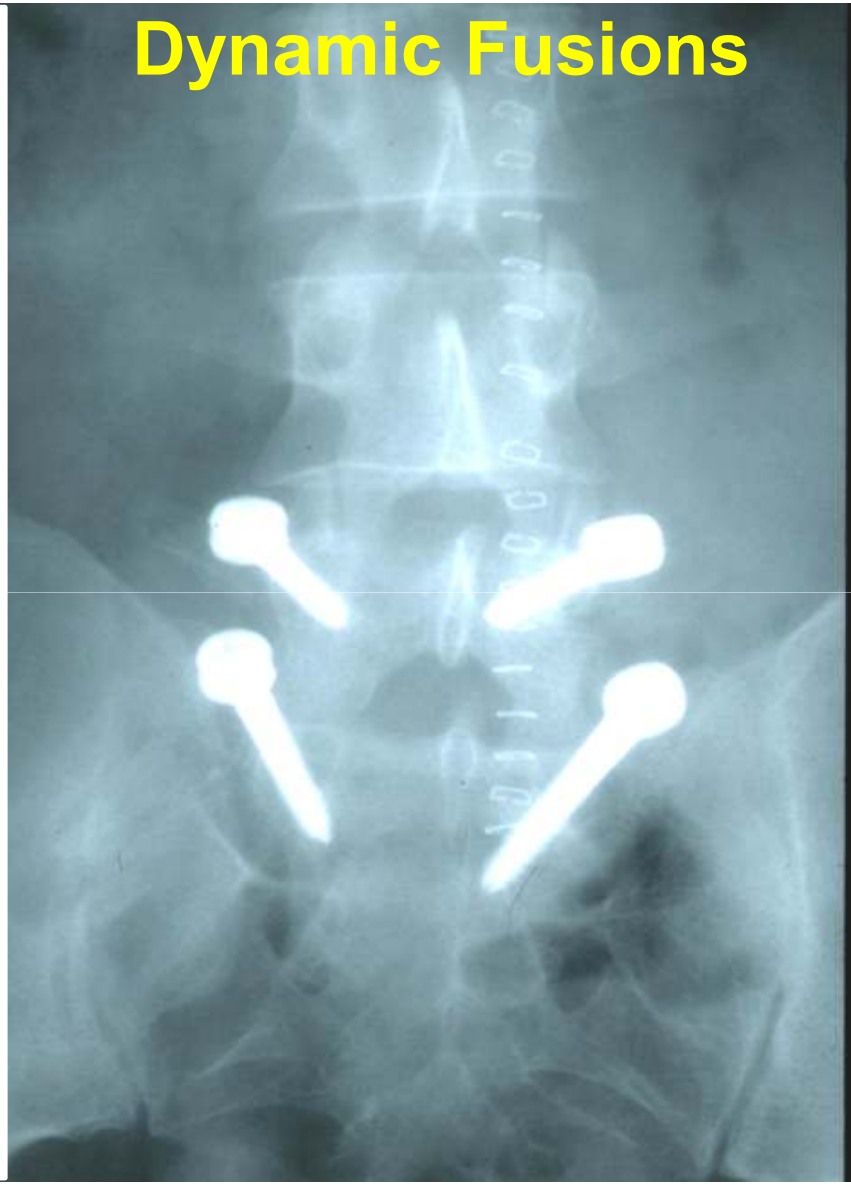

Wiltse Lateral Mass Fusion

Pedicle Screws with Bone Graft

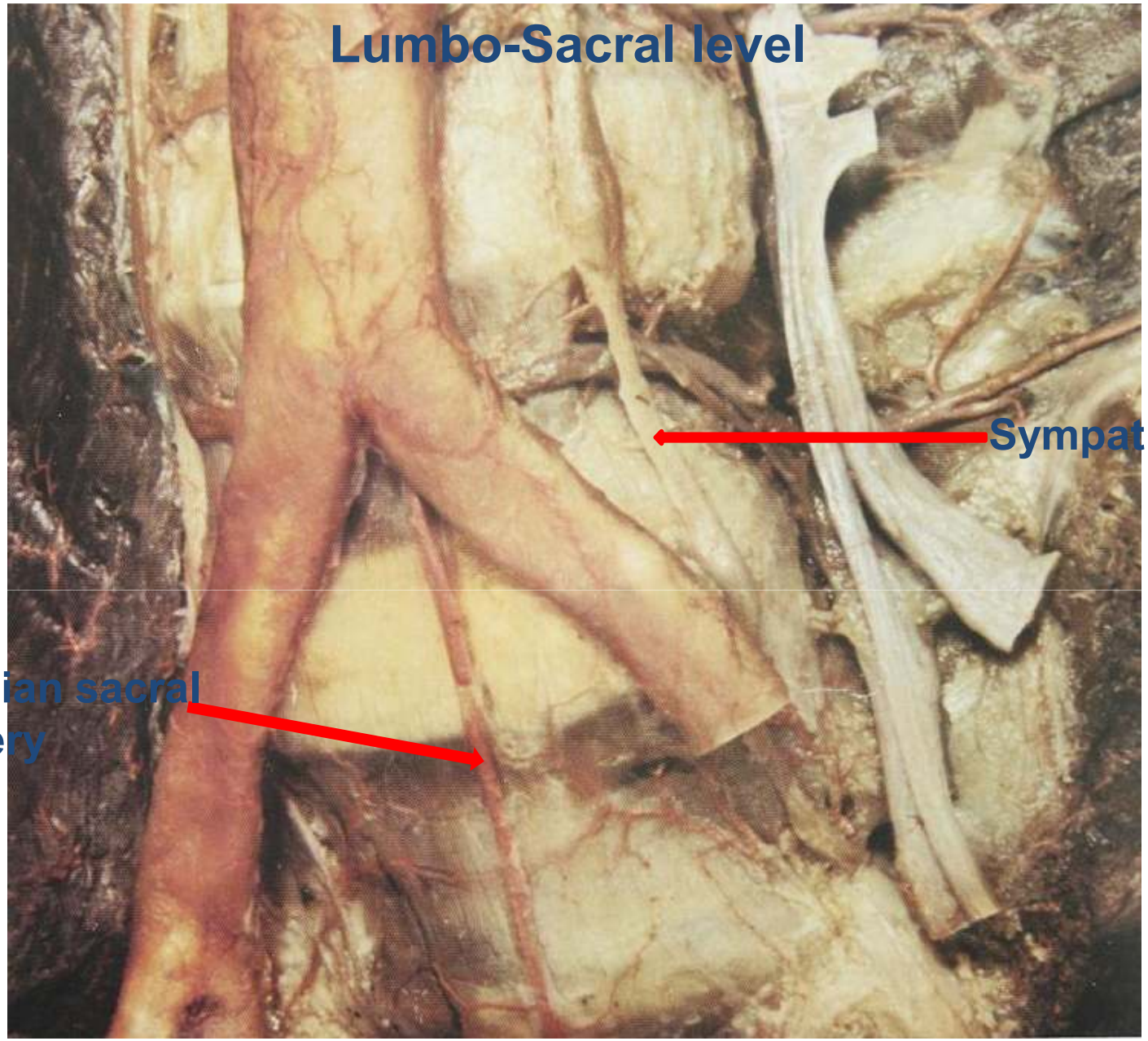


Rigid Fusions

Dynamic Fusions

