Biology of Distraction Osteogenesis

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History

Codivilla A.

(1905). On the means of lengthening in the lower limbs. Am J Orthop Surg. 2, 353-369

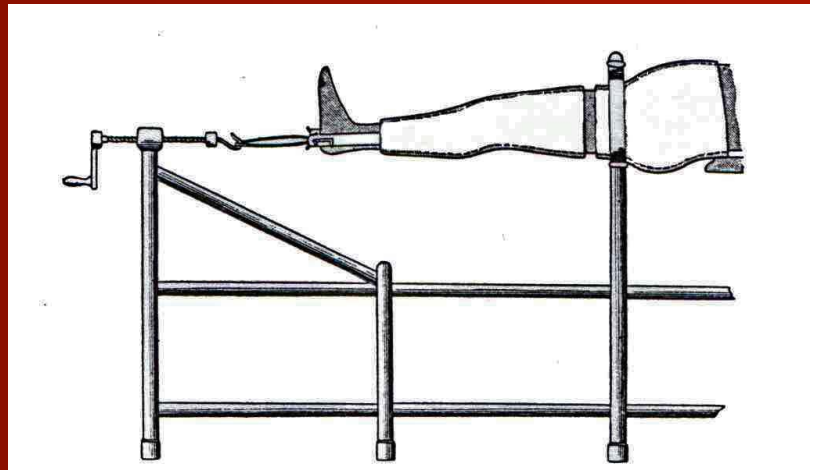


FIG. 11.—A diagram which shows the whole apparatus at work, while the traction and the counter-traction are applied to the two portions of the plaster apparatus.

- Anderson, W.V

(1952). Percutaneous manual osteoclasis. JBJS, 34B: 150

- Gavriil Ilizarov
- Wagner
- De Bastiani

Osteogenesis = bone tissue formation

Intramembranous

Membrane bones

formed directly from mesenchyme

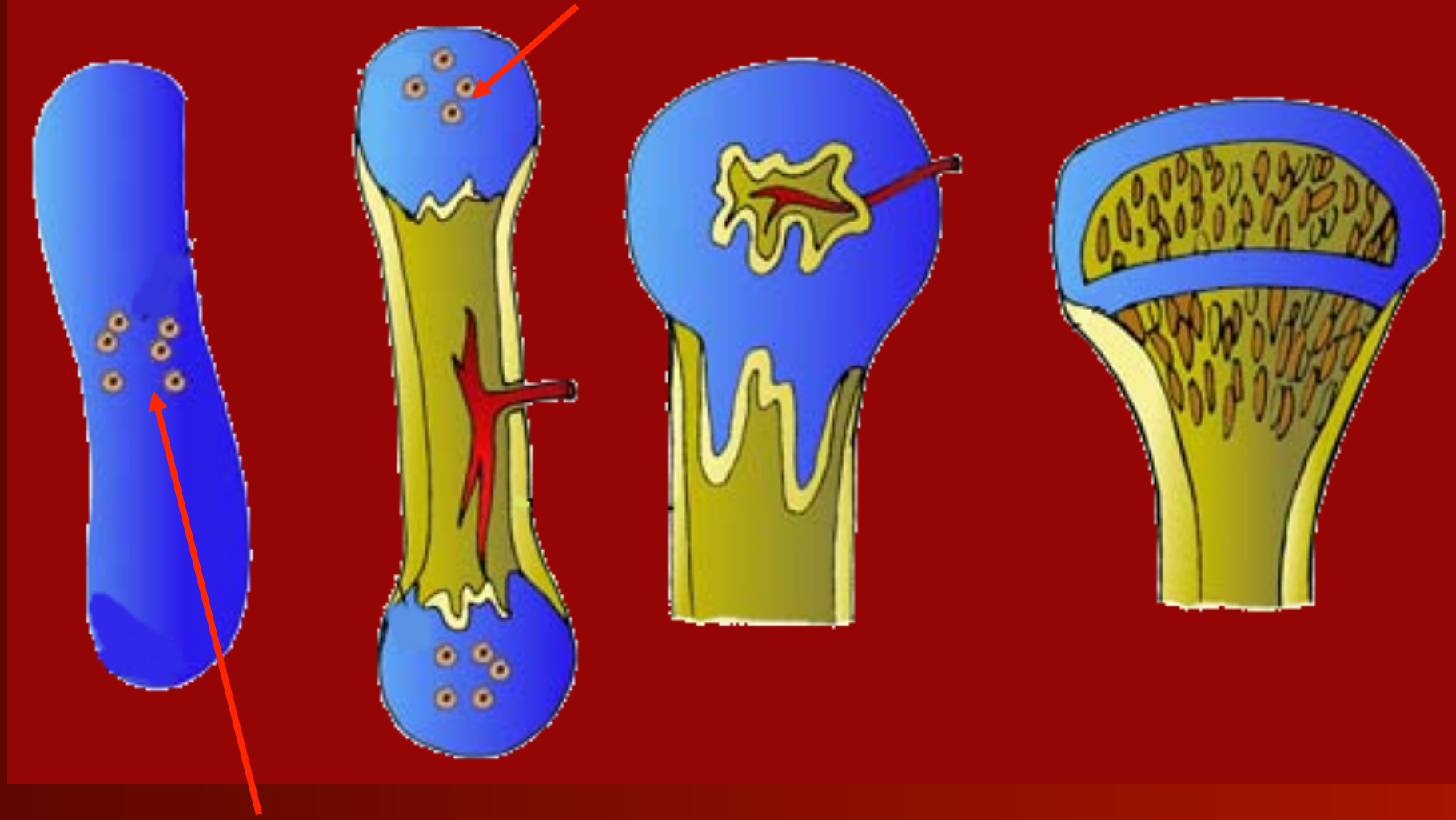
Endochondral

Other bones

develop initially from hyaline cartilage

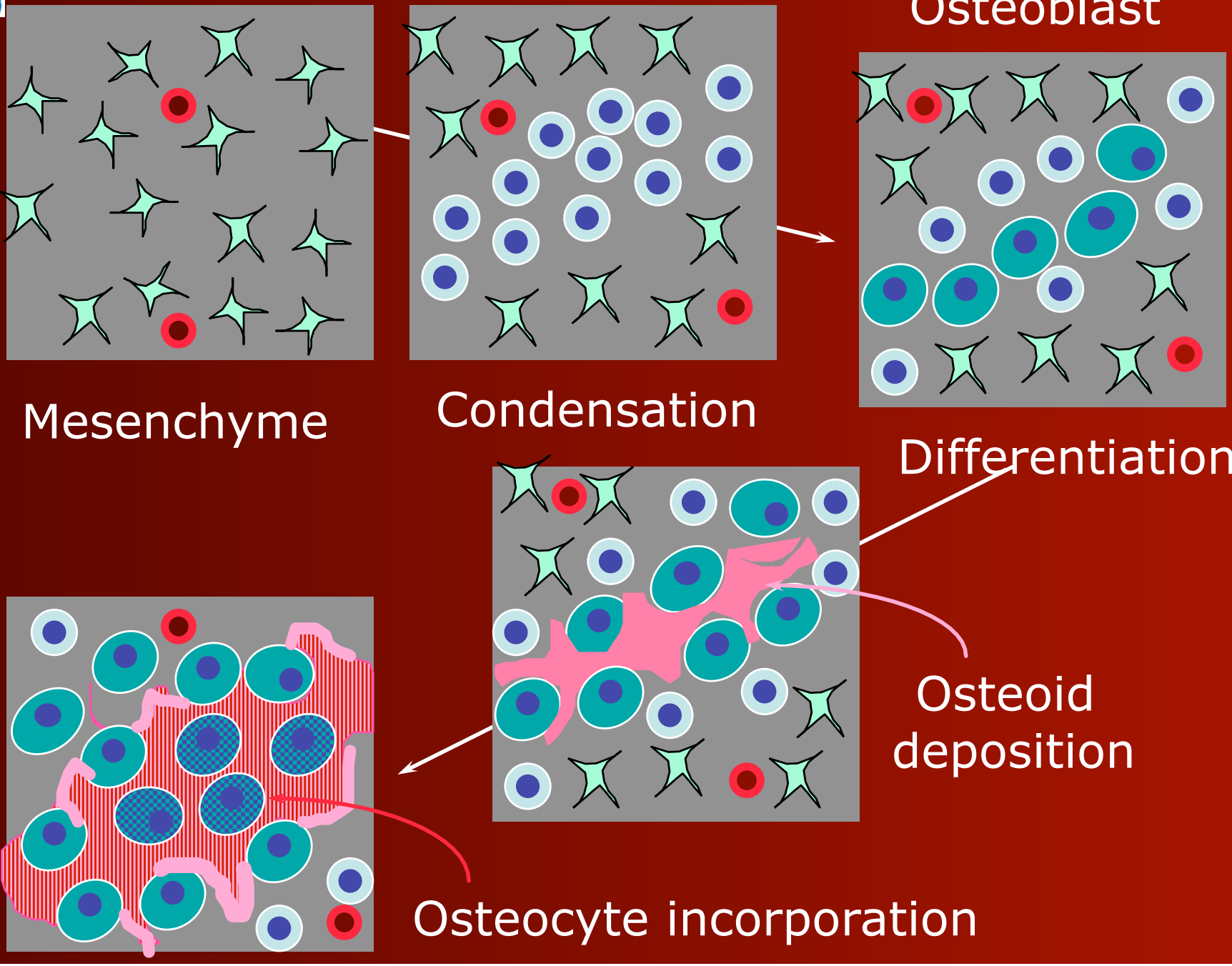
Endochondral Ossification

Primary ossification center

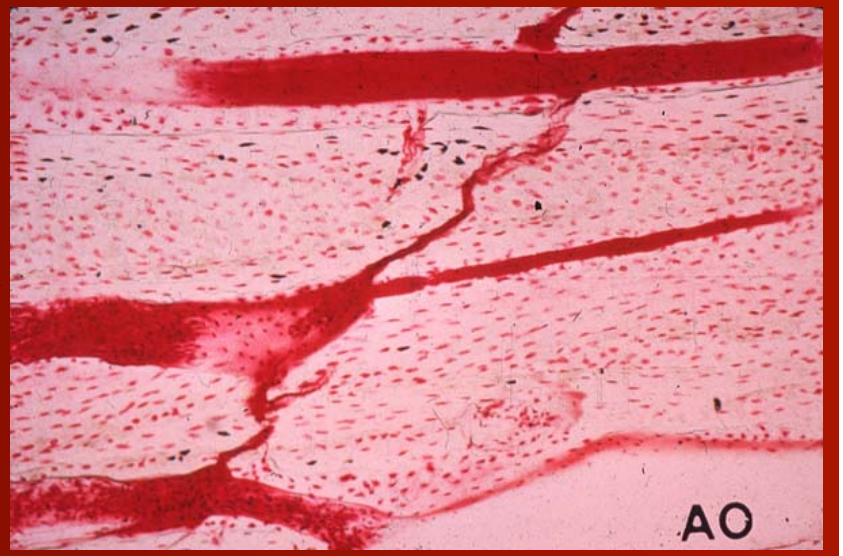


Primary ossification center

Intramembranous Osteogenesis



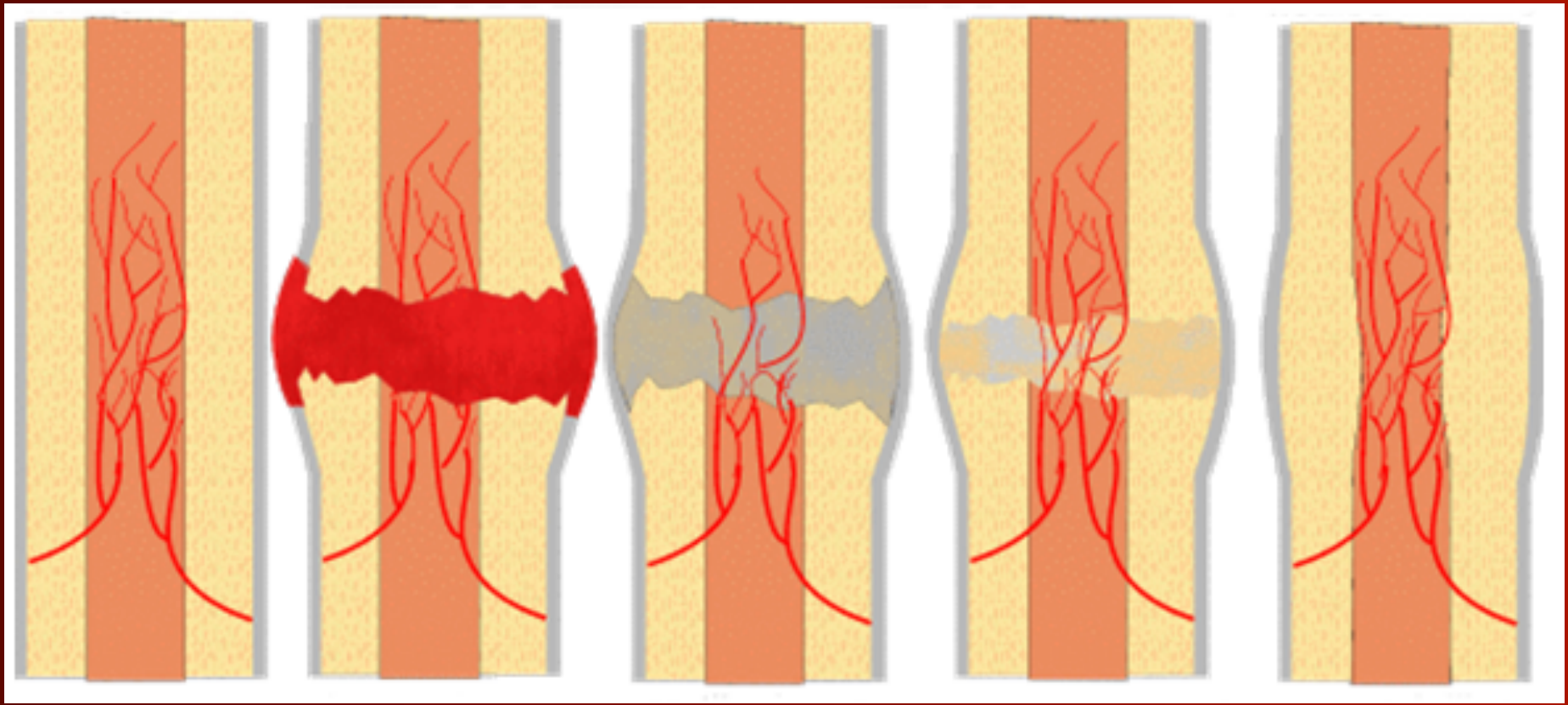
Modes of Fracture Healing in Cortical Bone



- Direct – Primary

- Indirect - Secondary

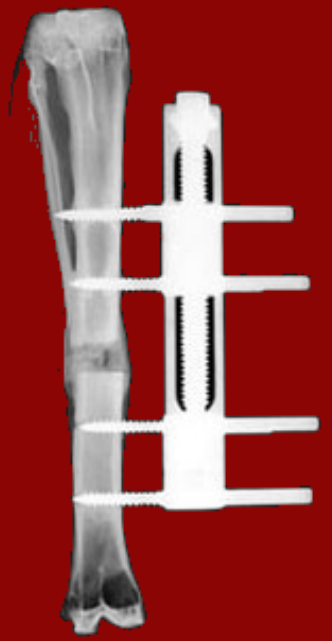
Stages of Fracture Healing



Impact, Haematoma formation, Induction, Inflammation, Soft callus, Hard callus, Remodelling

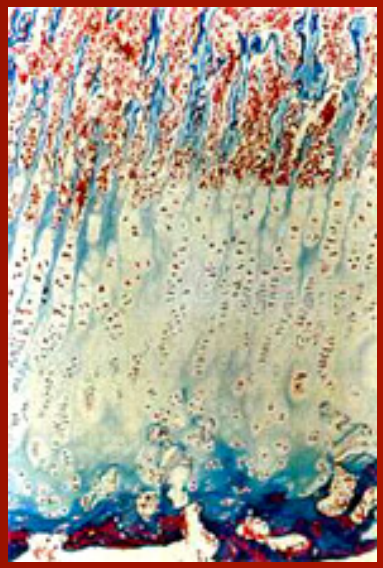
Distraction Osteogenesis

biologic process of gradual, controlled displacement of surgically created fractures that are gradually separated by incremental traction which results in simultaneous expansion of soft tissue and bone volume



Types of Distraction Osteogenesis

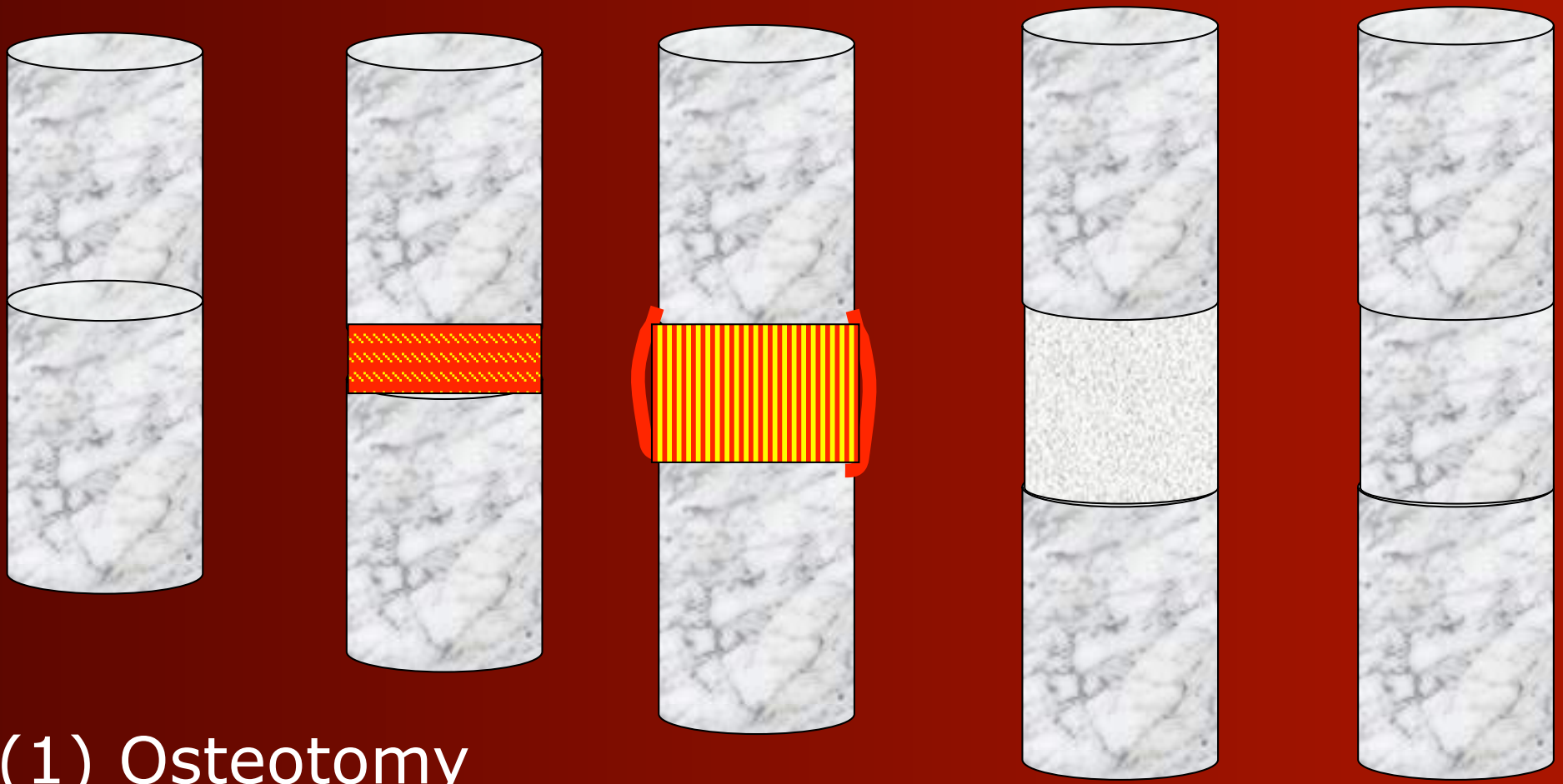
- ***callotasis*** = distraction of the fracture callus
- ***distraction epiphysiolysis and chondrodiatasis*** = distraction of the bone growth plate