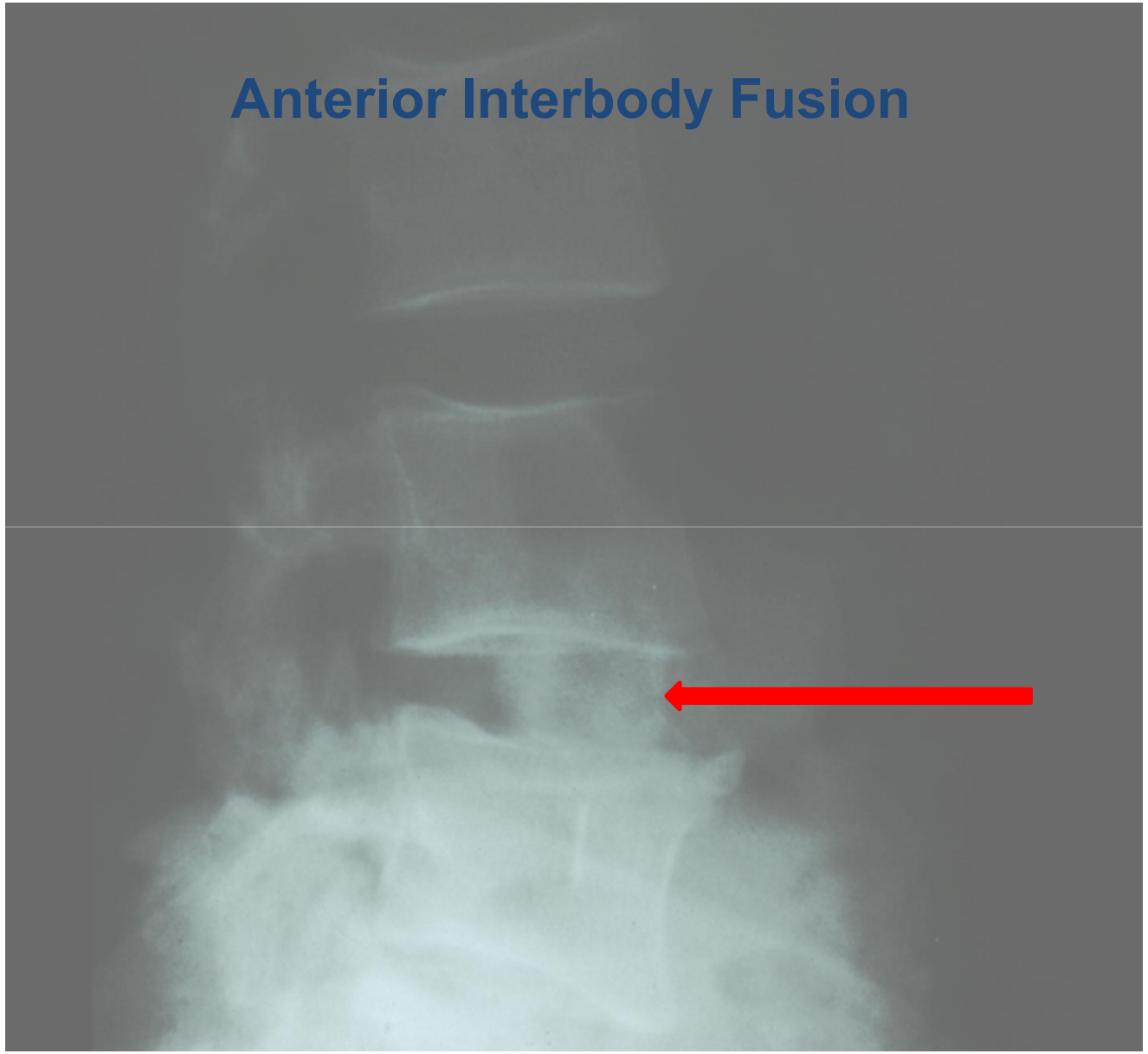


Lumbo-Sacral level

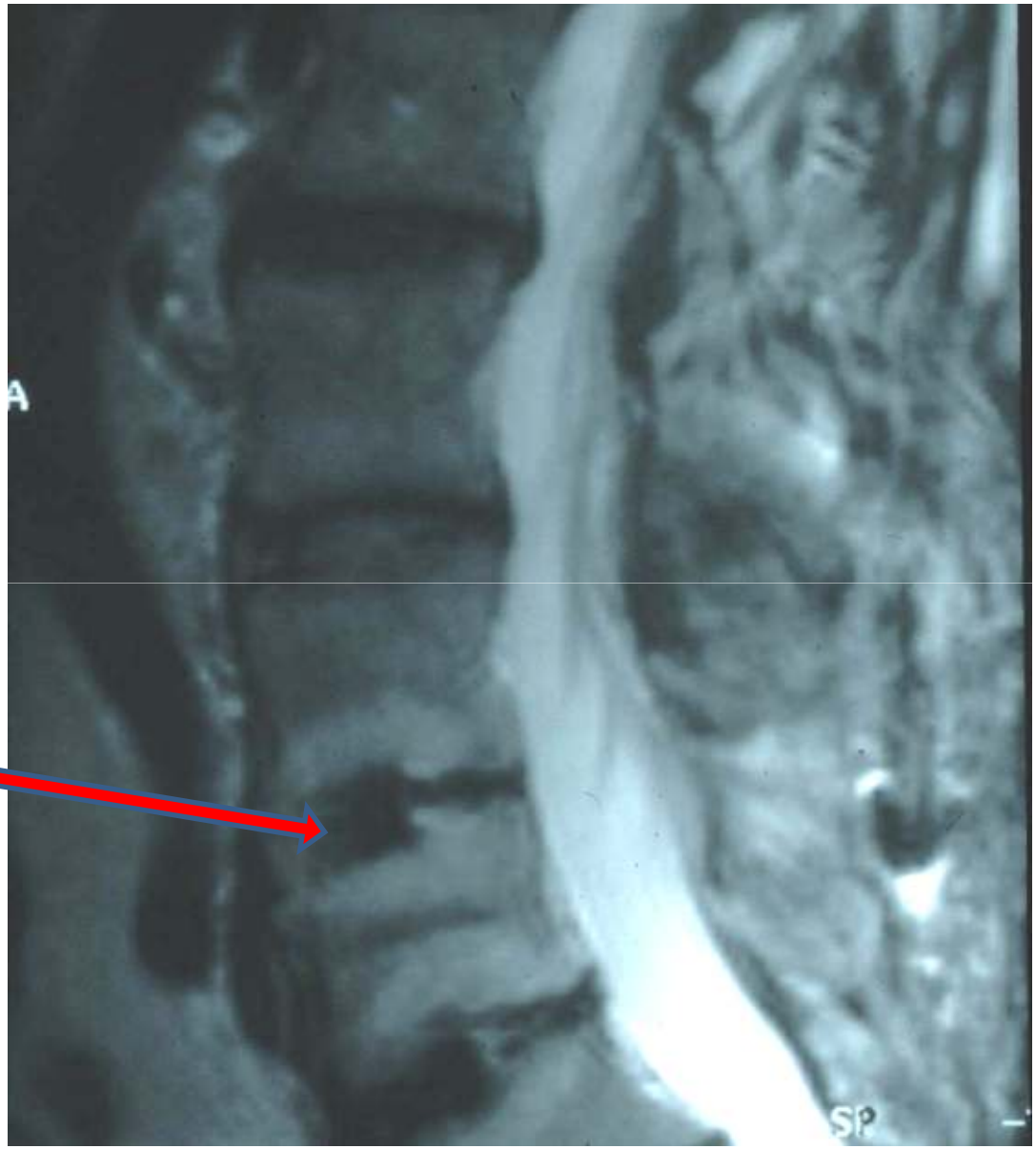


Crock

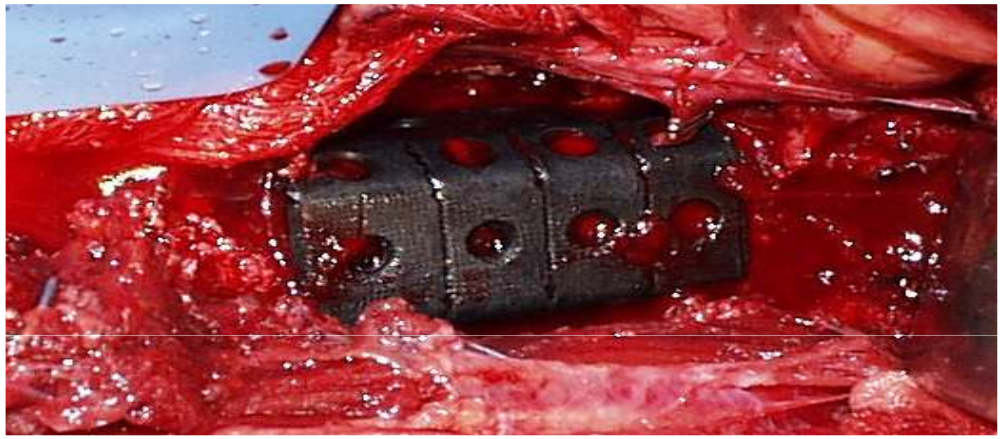
Anterior Interbody Fusion