Distraction osteogenesis shares many features with:

- ✓ embryonic growth
- ✓ fetal growth
- ✓ neonatal limb development
- ✓ fracture gap healing

The 4 stages of DO



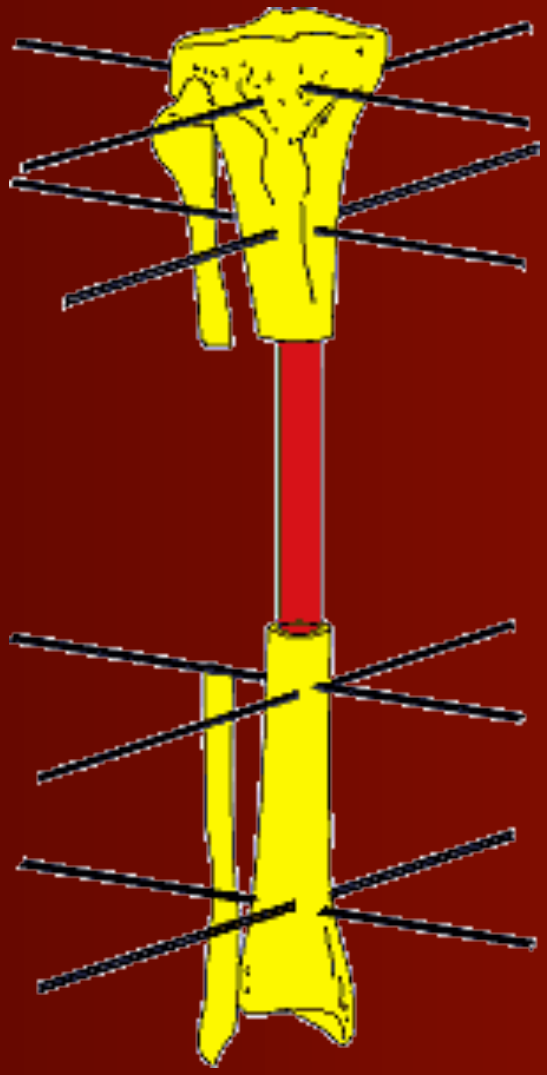
(1) Osteotomy

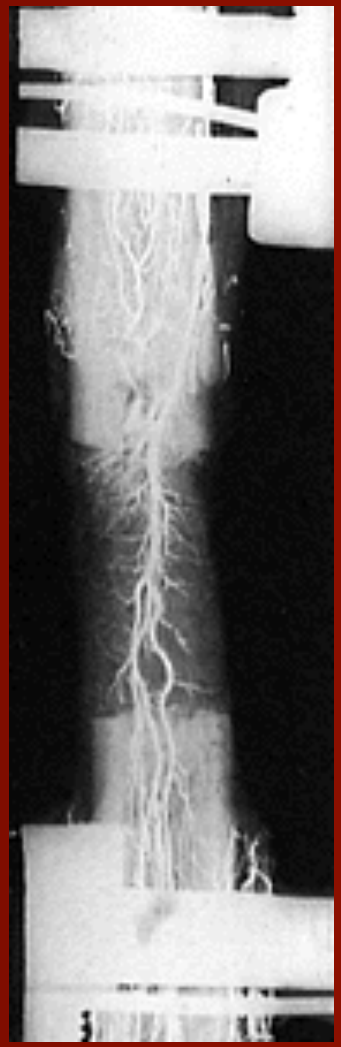
(2) Latency

(3) Distraction

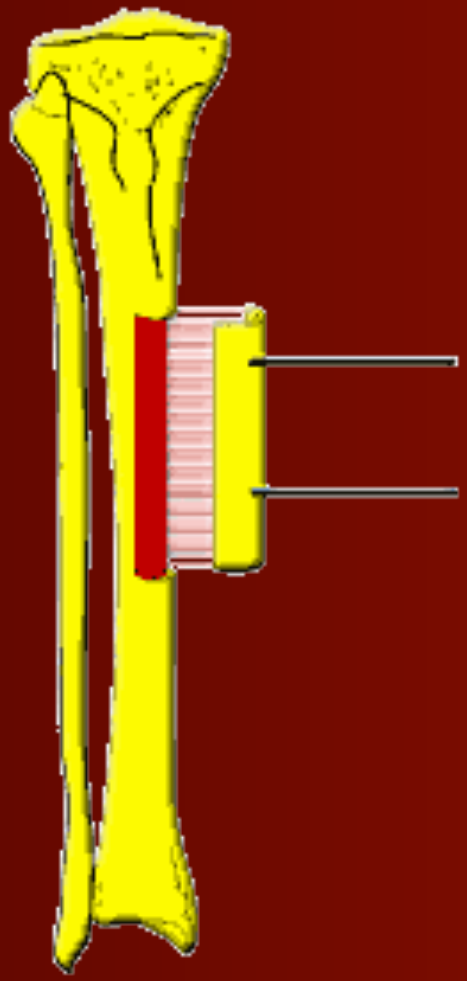
(4) Consolidation

The regenerate within the distraction gap is always formed along the axis of the applied traction





- circumferential tibial defect
- resection of the periosteum
- preservation of marrow tissues and the nutrient artery



Transverse distraction osteogenesis

The distraction regenerate within the intersegmentary gap formed along the axis of distraction

During distraction
endosteal and periosteal ossification occur

- "tension-stress effect"
- adequate blood supply
- adequate fixator stability

- membranous ossification without endochondral ossification occurring in uniform zones
- central zone with type I collagen
- no type II collagen (typical for endochondral ossification)

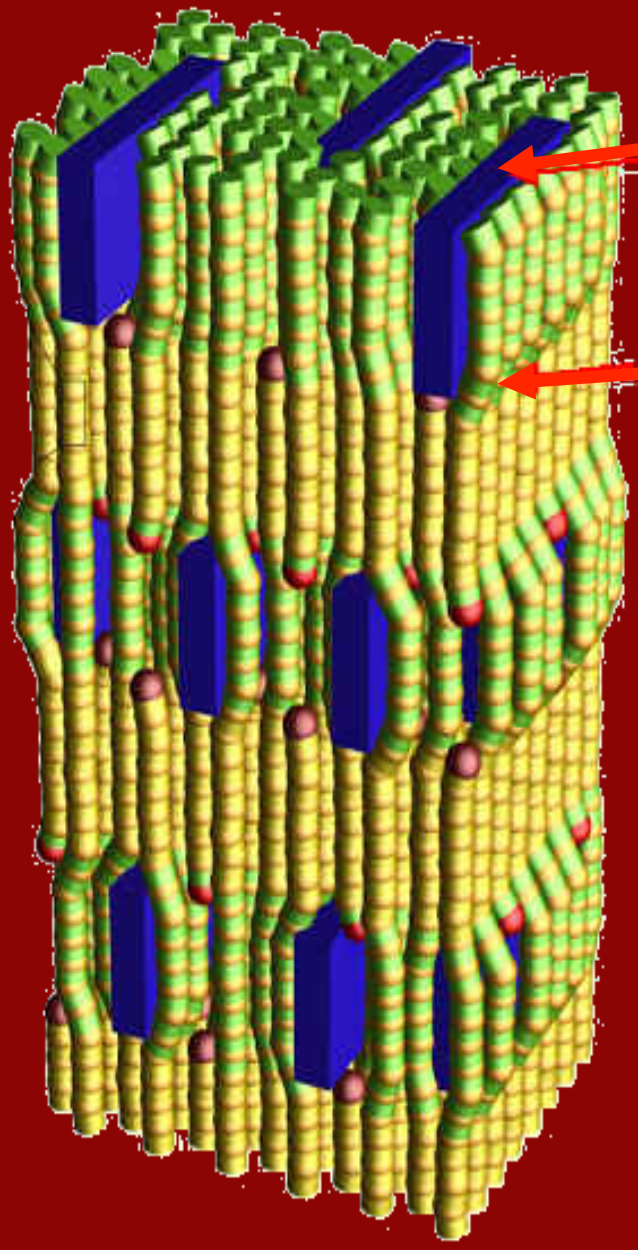
- Formation of collagen fibres
- Mineralization of older fibres
- Stretching of newer

electron micrographs x1000

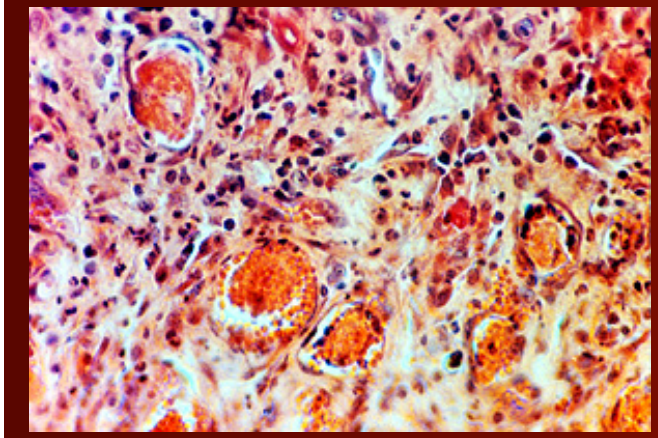
Normal and "distraction" fibroblasts in the intersegmentary gap
Spindle shape of the "distraction" fibroblast

Collagen mineralization

Mineralized
collagen fibril

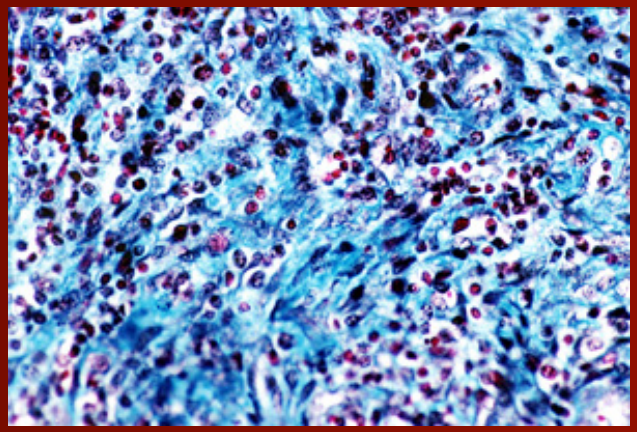


5 days
after osteotomy



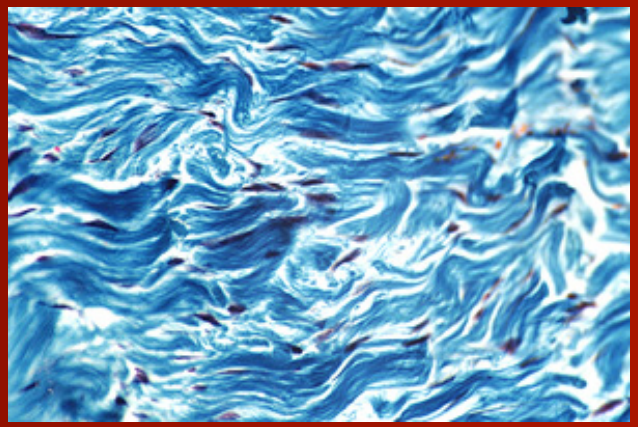
newly formed capillaries and granulation tissue infiltrate into the fibrin clot

5 days
of distraction



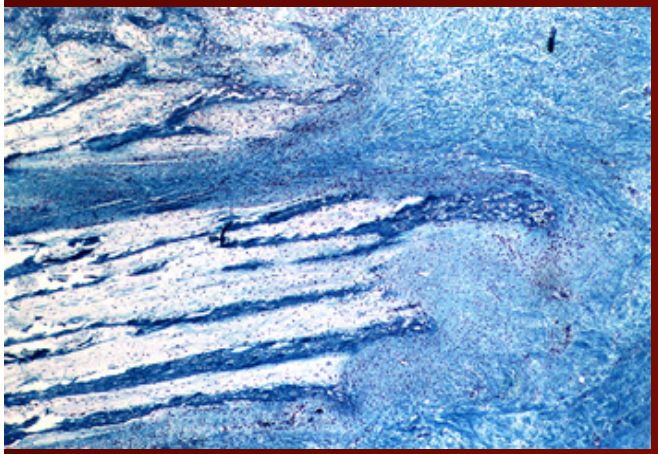
heterogeneity of the cells invading the fibrin clot

10 days
of distraction



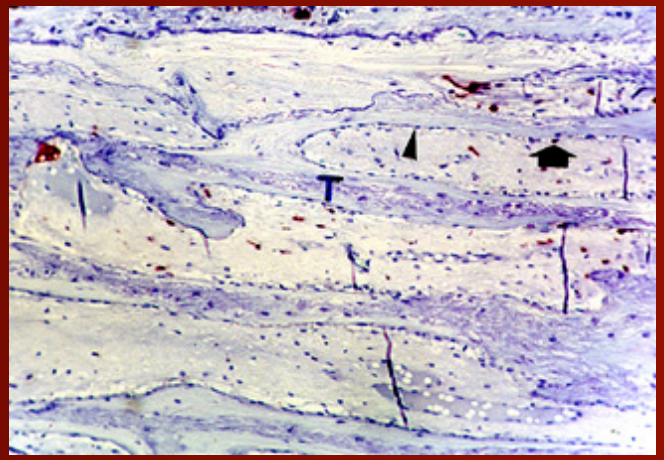
reduction of the number of cells that were replaced by wavy collagen fibers

15 days of distraction



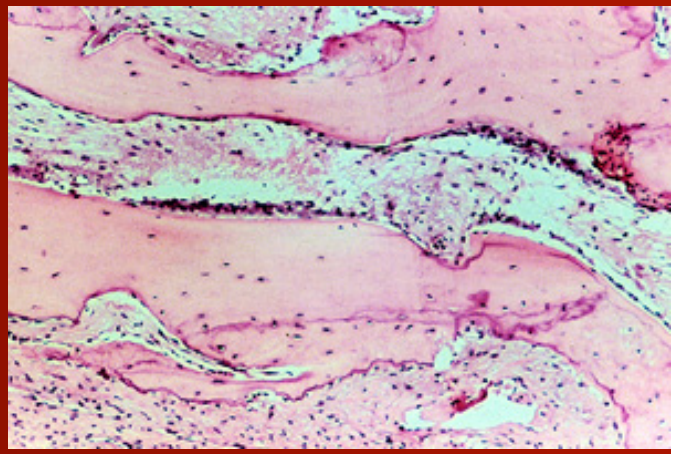
delicate trabeculae in the collagen-rich and woven bone area

20 days



bony trabeculae oriented in the direction of elongation, rimmed by osteoblasts and few TRAP positive osteoclasts

6 weeks

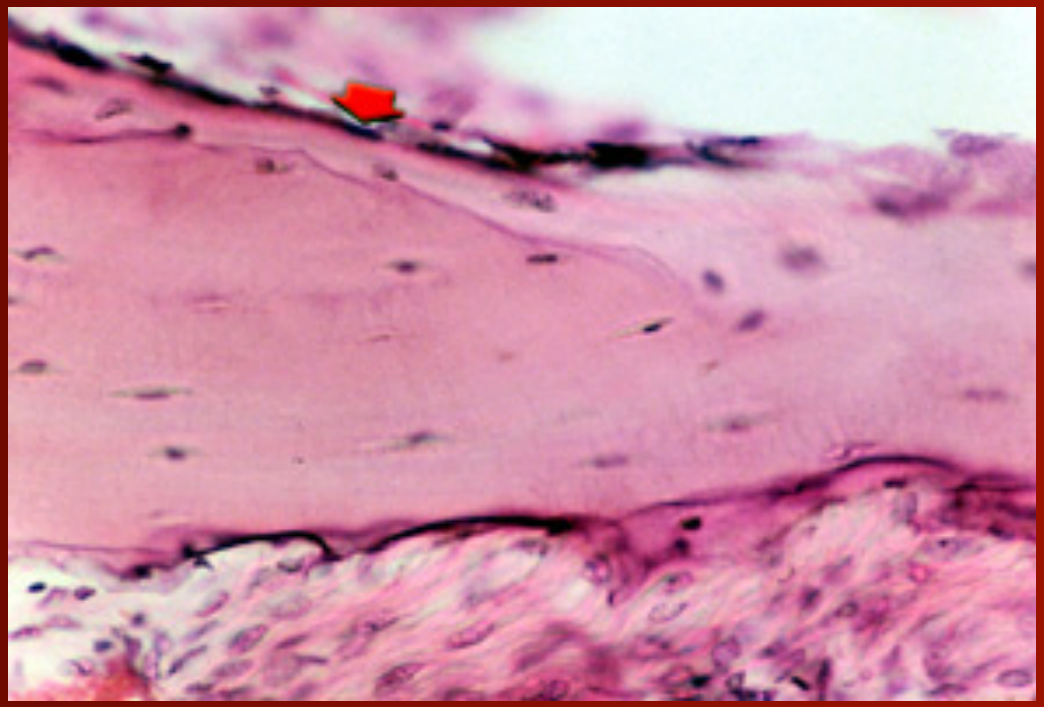


bony trabeculae are thicker and oriented in the direction of lengthening and rimmed by osteoblasts

Histology of the Regenerate

dense, longitudinally arranged collagen bundles with no cartilaginous tissue evident

1 year after distraction

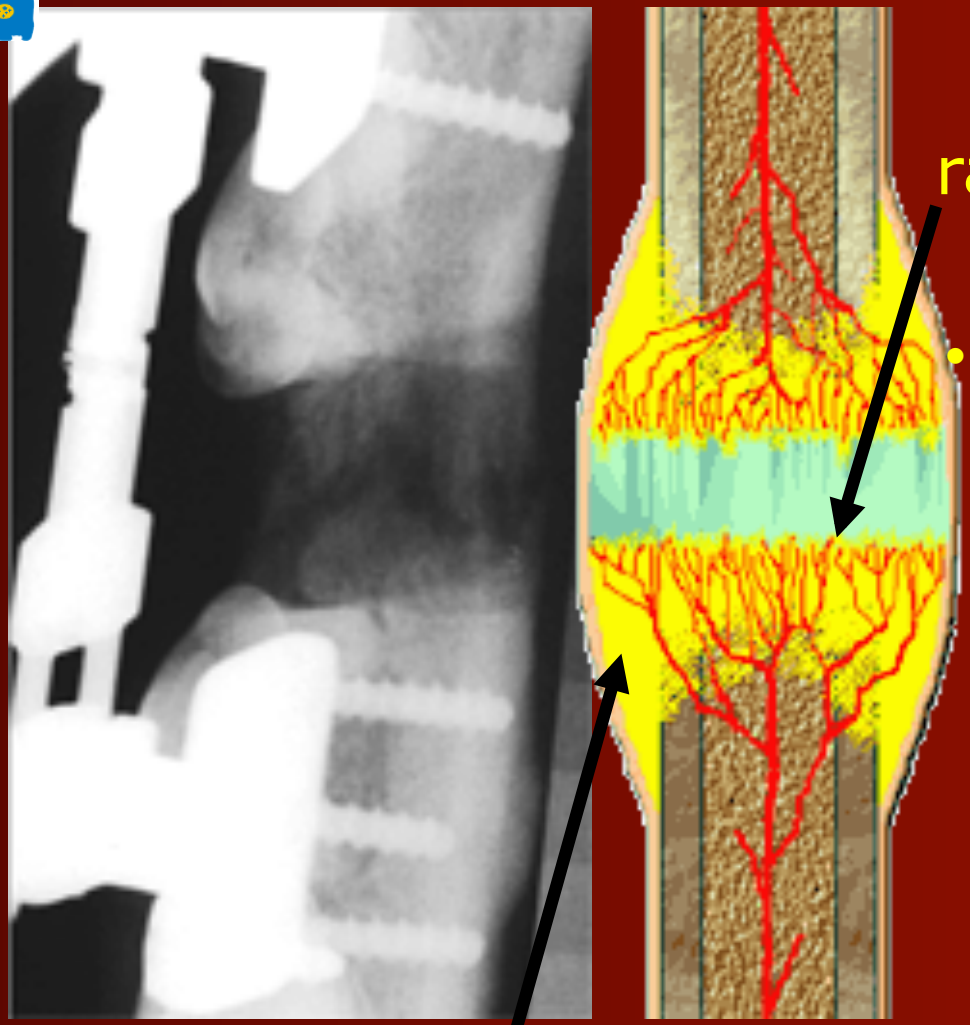


- most of the bone is composed of lamellar compact bone
- osteoblasts turn into flat bone lining cells