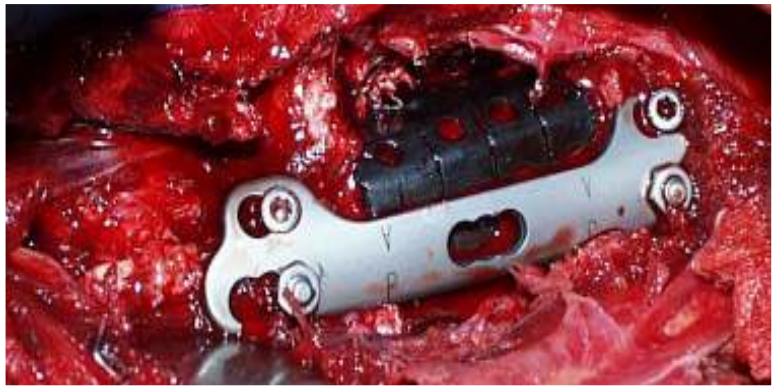


Cages



Brantigan Cages





Trial to compare surgical stabilisation with intensive rehabilitation

Fairbank et al BMJ May 2005

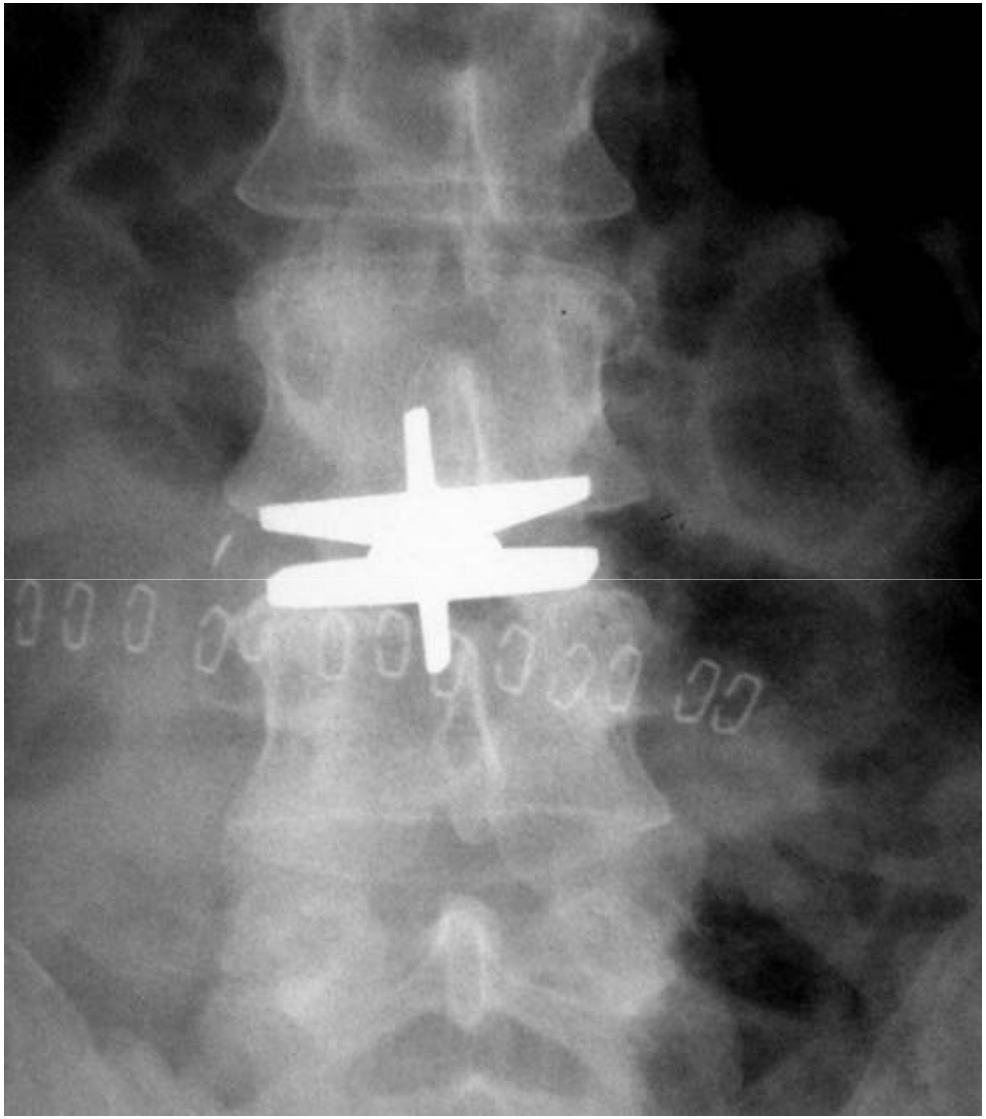
Fusion versus Rehabilitation

- 349 participants
- 15 orthopaedic and rehabilitation centres
- All patients considered for fusion
- 24 month follow up