The content of the newly formed bone

- water (15 %)
- lipid (5%)
- calcium (25%)
- phosphate (12%)
- collagen (24%)
- Calcium/phosphate = hydroxyapatite

Three-zonal structure of the distraction regenerate



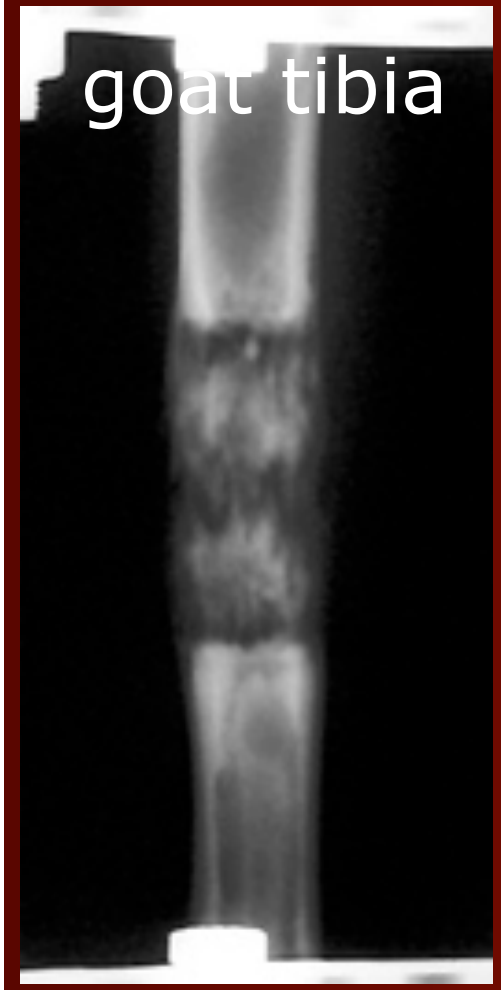
radiolucent fibrous interzone

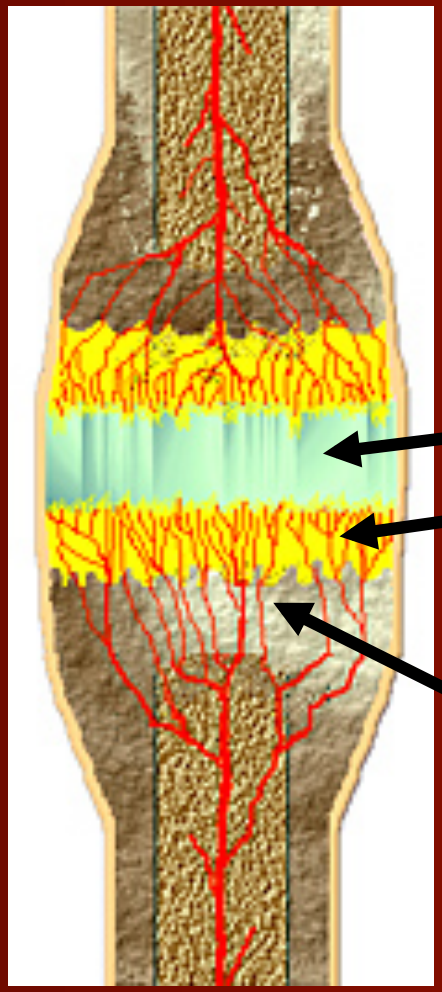
- maximal influence of tensional stress
- highly organized, longitudinally oriented, parallel bundles of collagen
- spindle-shaped fibroblast-like cells
- undifferentiated mesenchymal cells throughout the matrix

- two radiodence zones of primary osteon formation adjacent to the residual bone segments

longitudinally oriented cylindrical primary osteons that grow toward each other

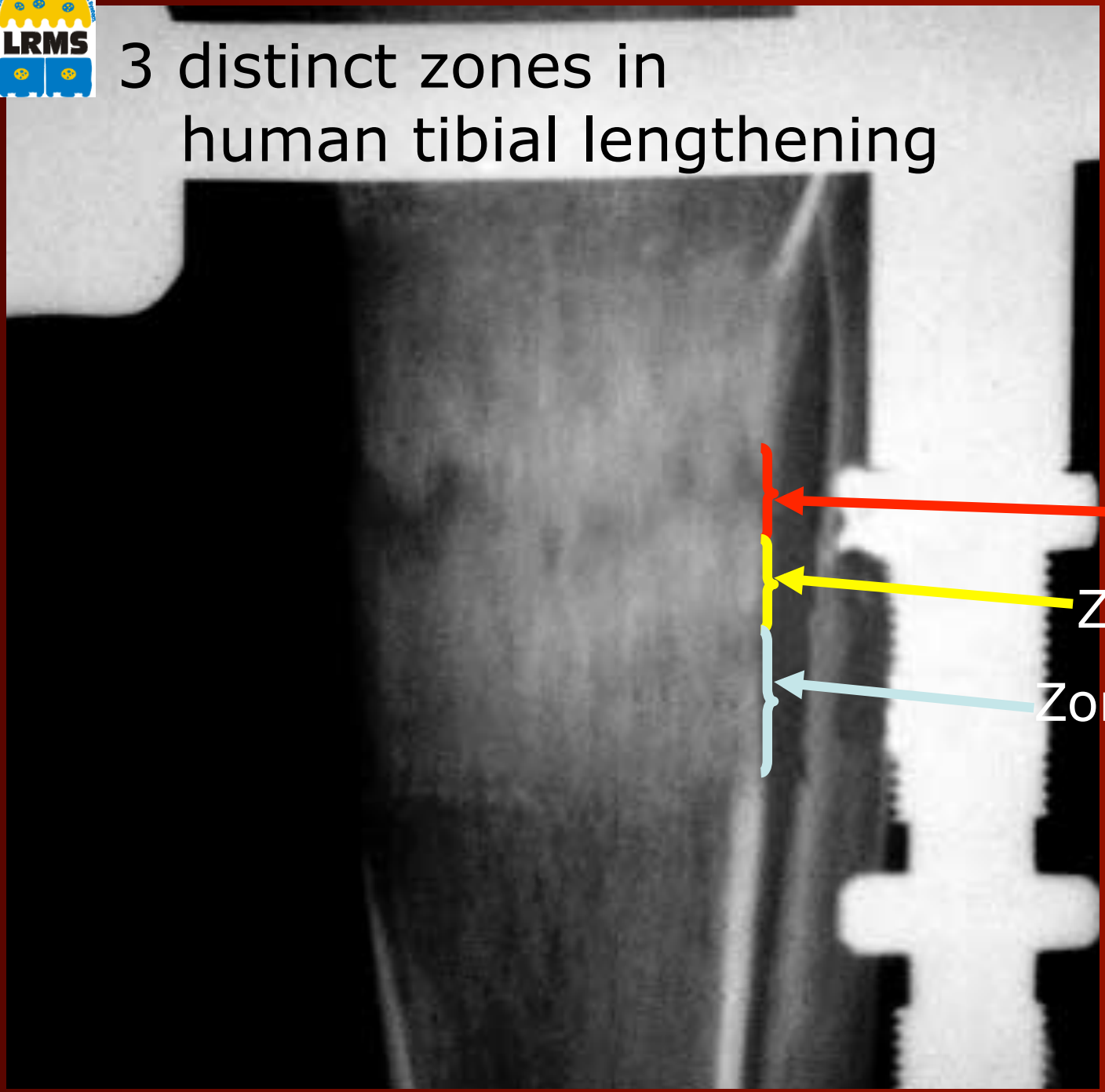
Five-zonal structure of the distraction regenerate

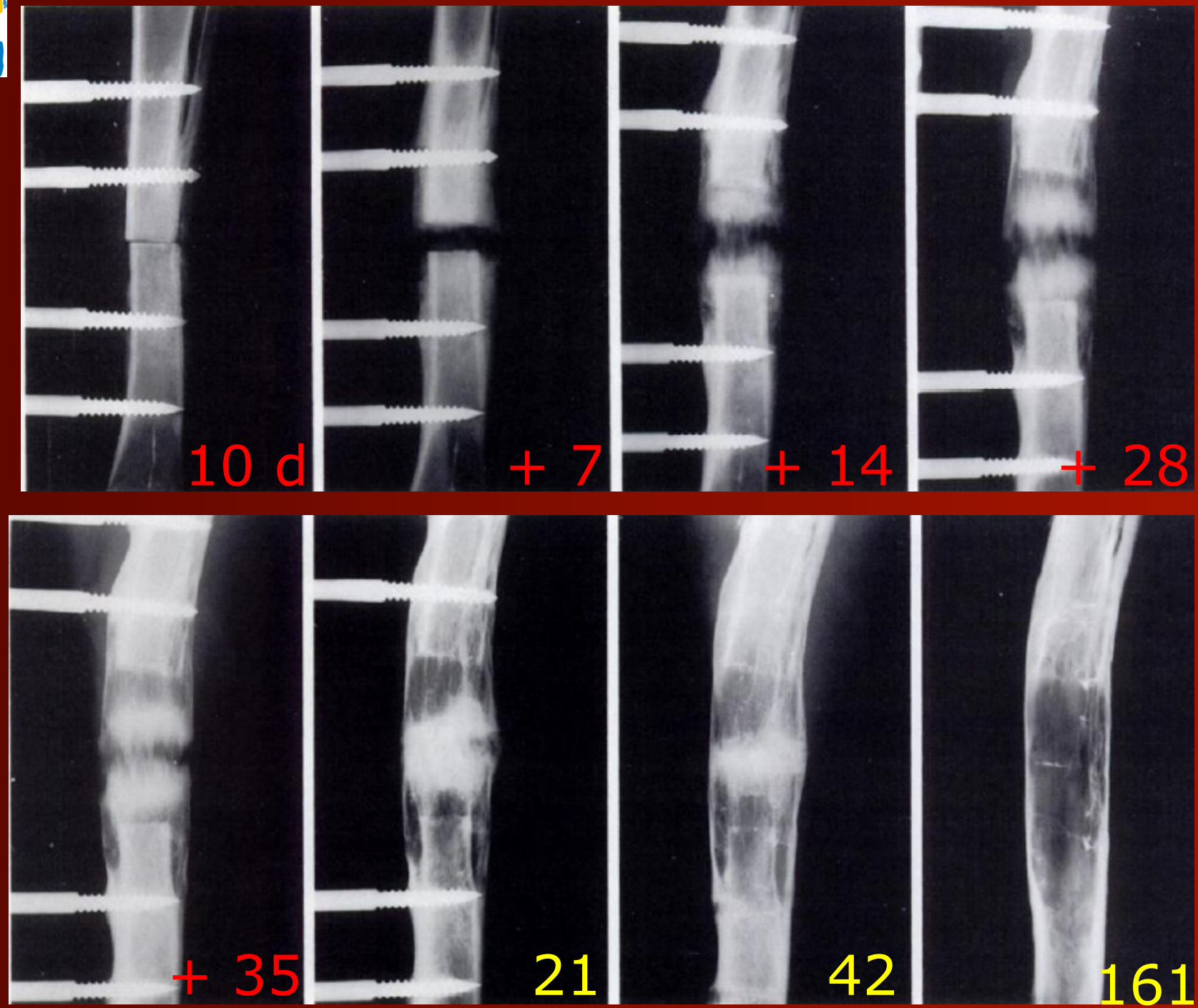




- radiolucent fibrous interzone
- 2 radiodense zones of primary osteon formation
- 2 radiolucent zones of remodeling adjacent to the residual bone segments

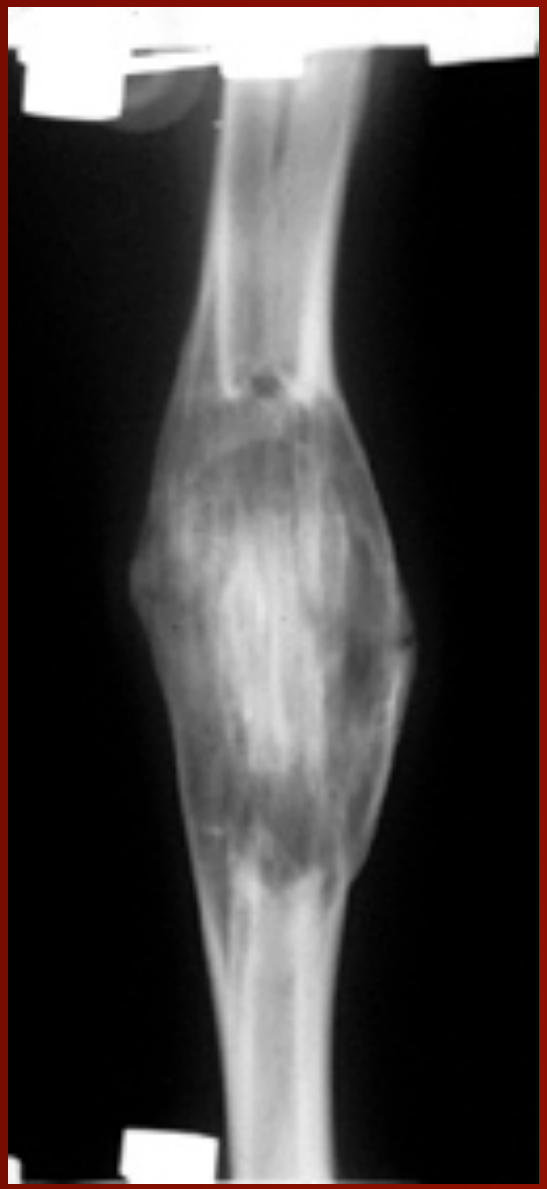
3 distinct zones in human tibial lengthening