Surgery versus Rehabilitation

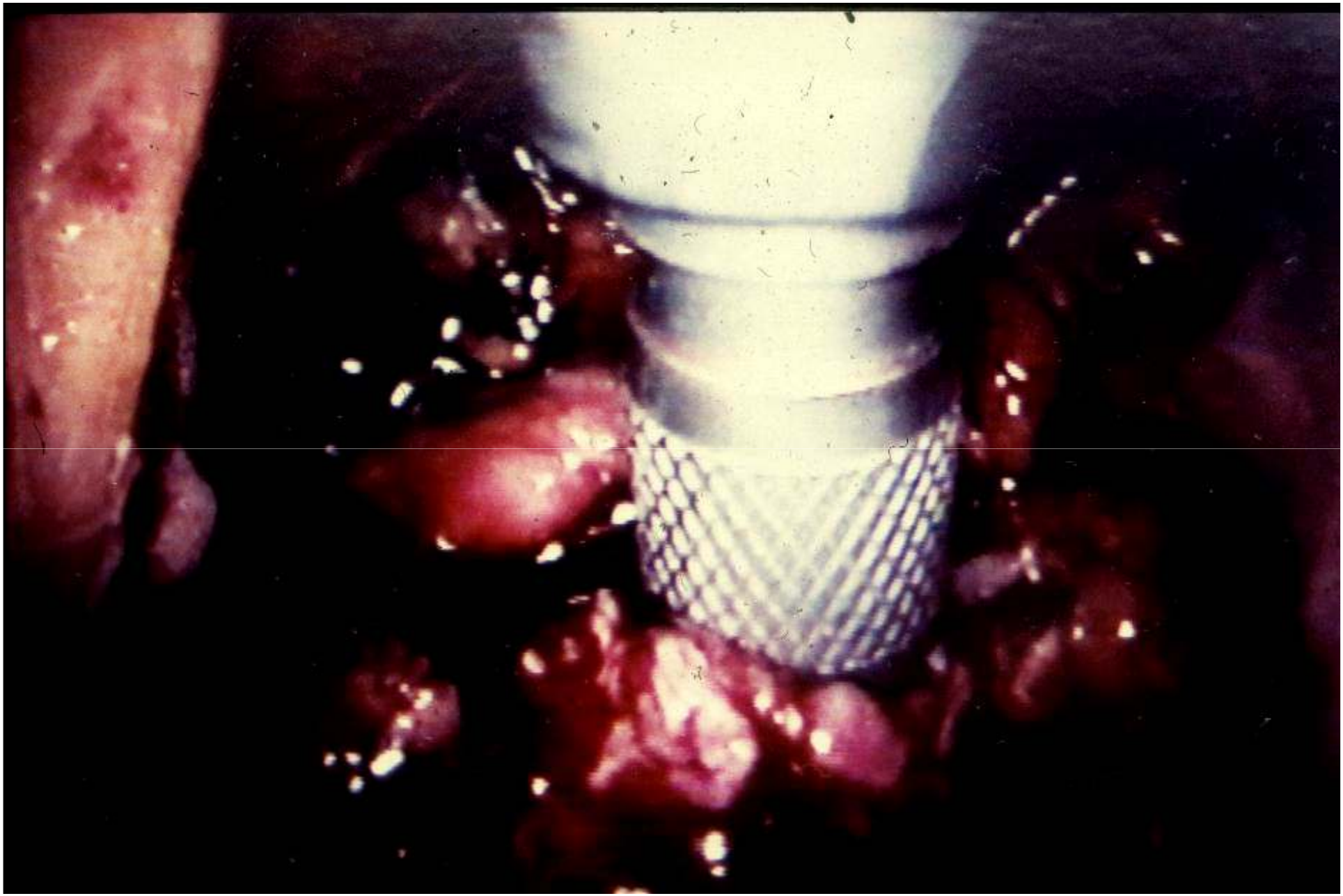
- No significant difference
- Both groups reduction in disability
- No clear evidence primary spinal fusion surgery more beneficial then intensive rehabilitation

Total Disc Replacement