10 d
+ 7
+ 14
+ 28
+ 35
21
42
161

Quality of the Bone Regenerate

normal

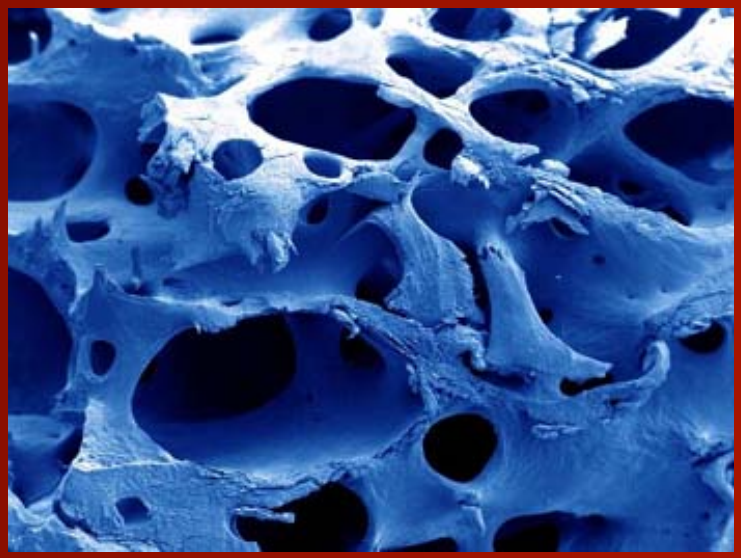


hypertrophic

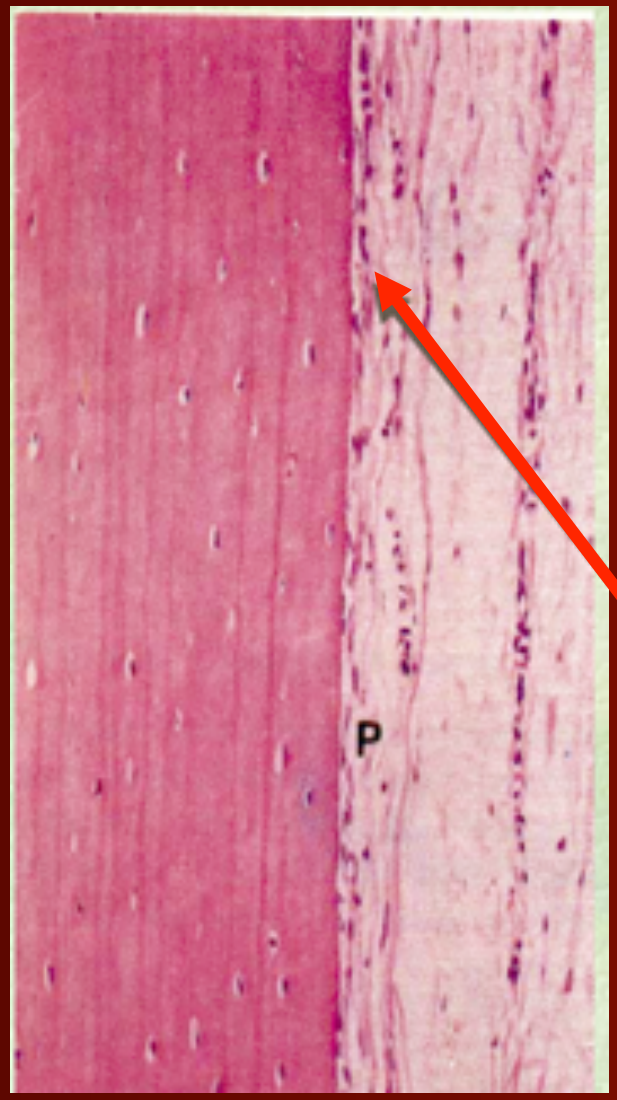
hypotrophic

Origin of bone forming cells

- Periosteum
- Endosteum
- Bone marrow
- Other sites

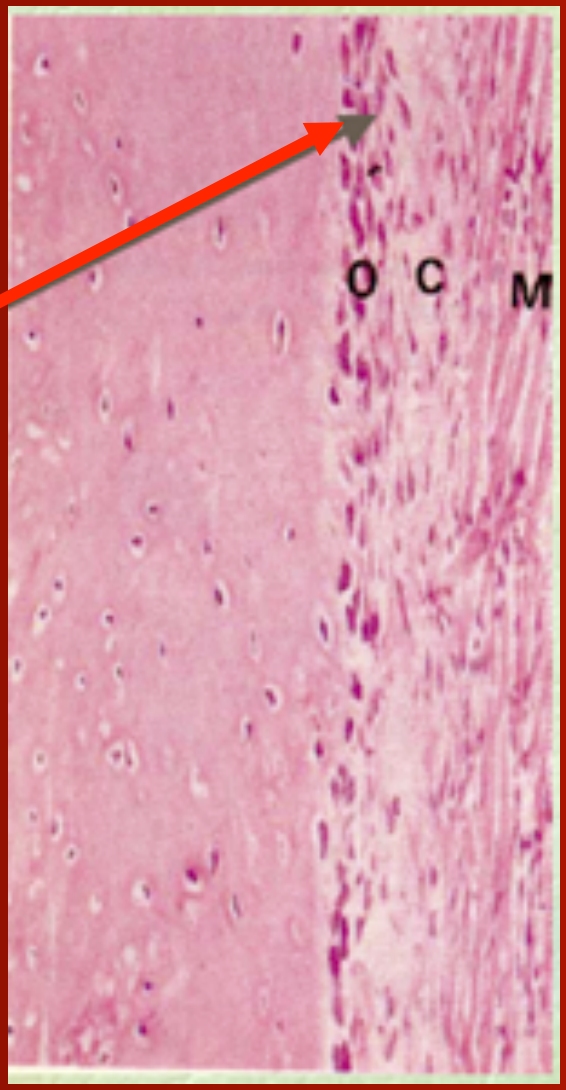


Periosteum: A source of bone-forming cells

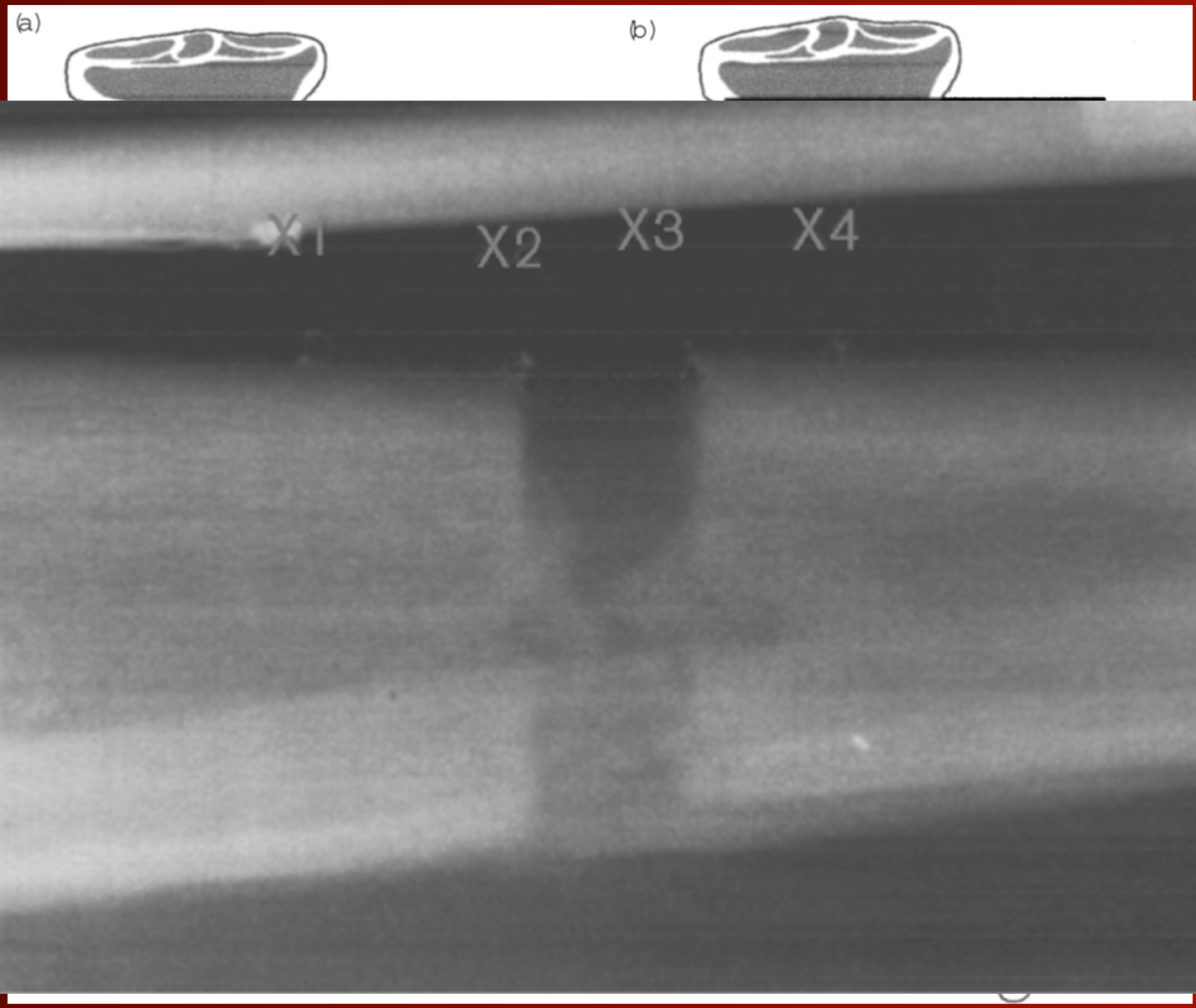


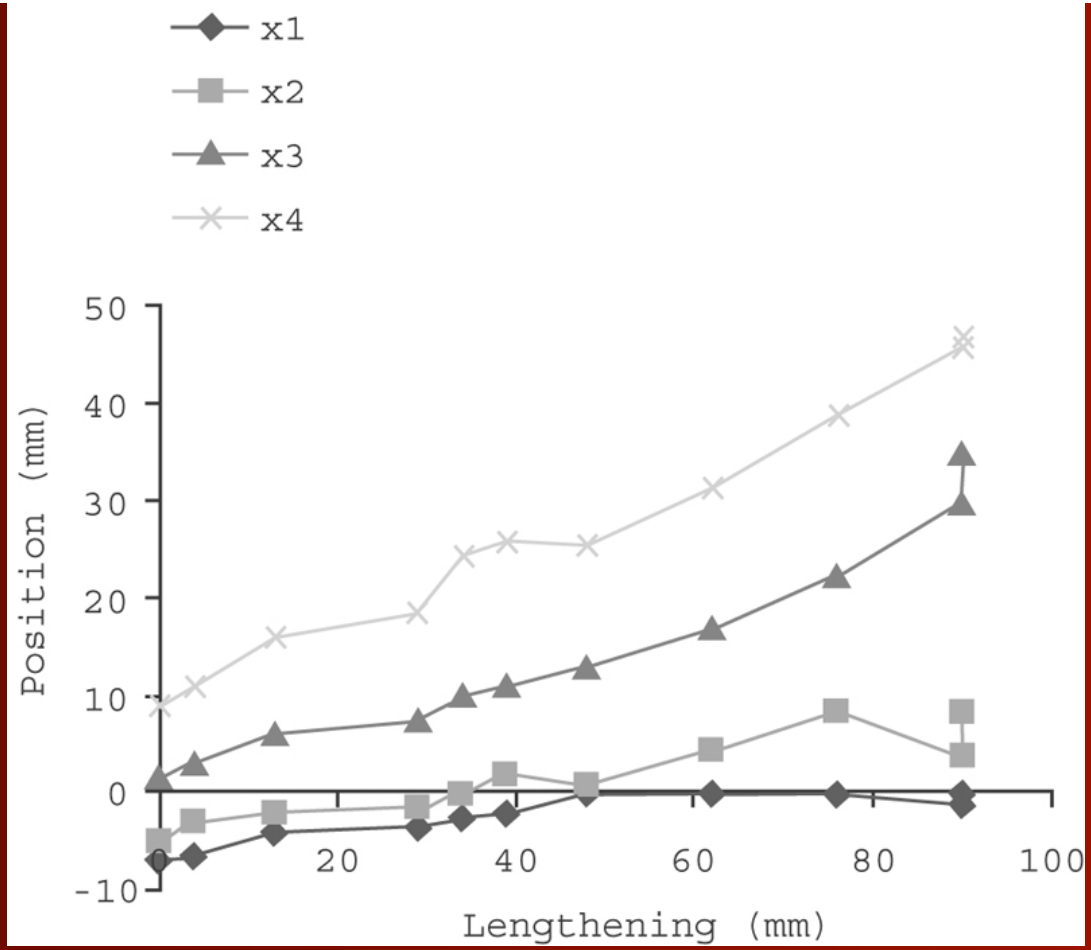
inactive

inactive



The behaviour of the periosteum during callotasis

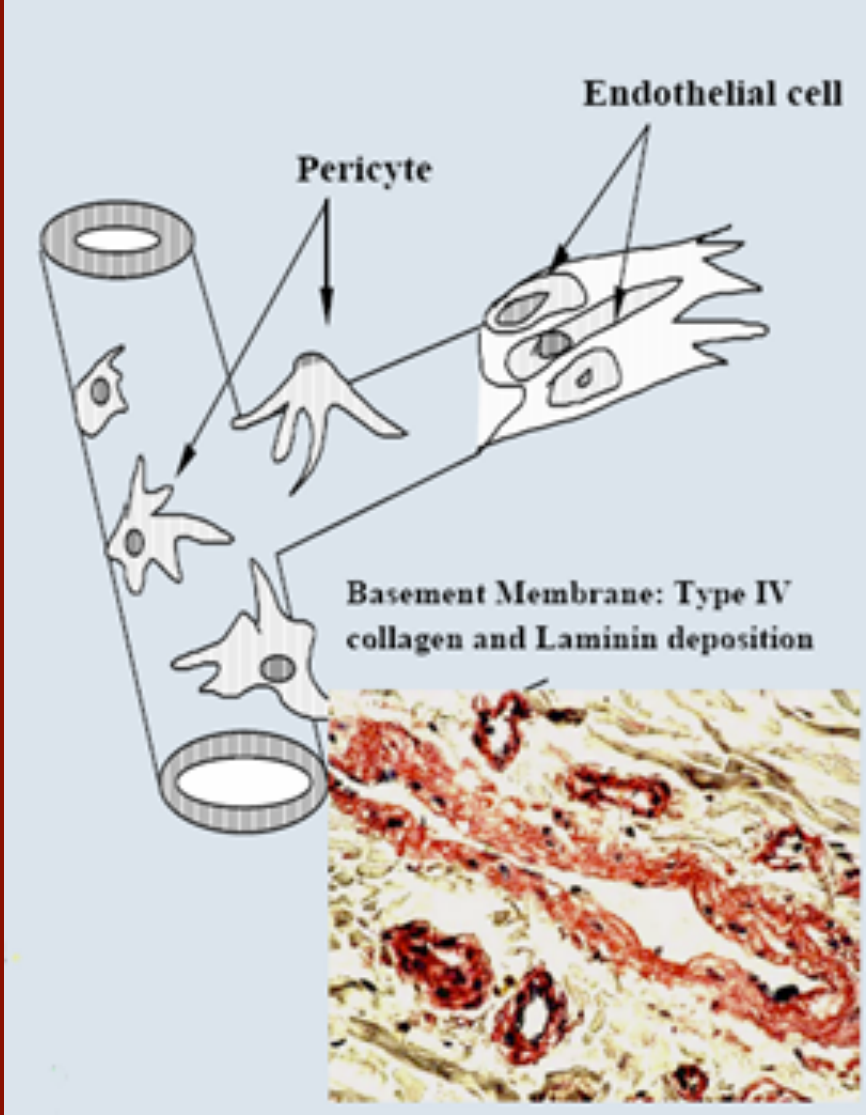


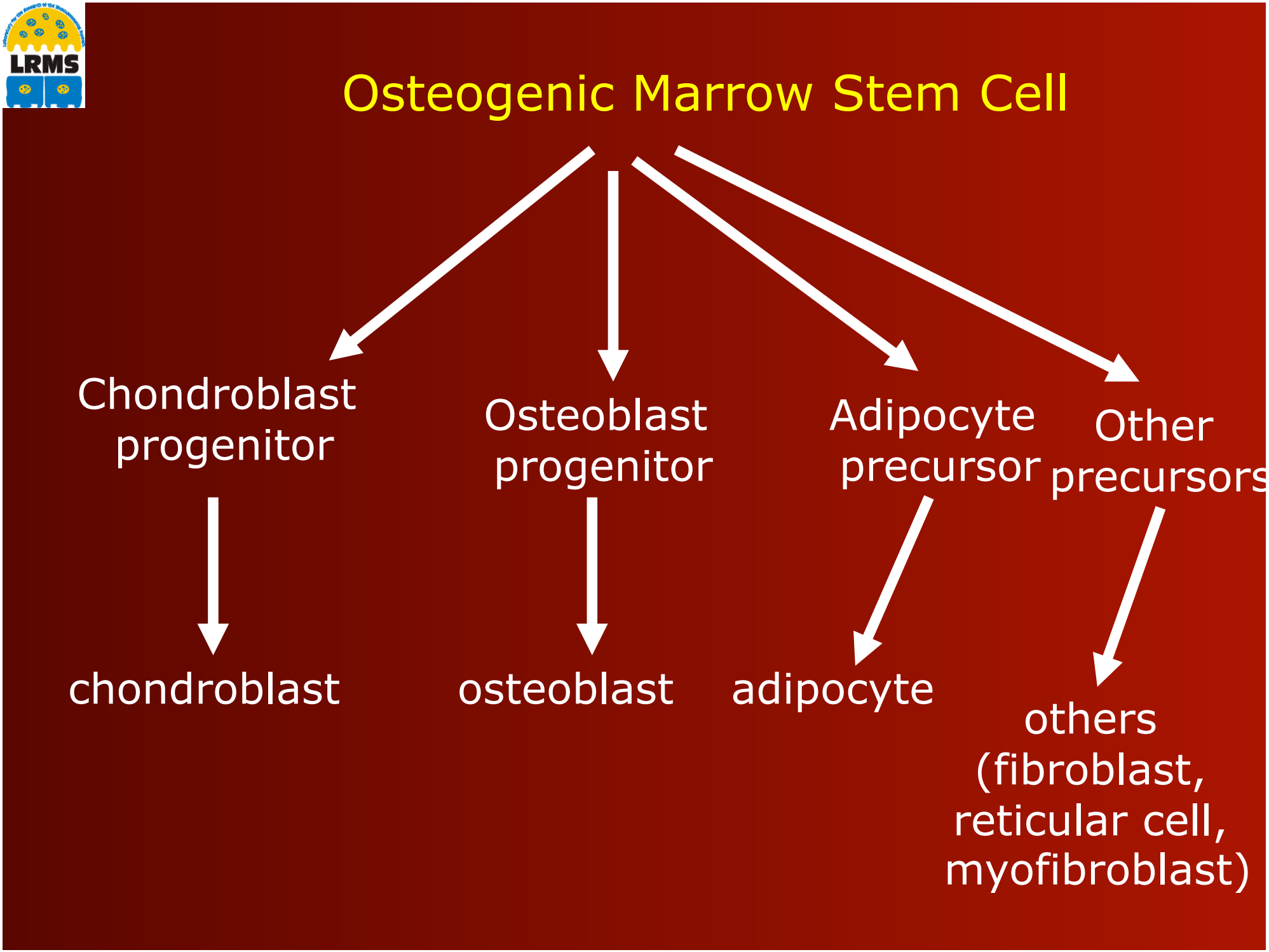


- the periosteum acts as an elastic sleeve surrounding the newly formed tissue during lengthening
- the site of attachment between sleeve and cortex becames established early during lengthening, and hardly changed position at later stages

Endothelial cells

- synthesize Type IV collagen and VEGF
- have more active role in angiogenesis, wound repair and bone formation




Osteogenic Marrow Stem Cell
Chondroblast progenitor
Osteoblast progenitor
Adipocyte precursor
Other precursors
chondroblast
osteoblast
adipocyte
others (fibroblast, reticular cell, myofibroblast)

Molecular Biology of DO

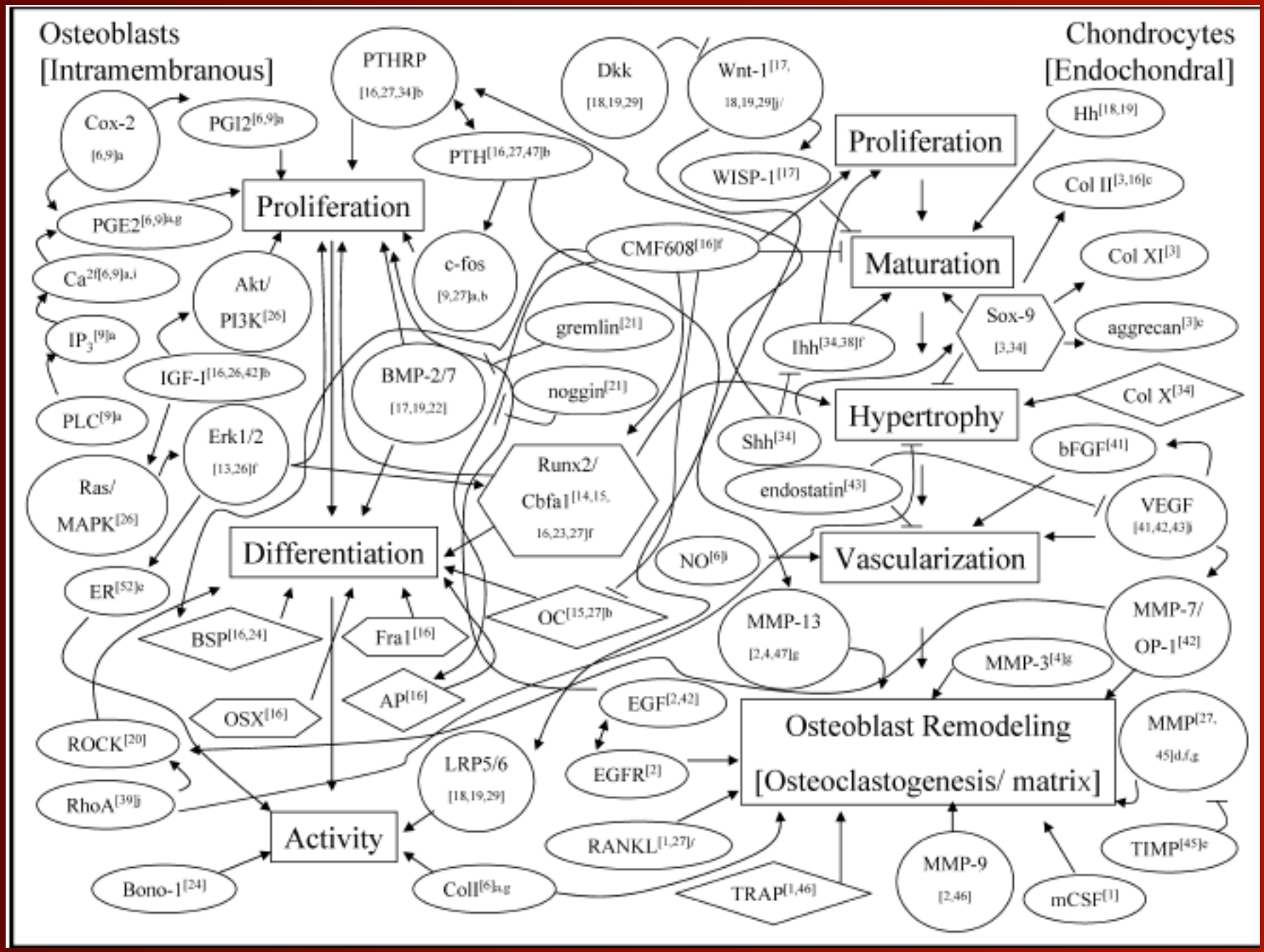
successful distraction (bony regenerate)

differs from

ineffective distraction (fibrous union)

- ✓ bone-specific extracellular matrix products
- ✓ decrease in the production of bone scaffold (collagen I)
- ✓ reduced mineralization (osteocalcin)

Gene interaction in bone growth

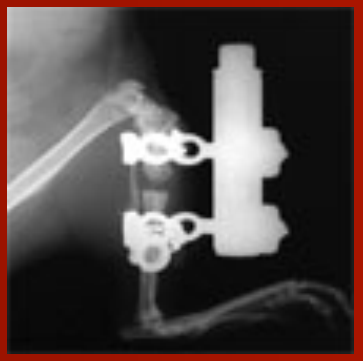


- Many genes are being upregulated or downregulated in the bone cells responding to mechanical stimulation
- The nuclear proto-oncogene c-fos and c-jun were found to be upregulated at early stages of DO
- Fos- and Jun related genes are related to mechanotransduction and embryonic bone development
- Their strong expressions during DO support Ilizarov's hypothesis that DO resembles some aspects of embryonic development

Distraction

production of

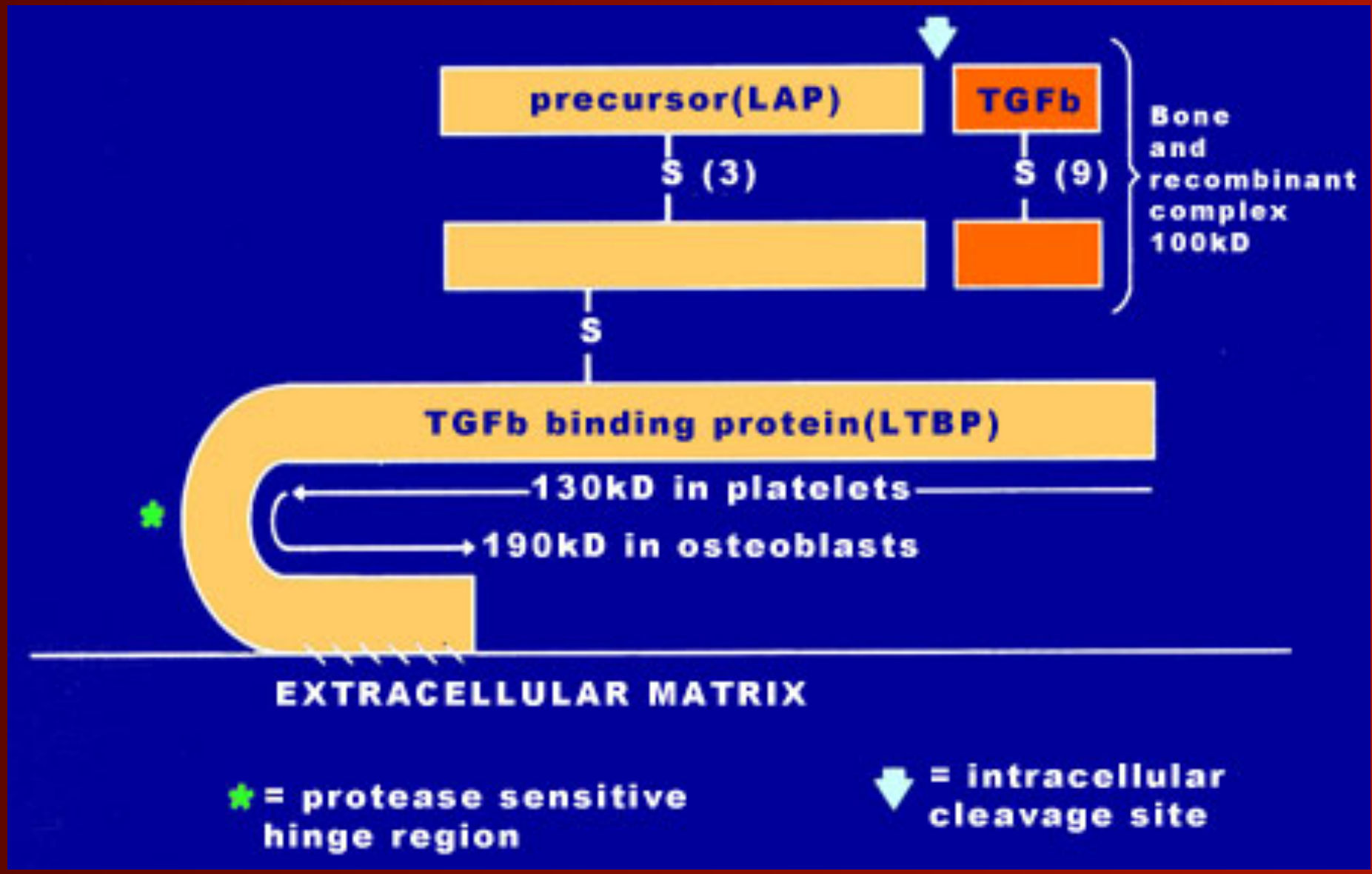
- osteoinductive growth factors
- extracellular matrix molecules (ECM, collagen I and osteocalcin)



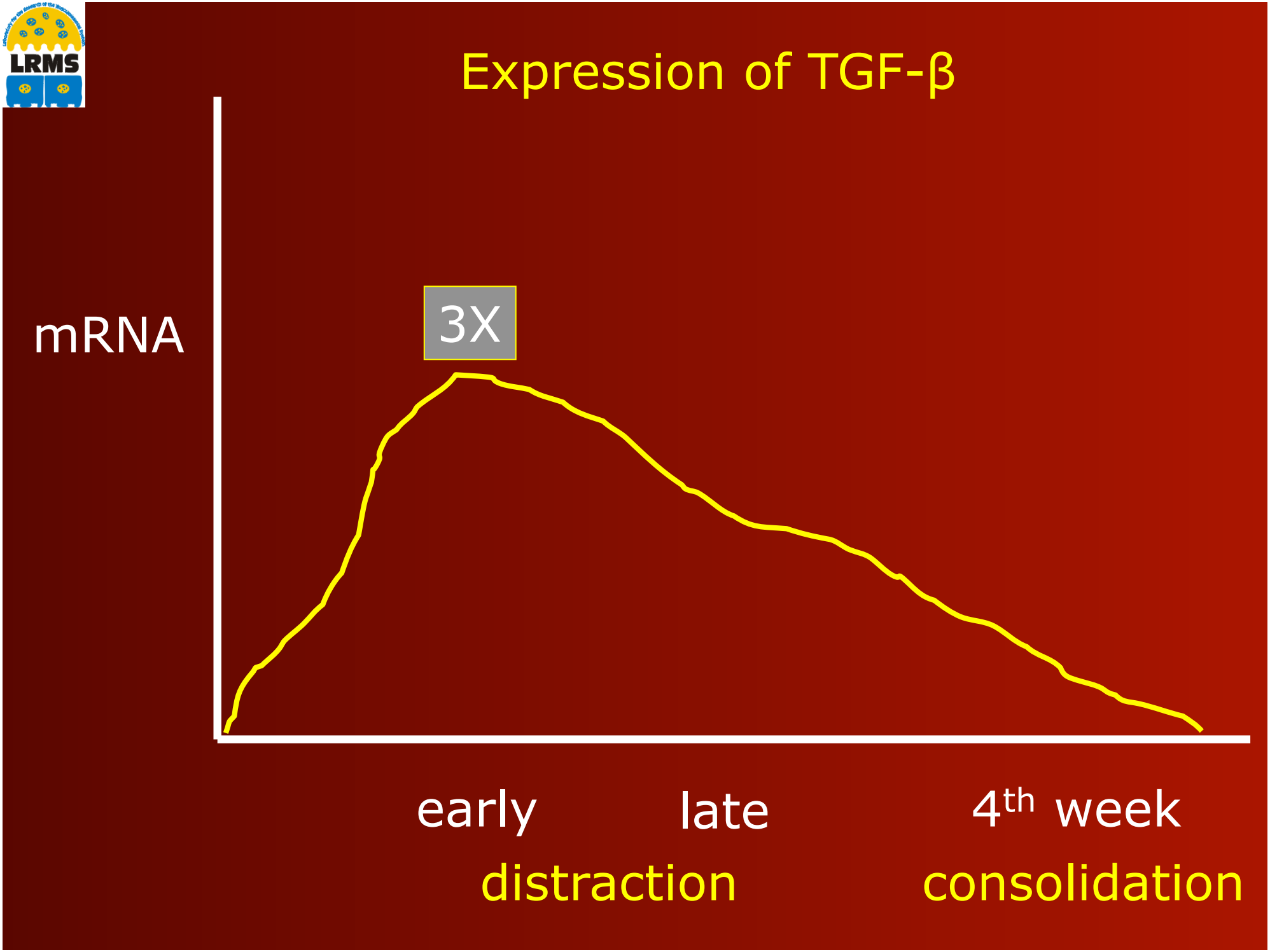
Cytokines involved in the regulation of bone synthesis and turnover

- transforming growth factor-betas (TGF-b1, b2, b3)
- bone morphogenetic proteins (BMPs)
- insulin-like growth factor-1 (IGF-1)
- basic fibroblast growth factor (FGF-2)
- vascular endothelial growth factor (VEGF)

transforming growth factor beta (TGF b)



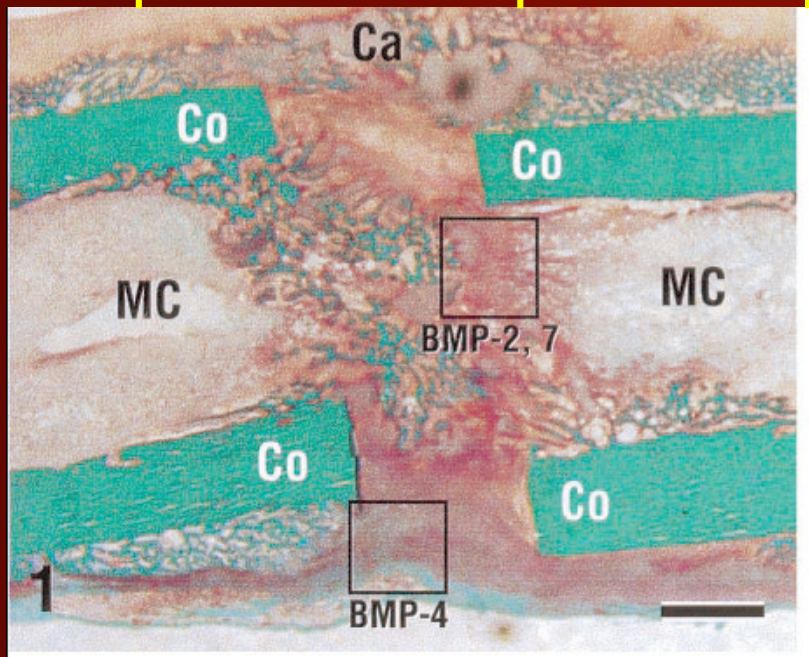
Expression of TGF-β

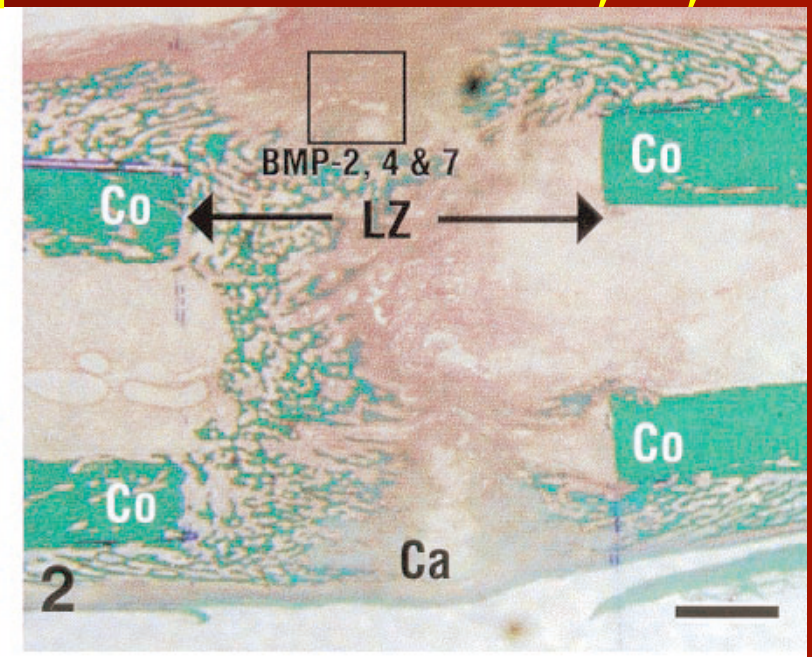


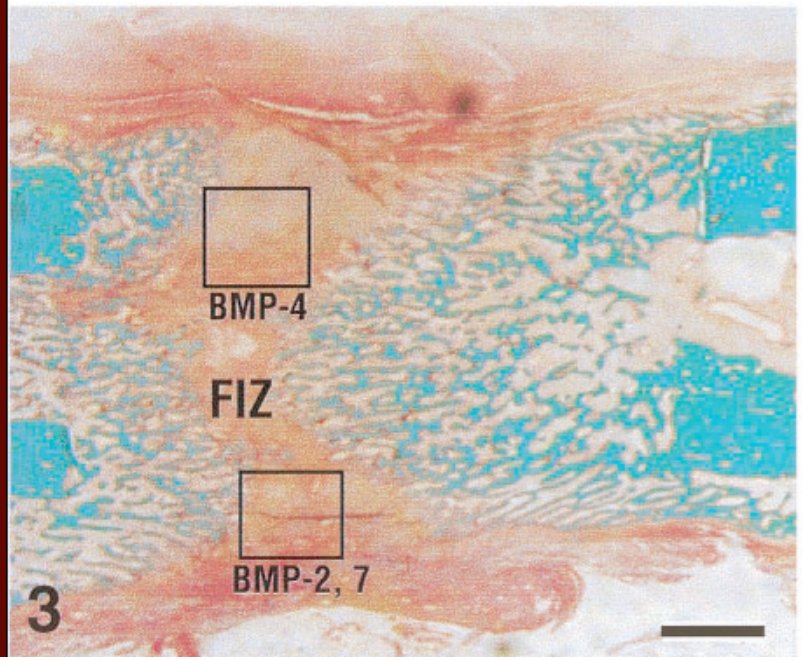
Localization of TGF-b1

- ✓ fracture haematoma: inflammatory cells, platelets
- ✓ early phases of distraction: osteoblasts, primitive mesenchymal cells, extracellular matrix, connective tissues adjacent to the osteotomy
- ✓ consolidation phase: osteoblasts within the matrix of the distraction gap
- ✓ after 4-weeks of EF: osteoblasts within the remodelling bone

Goldner stain of rabbit tibiae during DO
Temporal and Spatial Expression of BMP-2, 4, 7