Minimal Invasive

Spinal Surgery



Future

Stem Cells ?

Stem Cells

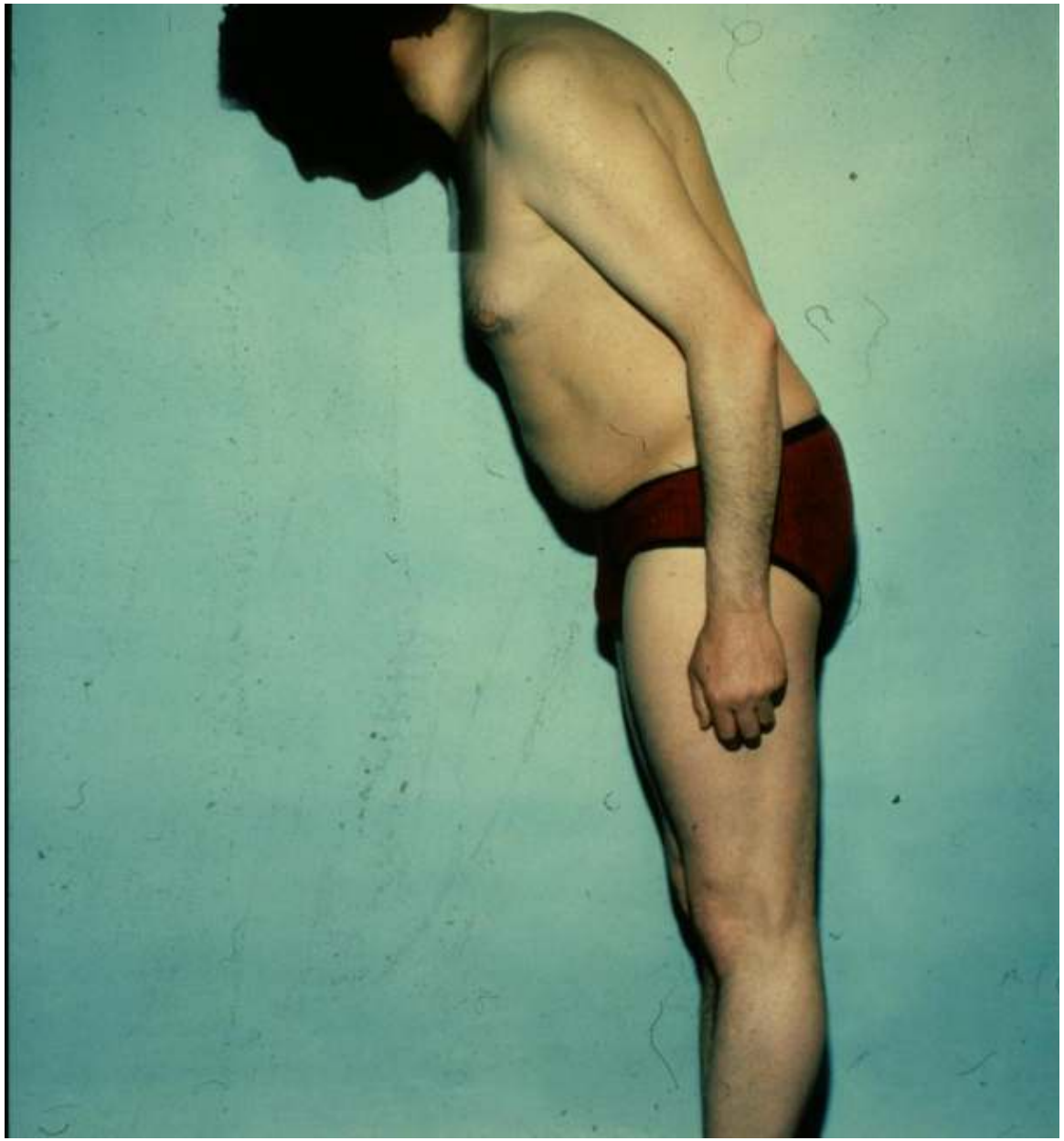
- Adult derived cells implicated in regeneration and repair
- Readily harvested and expanded
- Mesenchymal Stem Cells (MSCs)
- CD34+

Mesenchymal Stem Cells

- Derived from bone marrow stroma
- Differentiates into osteo/chondro-blasts
- Promote vasculogenesis in bone growth (Kahling *et al*, 2008) and myocardial ischaemia

CD34+ cells

- Used extensively as HSCs in bone marrow transplants/grafts
- Multilineage potential, including osteogenic (Matsumoto *et al*, 2006)
- Endothelial differentiation in murine MI (Yeh *et al*, 2003), rodent fracture (Matsumoto *et al*, 2006)



Can stem cells work in the presence of a degenerate disc ?

Degenerative Changes

- ***Boos et al 2002 Histological analyses of cadaveric discs***

- Progressive reduction in vascularity of end plates from 2nd decade

- Associated cell death and ECM degradation - Degeneration

Disease vs Degeneration

- Degenerative disease of IVD cycle of
  - Cellular anoxia/death
  - INFLAMMATION
  - Cytokine release eg. MMP
  - ECM degradation
  - Dessication and macroscopic damage

Objective of Regeneration

- Repopulate cells
- Repair ECM
- Restore Disc height
- Arrest or reverse degenerative processes?

Timing

- Early vs. late stages of disc degeneration
- Number of surviving NP cells
- Degree of ECM degradation

In Vitro Studies

- Differentiation to IVD cells
  - **Steck et al, 2005**
  - TGFβ 3D culture
  - Produce high levels of collagen I & osteonectin
  - similar gene expression to IVD culture
- NP cell potential
  - **Richardson et al, 2006**
  - NP-marker genes in co culture with NP cells

Animal Models – MSC viability

- **Crevensten et al, 2003**
  - Injection of collagen gel of autologous MSC into rat coccygeal disc
  - Preserved viability in 28 days, increased height compared to blank gel injections
- **Zhang et al, 2005**
  - Injection of allogenic MSC into rabbit discs
  - Increased proteoglycan & collagen II content and gene expression

Patients
EuroDISC

- Prospective randomised controlled trial started in 2002
- Single level microdiscectomy, reinjection of harvested and cultured disc chondrocytes
- 28 patients at 2 yrs
  - Reduced pain and disability scores
  - No significant difference in disc height