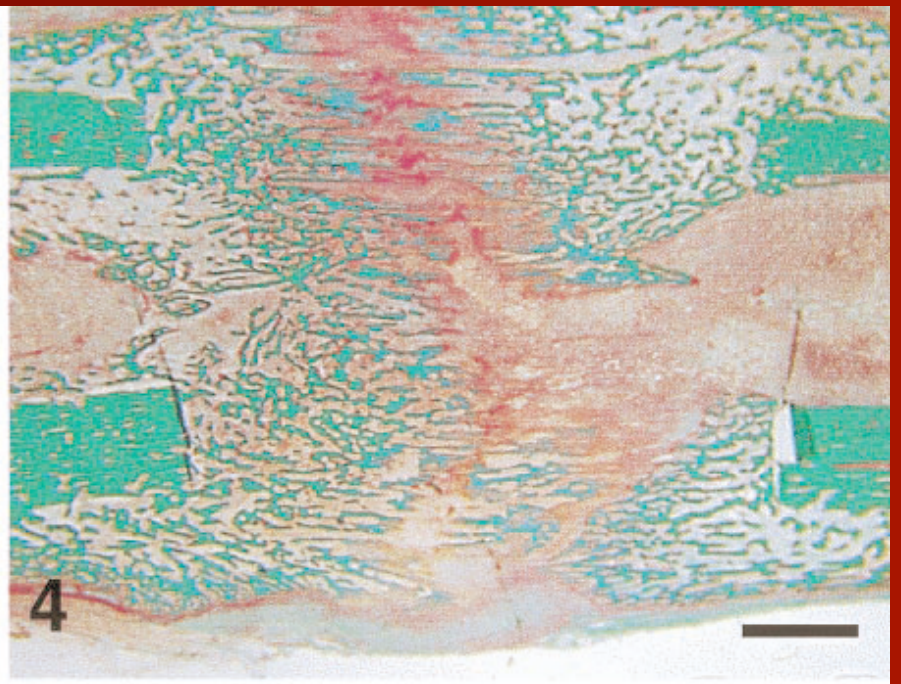


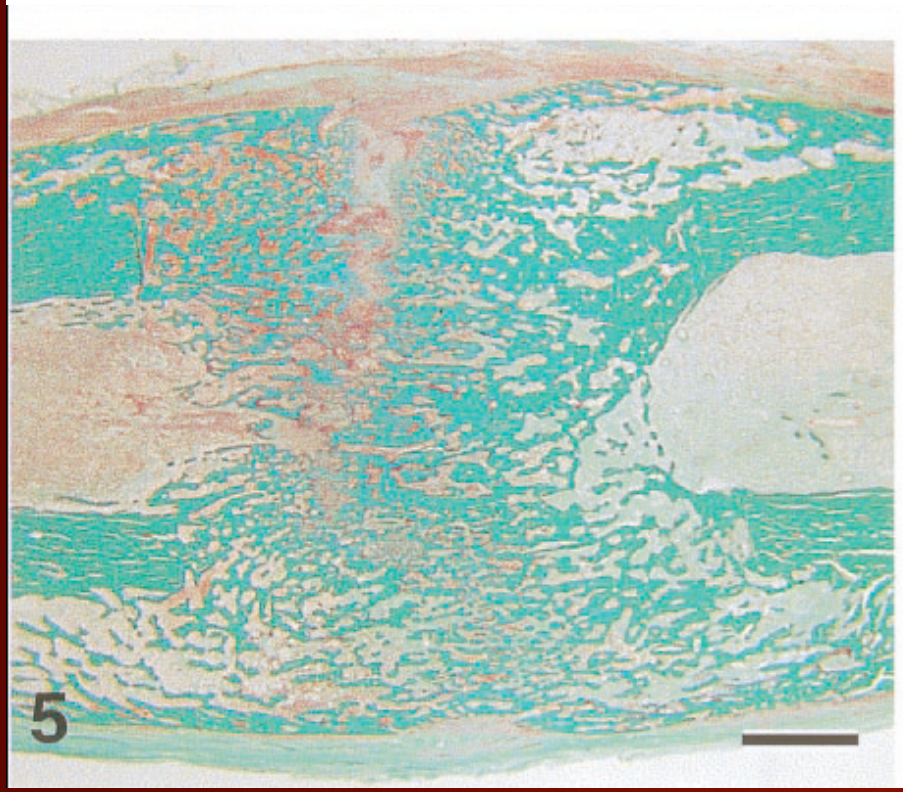
1–3 weeks
distraction phase

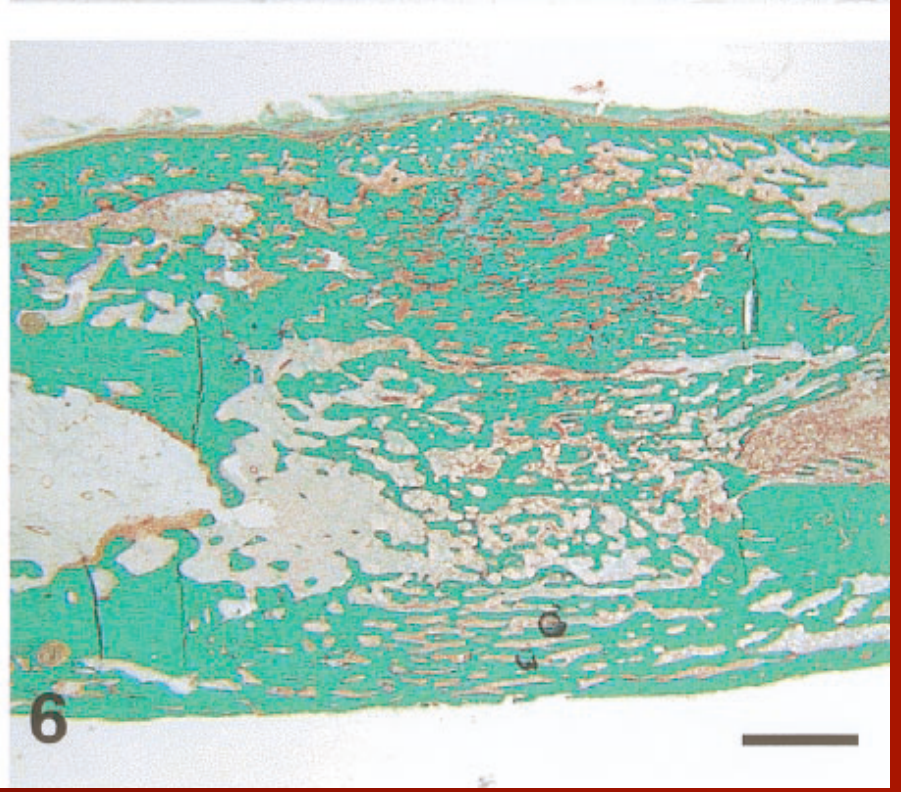
Mineralized bone
stained green

4-6 weeks

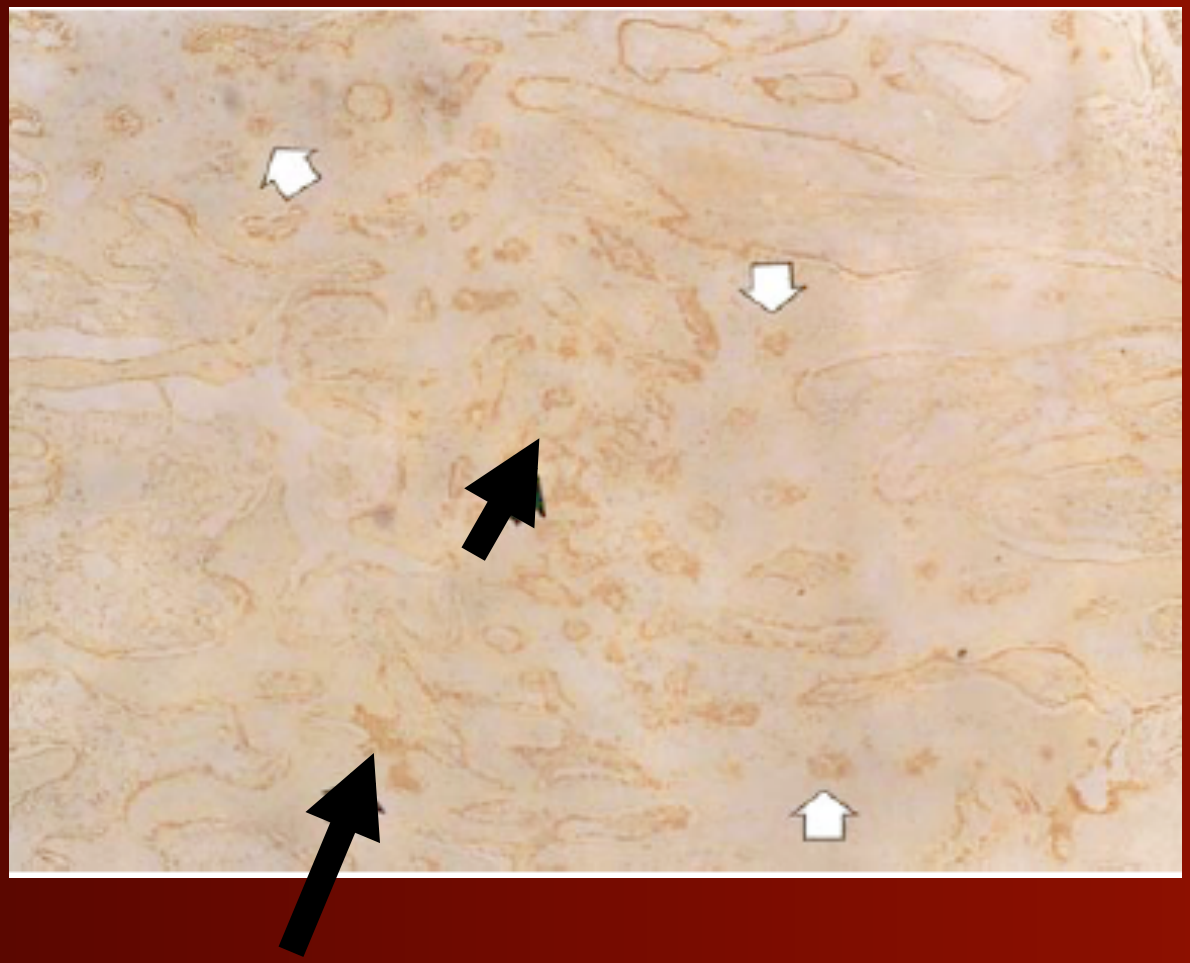
Consolidation phase







Immunohistochemical staining of (VEGF)
28 days after completion of distraction



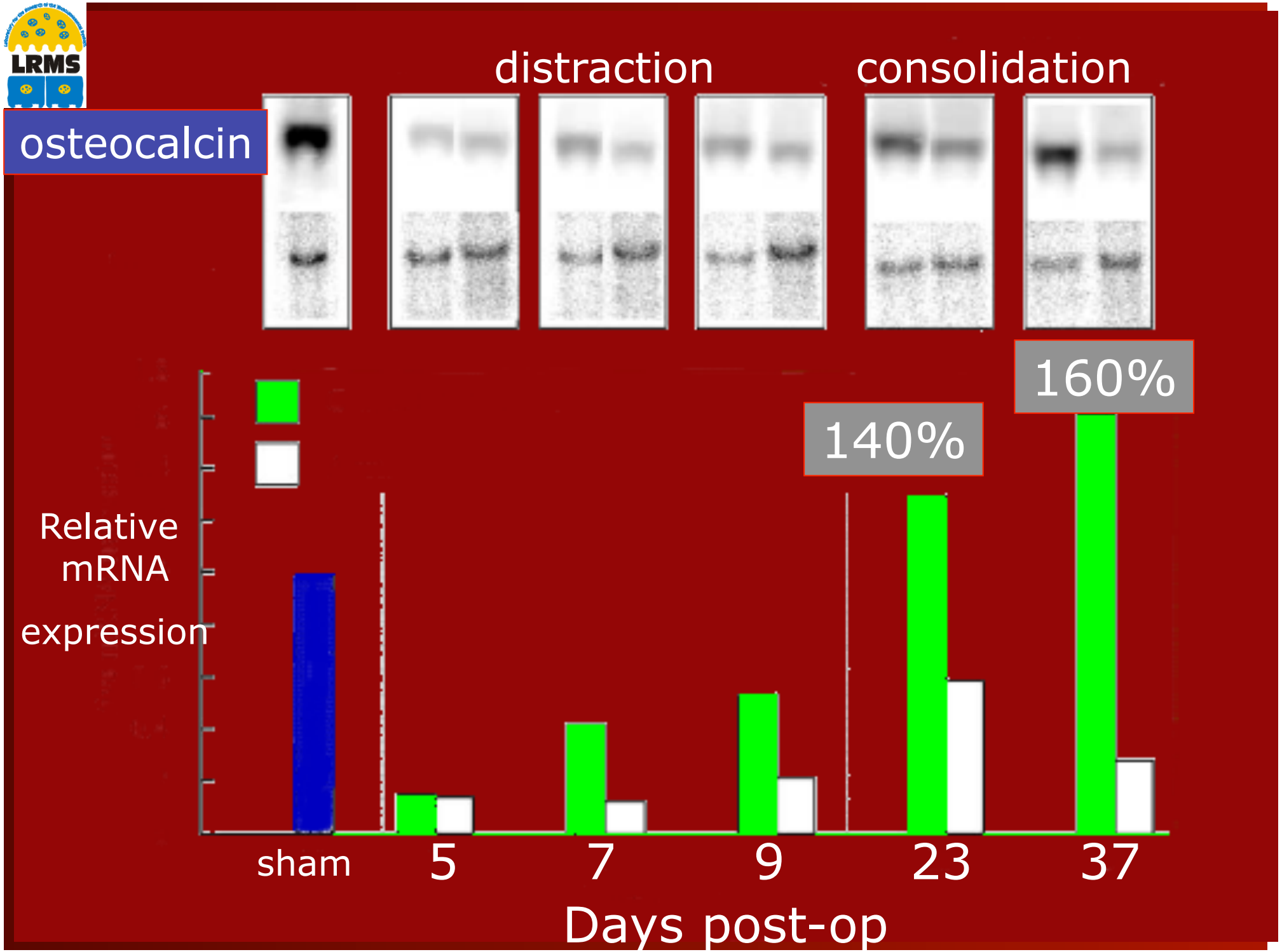
Diffuse vascularization
with positive staining

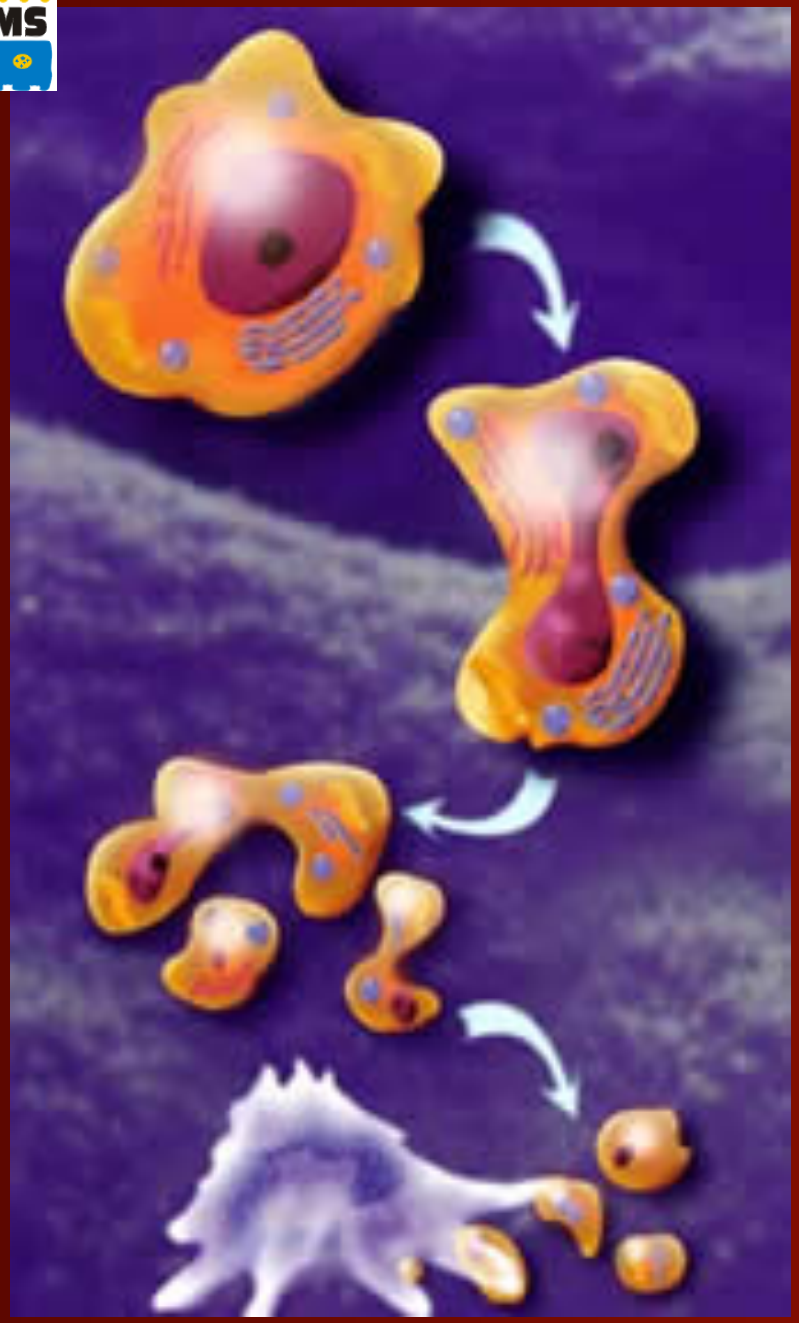
The osteoblasts at the trabeculae
are also positive (partially strong)

extracellular matrix proteins

- Collagenous
- Non-collagenous (osteonectin, osteopontin, osteocalcin)

Facilitation of early bone spicule formation
extending from the osteotomy edges
towards the centre of the distraction gap

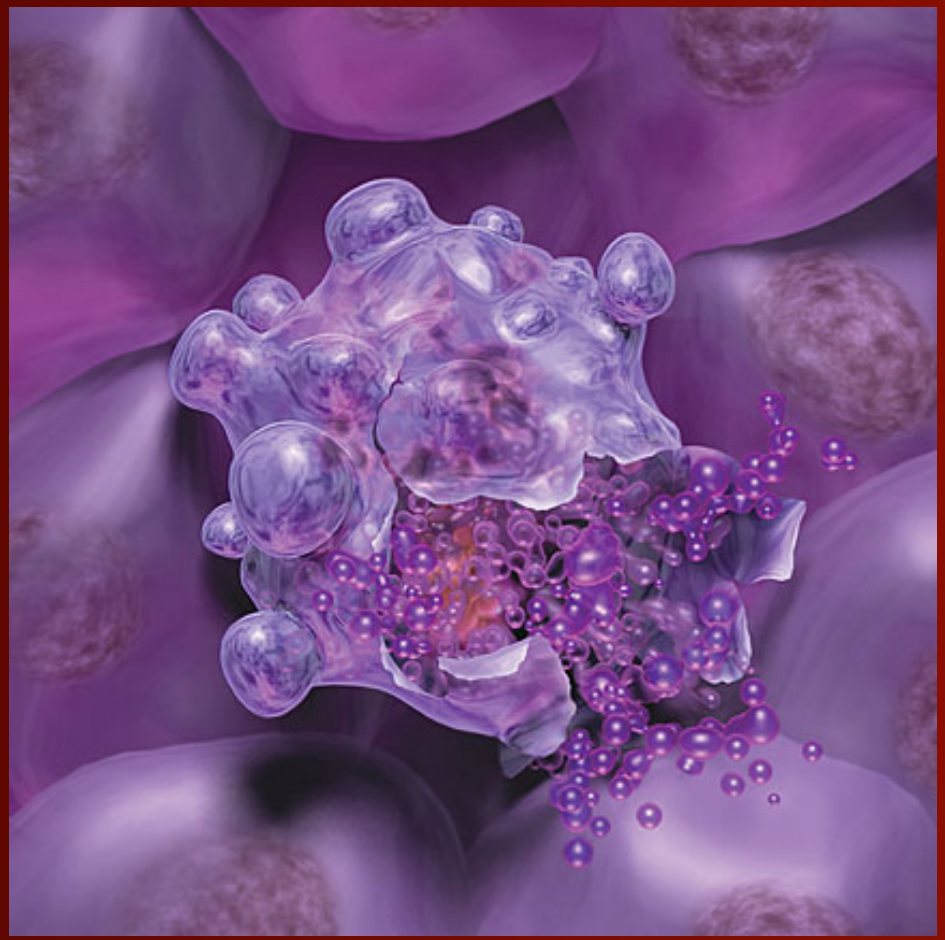

LRMS
osteocalcin
distraction
consolidation
160%
140%
Relative
mRNA
expression
sham
5
7
9
23
37
Days post-op

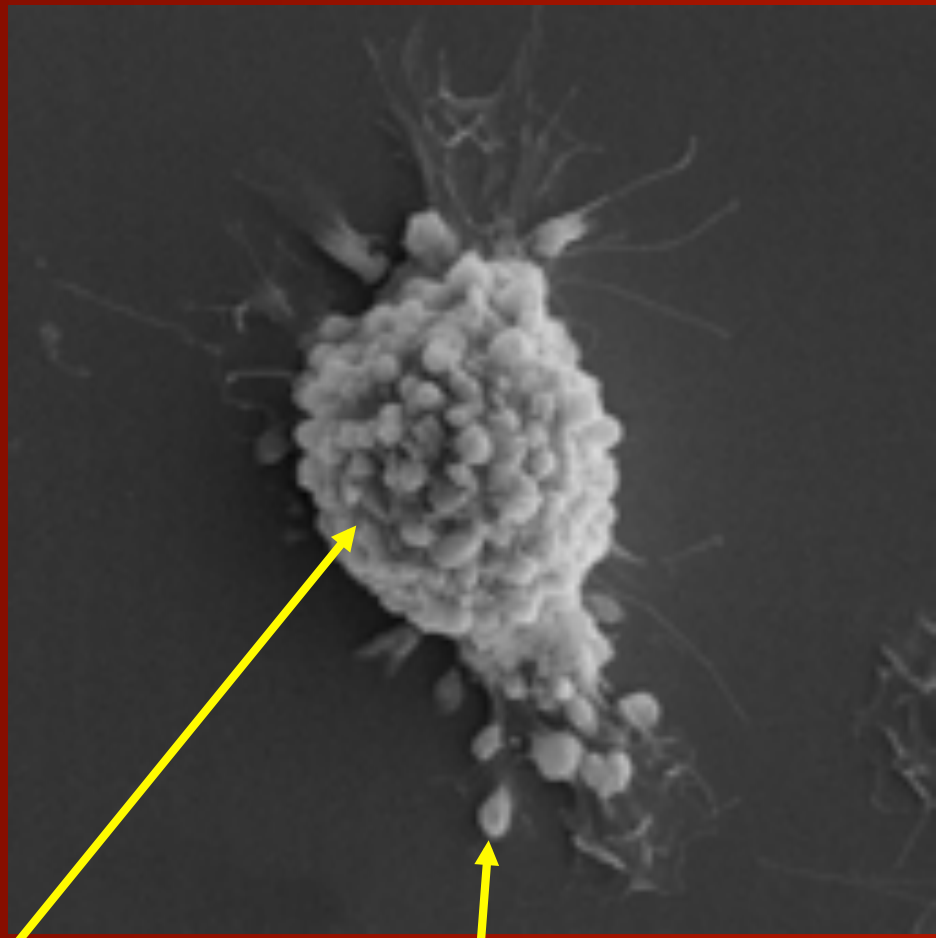


Apoptosis

- change in shape followed by fragmentation and absorption by macrophages
- the process allows clearance of the dying cells without damage to the surrounding tissue

apoptosis

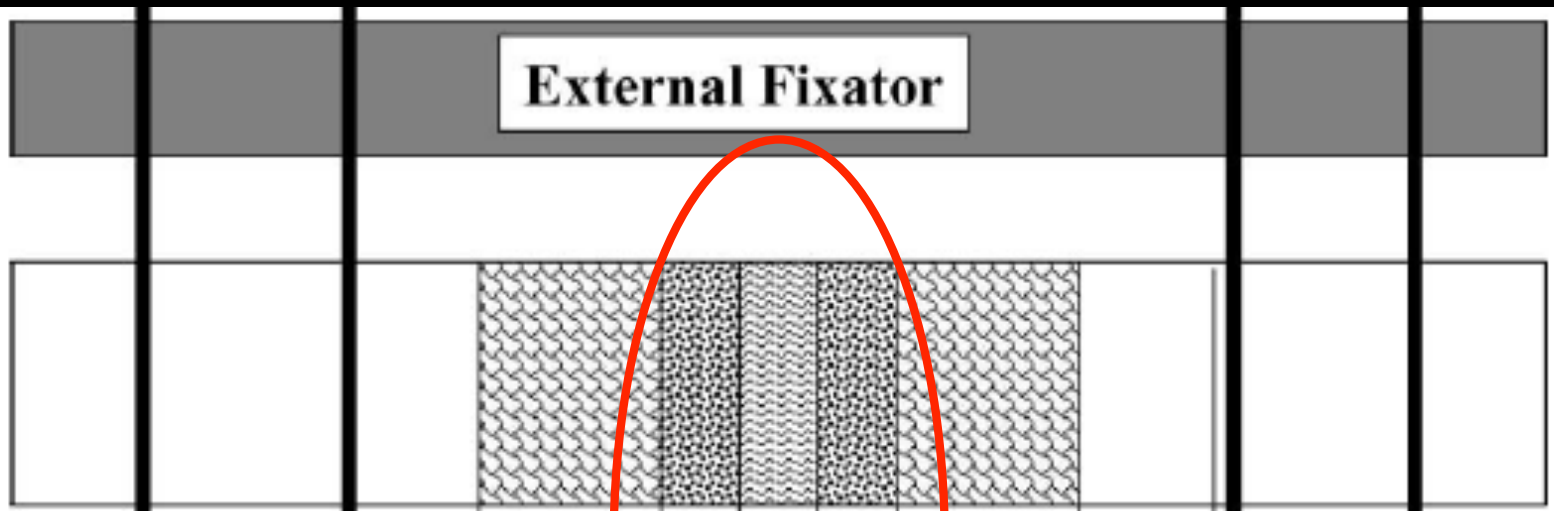




blebs

apoptotic bodies

morphological features of the distraction regenerate



	NBZ	PMF	FZ	PMF	NBZ	Intact Bone
Extent of TUNEL Labeling (Apoptosis)	+	+ + +	+ + +	+ + +	+ +	−
Extent of TRAP Labeling (Remodeling)	+ + +	+ + +	−	+ +	+ + +	+ +	+