Treatments possible

1. Cell Therapy

2. Disc Replacement

3. Tissue Engineering

1. Cell Therapy

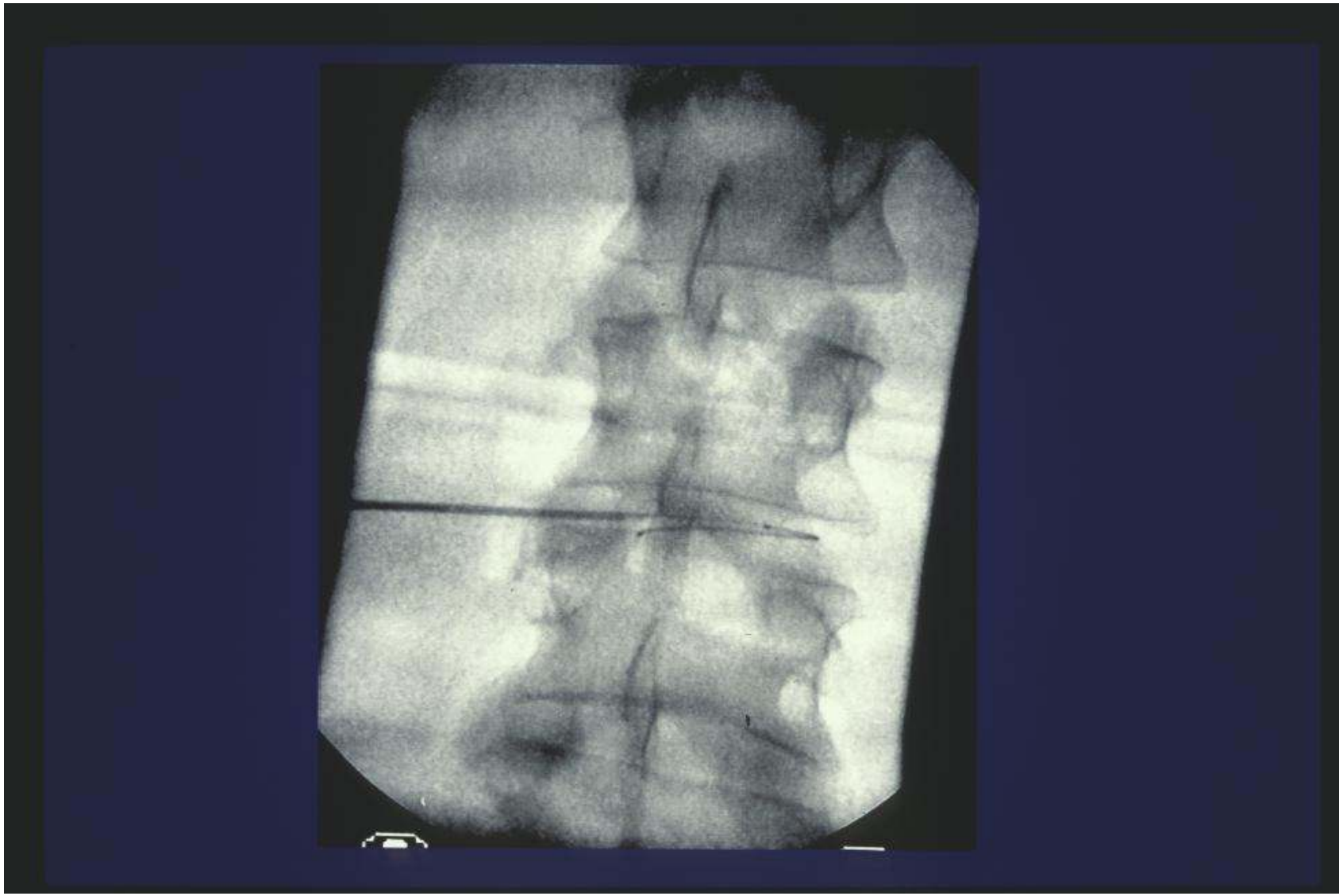
- Established animal models with MSCs
  - Increase proteoglycan
  - Restoration disc height in stab model
- Anti-inflammatory role of MSCs through release of cytokines IL10, TGFβ etc.
- …but could it only buy time?

Stem Cell Enhancement

- Pre-establish vascular channels for early graft take
- Repopulation of NP cells
- Re-engineer endplate (bioscaffold) to resist degenerative changes and increase vascular channels

- **Mesenchymal Stem Cells Arrest Intervertebral Disc Degeneration through Chondrocyte Differentiation and Stimulation of Endogenous Cells**

- *Yang; Leung; Luk; Chan*
- *Molecular Therapy 2009*



2. Disc Replacement

- Cadaveric Disc Replacement **Luk *et al, Lancet* 2006**

- Does not prevent disc height loss, but patients reported no pain

- Is it because of delayed vascularisation and prolonged nutritional deficiency of graft?

3. Tissue Engineering

- Complete re-engineering of tissues
- Combine different stem cell types
- With microarchitecture and self-sustaining
- Pre-engineered with its own vascularity ready for implantation

Challenges

- **Cells**
  - What? When? Where?
- **Bioscaffolds**
  - Attachment, commitment, niche environment
- **Revitalisation**
  - Understand pathogenesis.

78 Years Ago

Ruptures of the intervertebral disc with involvement of the spinal canal

Mixter and Barr

New England Journal of Medicine

211, 210-215, 1934

Imagination

- Material atheism
- **Music** – science can describe discord and harmony but not melody
- Melody is experienced
- By imagination

William Blake