TUNEL labeling = apoptosis
TRAP staining = osteoclastic activity

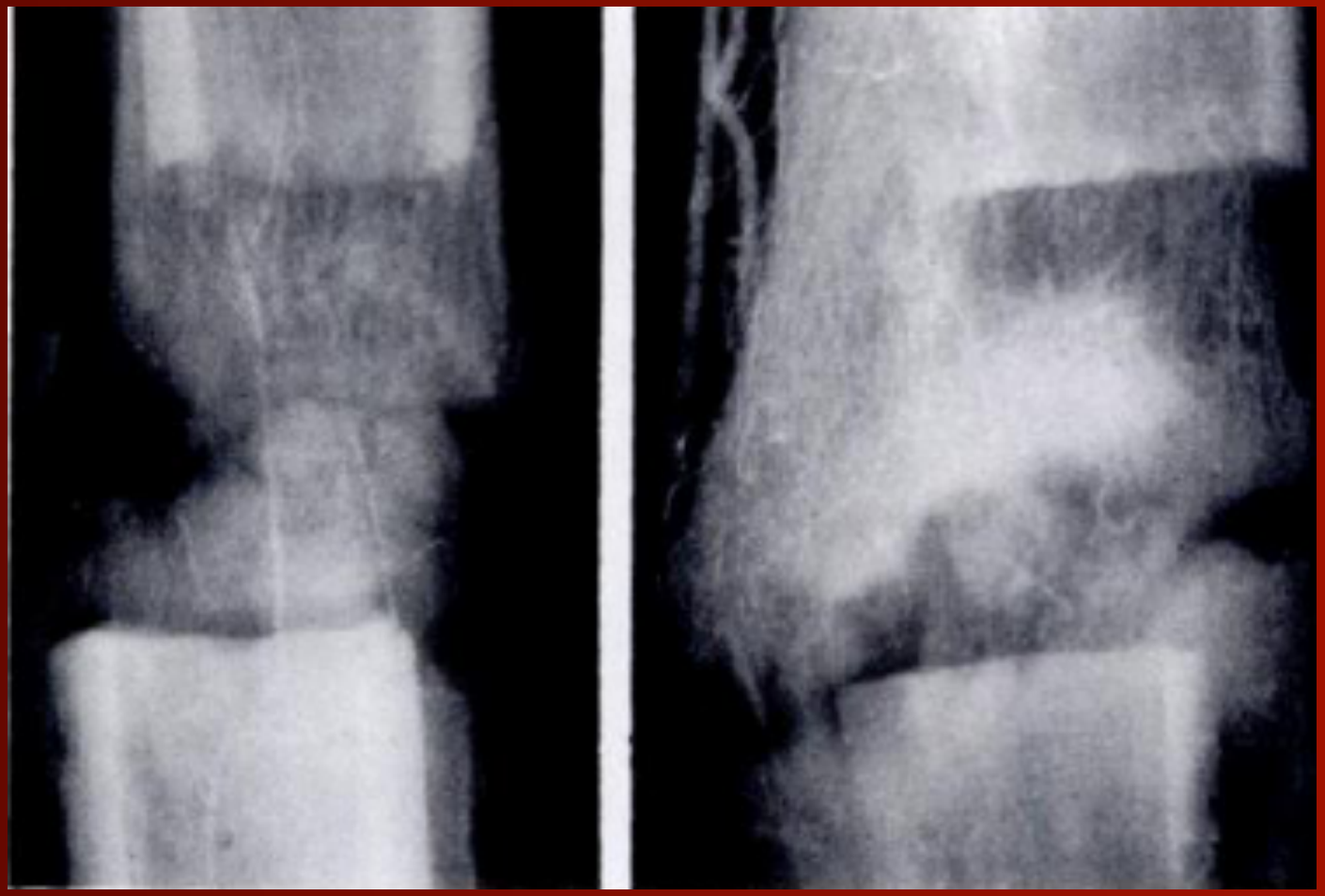
Promoting bone consolidation in DO

Mechanical
- Weight-bearing (mechanical compression)
- Ultrasound (low velocity)
- Electromagnetic field stimulation
- Electrical currents stimulation
- Short-waves treatment
- HBO

Biomaterials/cells
- Calcium sulfate
- Tri-calcium phosphates
- Autologous bone grafts and allografts
- Chitosan and other biopolymers
- Osteoblastic cells
- Bone marrow extracts
- Platelets

Hormones/anabolic and antiresportive agents
- Growth hormone
- PTH
- Estrogen
- PGE2
- Bisphosphonates
- Zoledronic acid

Biomolecules/growth factors
- BMP-2/BMP-4
- BMP-7/OP-1
- VEGF
- FGF-2
- TGF-β

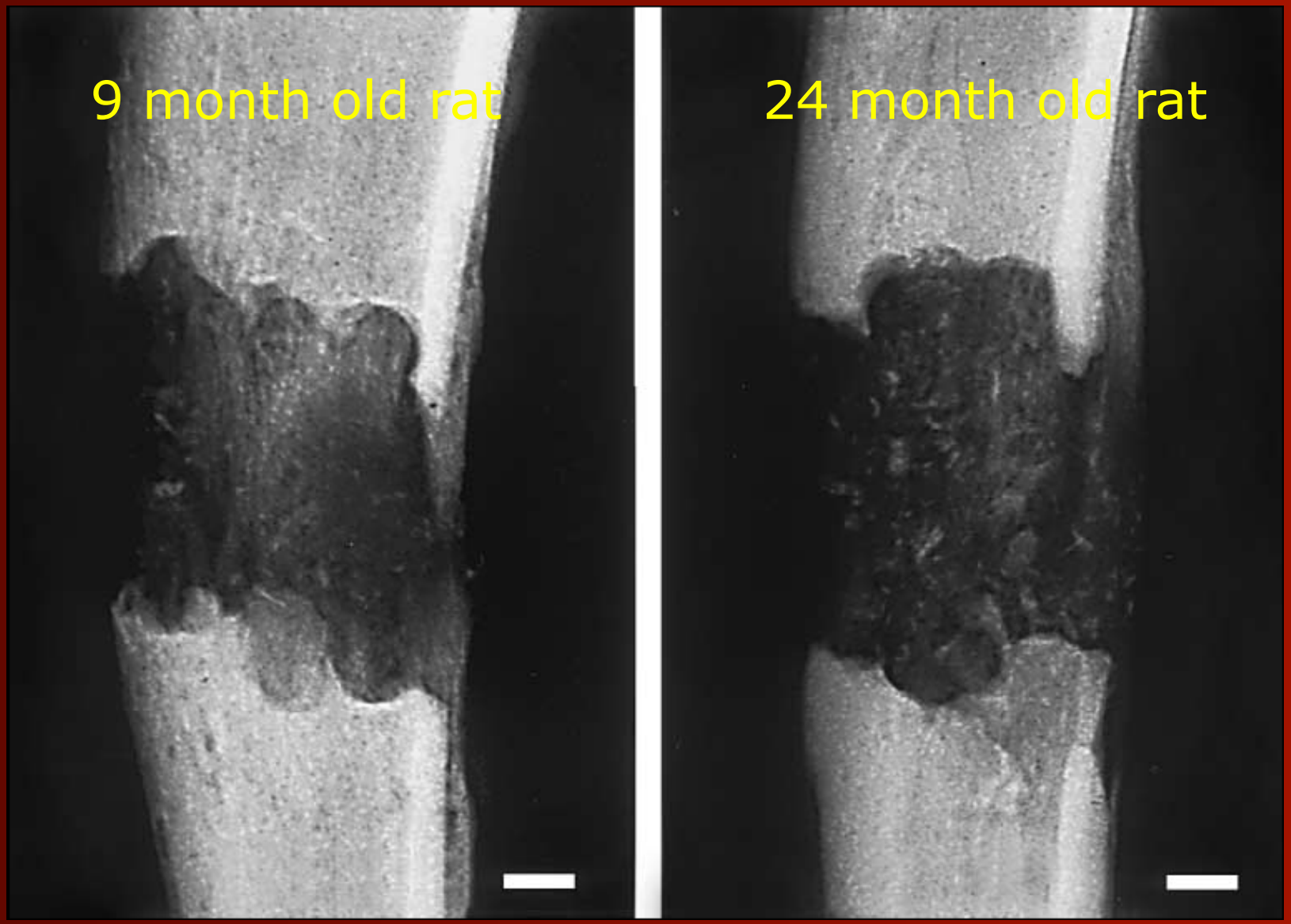


Immediate vs delayed distraction

in the rabbit tibia, 6 wks

White JBJS, 1990

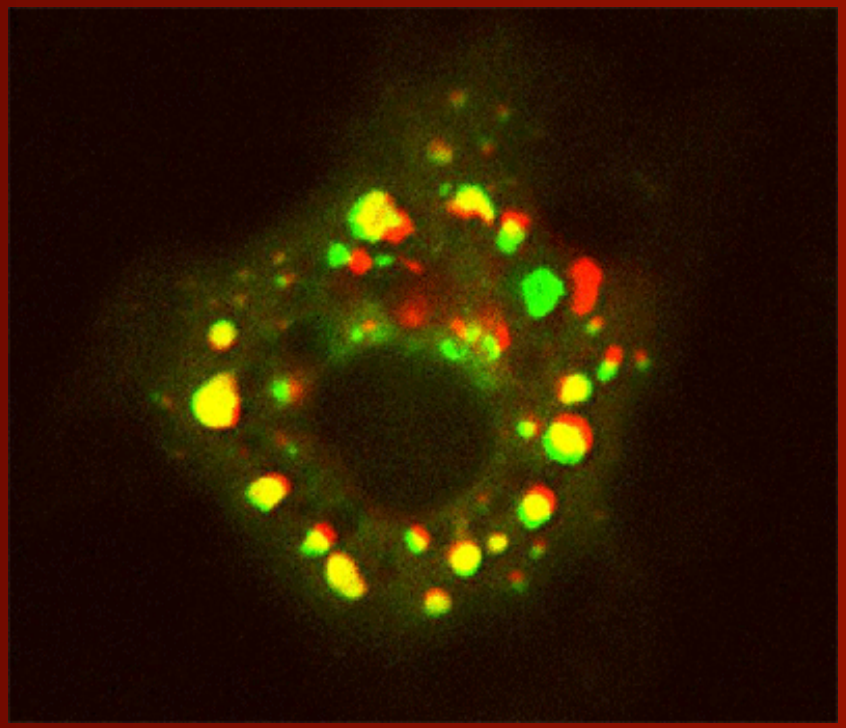
Aging and DO



Mineralization in the older rat
is diminished and irregular

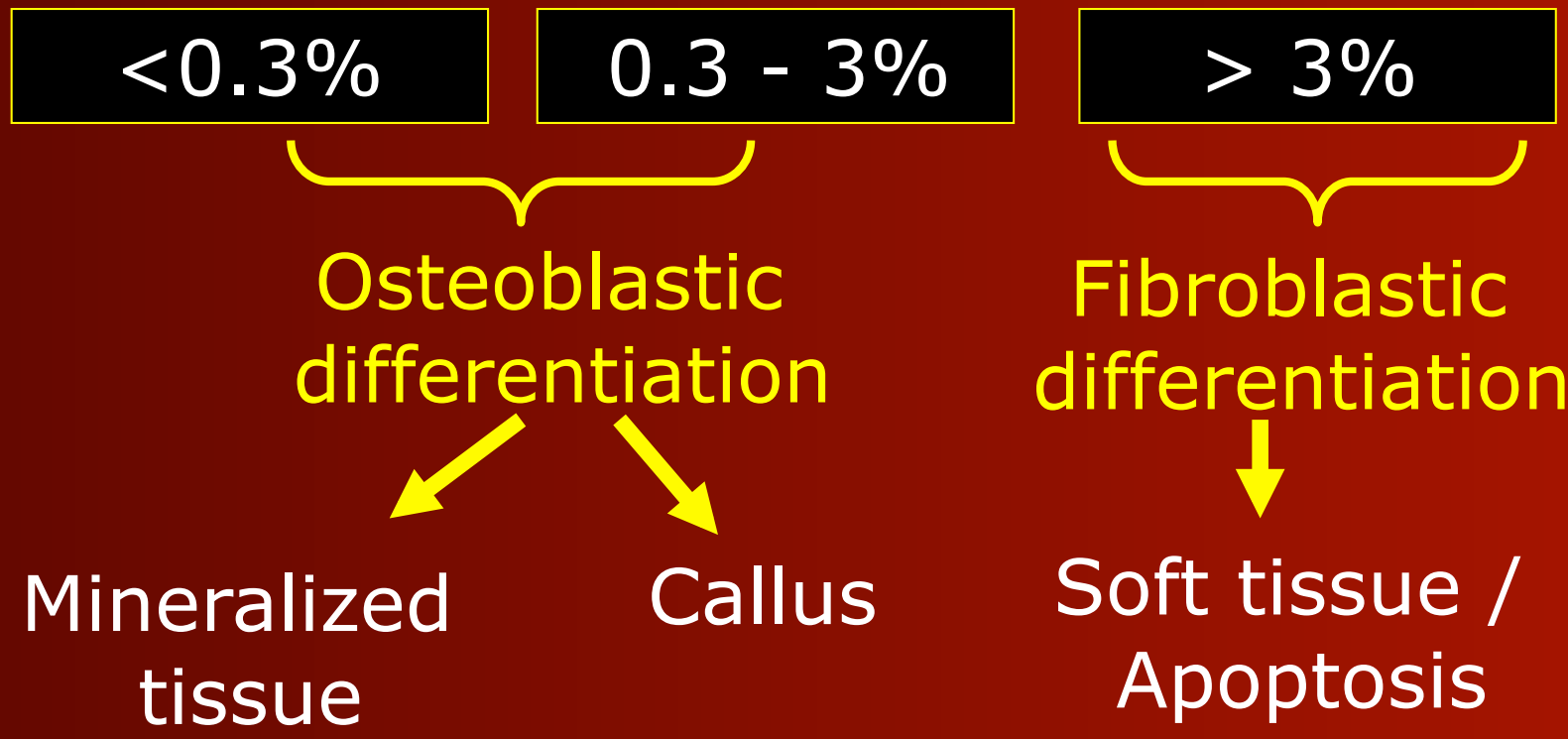
mechanobiology

externally applied forces affect
and guide cell function



mechanobiology merges mechanics
with molecular biology and genetics

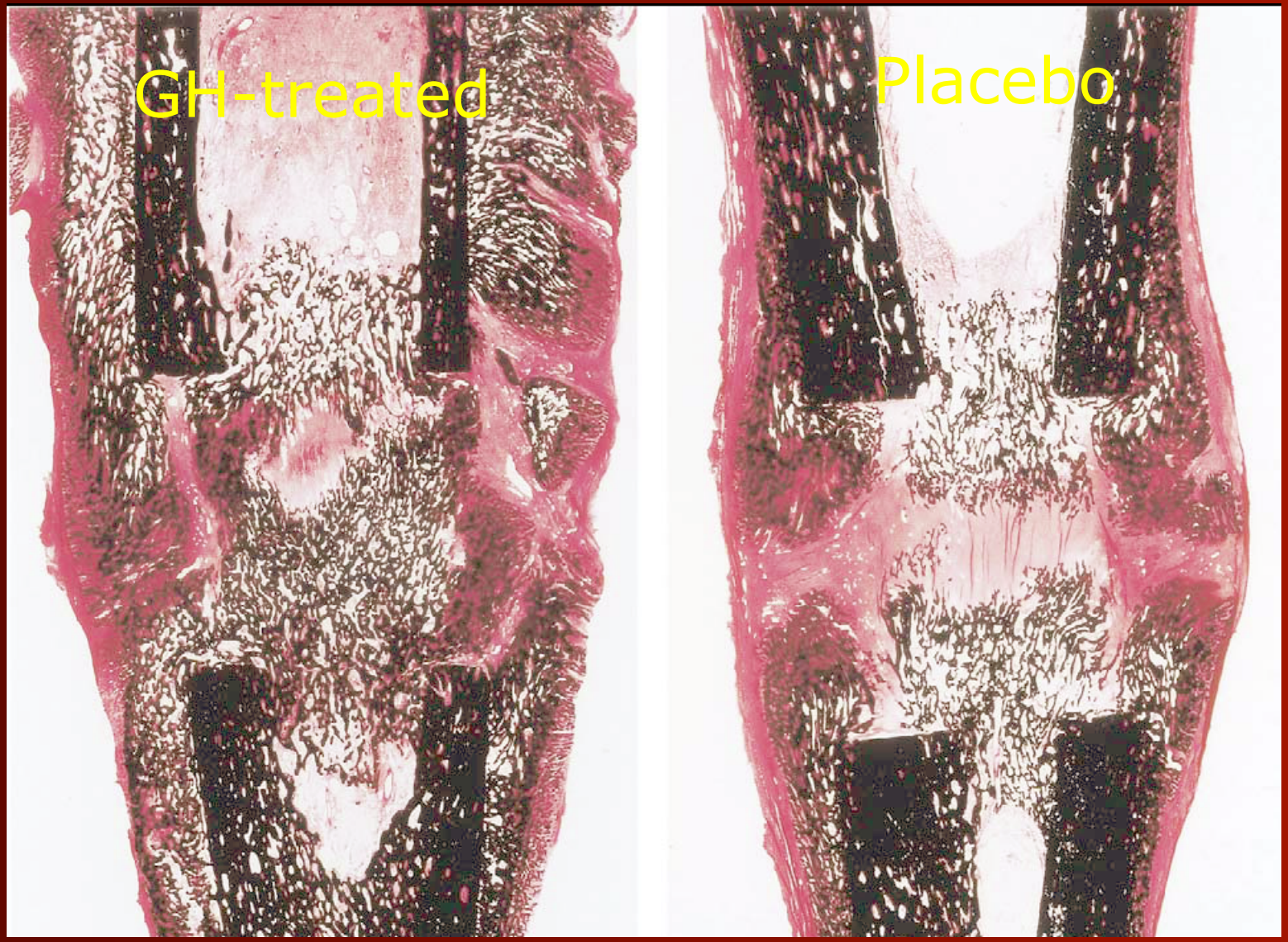
Strain-related distraction healing



Possible mechanisms for transformation of mechanical stimuli to biochemical signal for bone formation

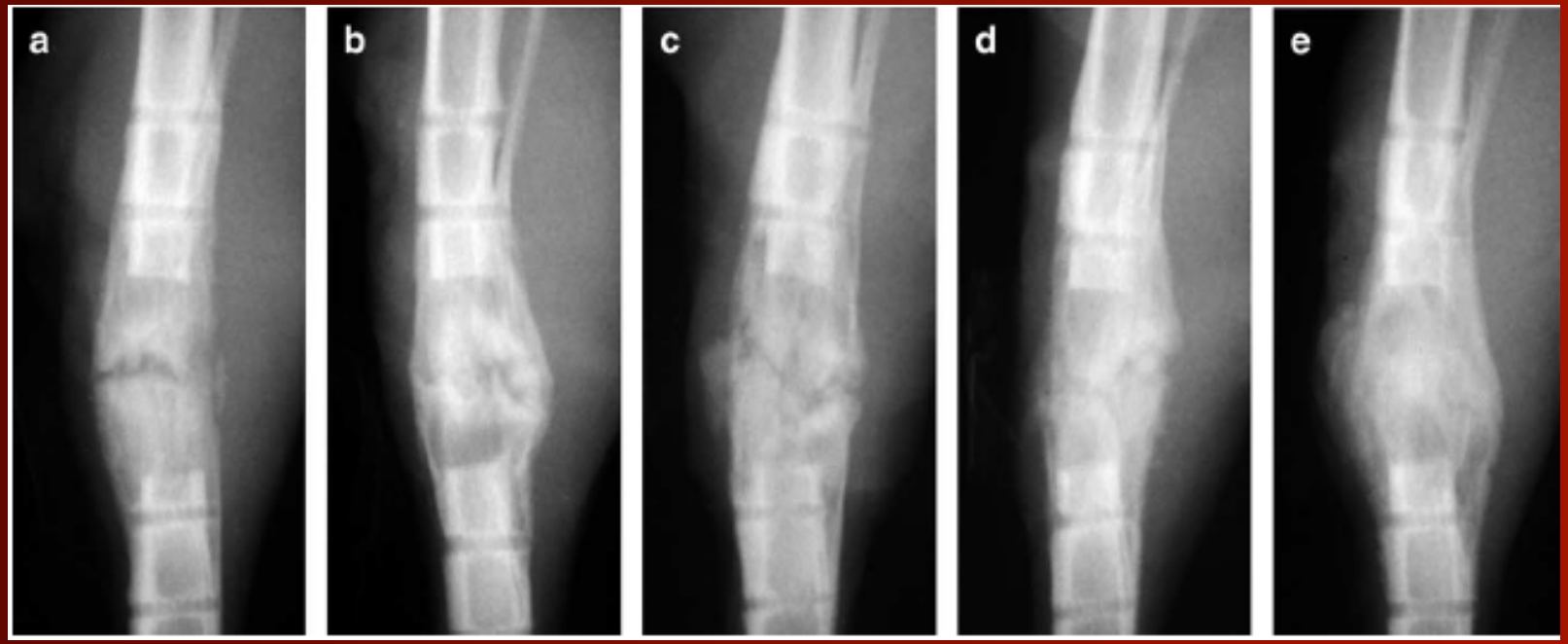
- ✓ Prostaglandin release
- ✓ Electromagnetic potentials
- ✓ Increased bone blood flow
- ✓ Response to microdamage
- ✓ Hormonally mediated mechanisms

daily sc 100 g r-pGH/kg BW



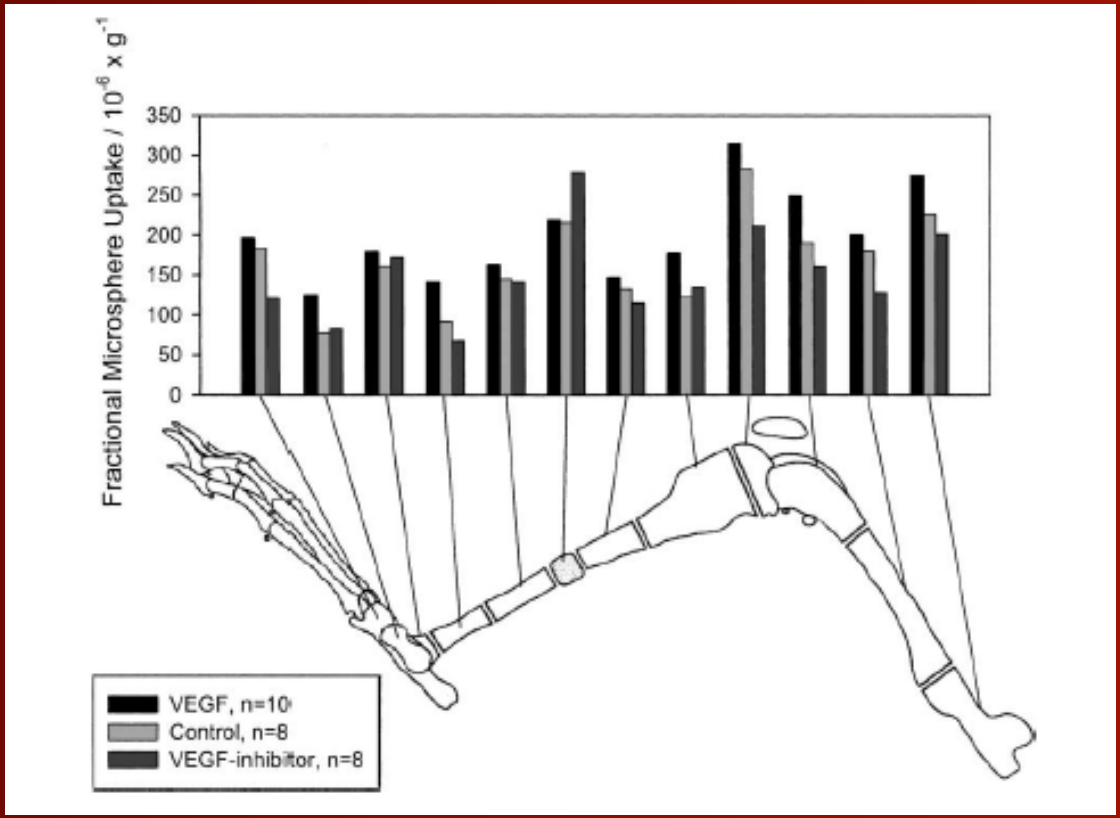
Safranin-O/von Kossa stain, X 2.5

Late adminstration of OP-1



- Strong expression of BMP receptor IA, IB, and II during the early distraction phase, but not during later stages of the process.
- The lack of receptor protein in the target tissue impairs the effect of OP-1 given at the end of the distraction period

VEGF and VEGF-inhibitor treatment



The regenerate was unresponsive to VEGF and VEGF-inhibitor treatment in contrast to the neighbouring bone, which implies different biological properties of the vasculature in native and regenerating bone

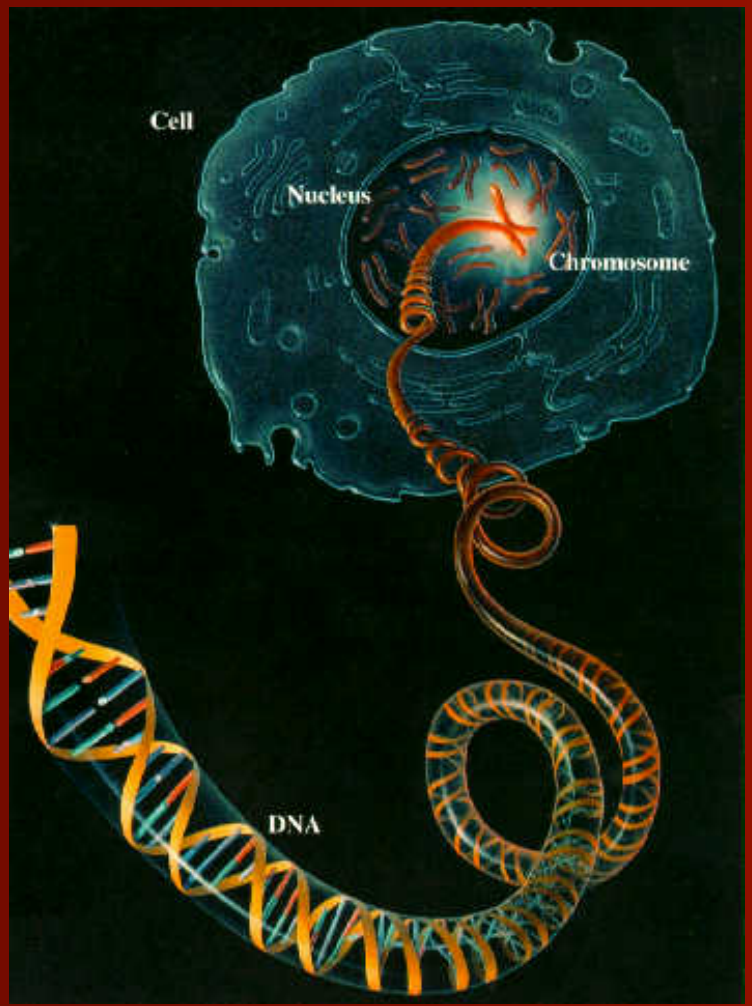
Microangiograms of the distracted site

Control group

15-Gy irradiation group

Modern clinical applications

of distraction osteogenesis



Manbibular Lengthening

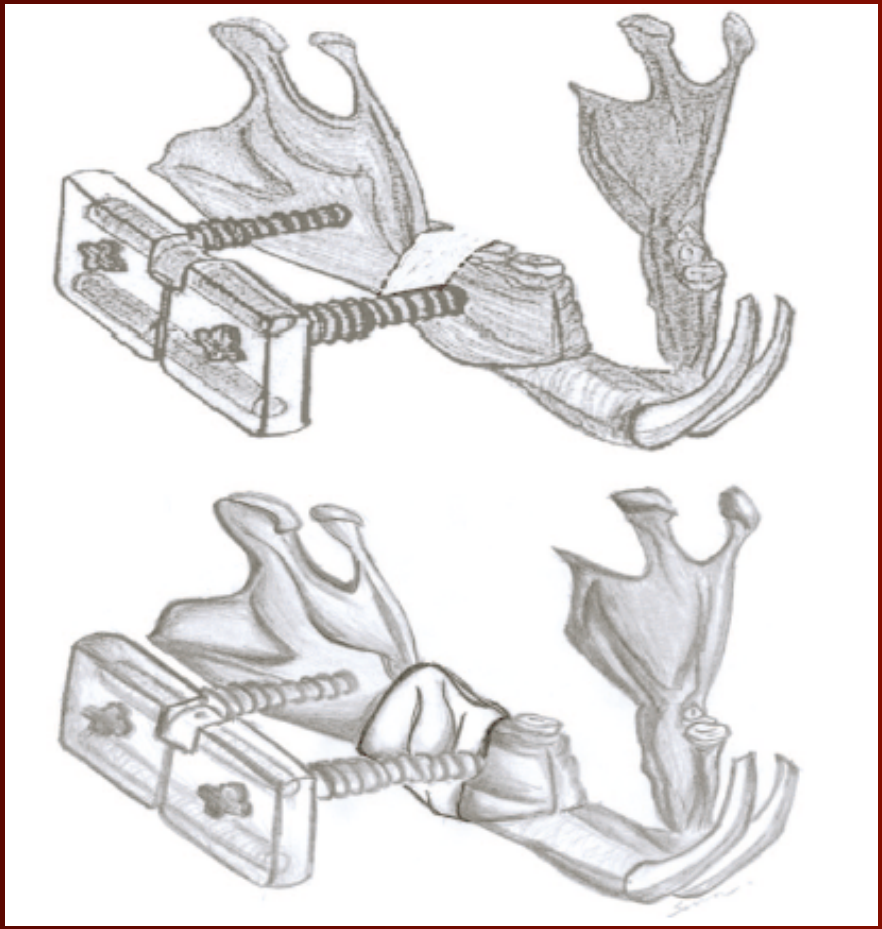
Lengthening over an intramedullary nail

Nonunion Treatment



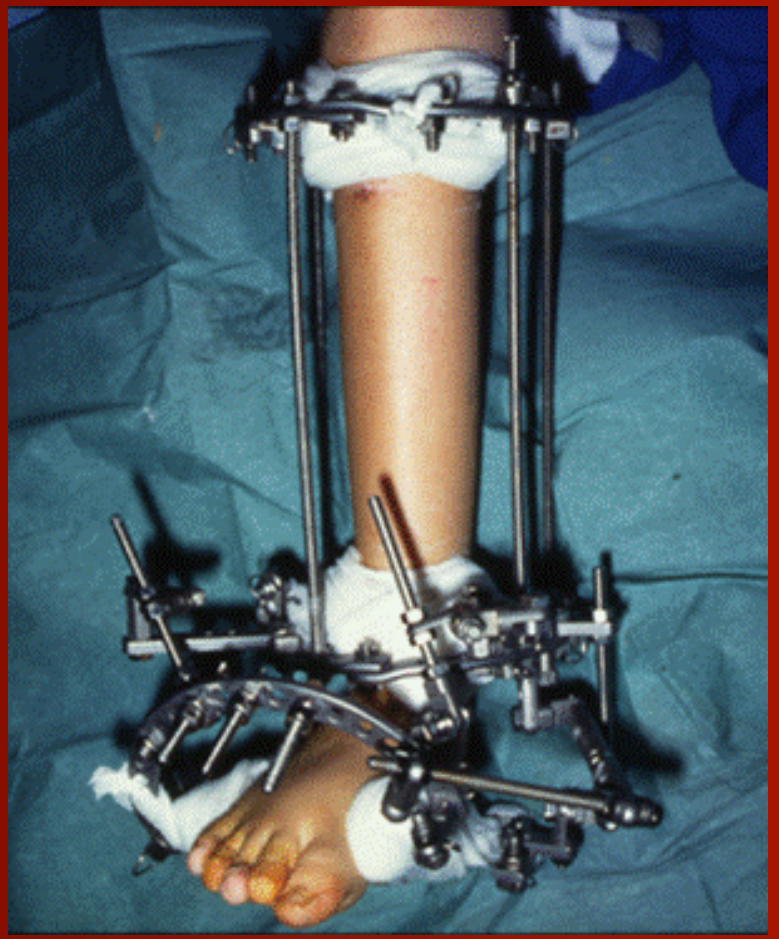
- initial distractive forces to stimulate distraction osteogenesis
- then apply compression to unite stiff, fibrous non-unions

Guided Tissue Regeneration

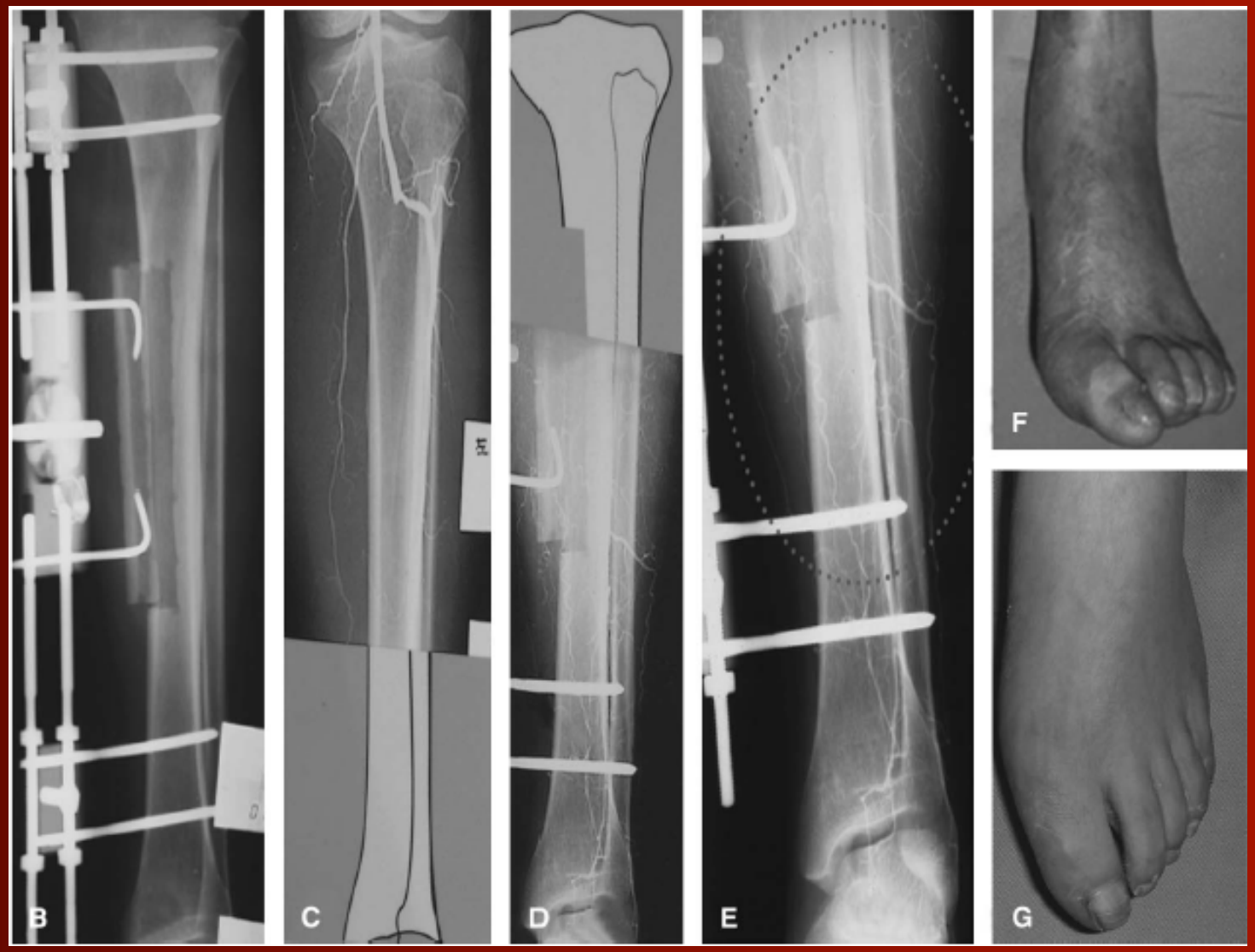


Gore Resolut XT membrane

Soft Tissue Stretching



transverse bone transport in thromboangiitis obliterans



25 days after DO