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Bone Tissue

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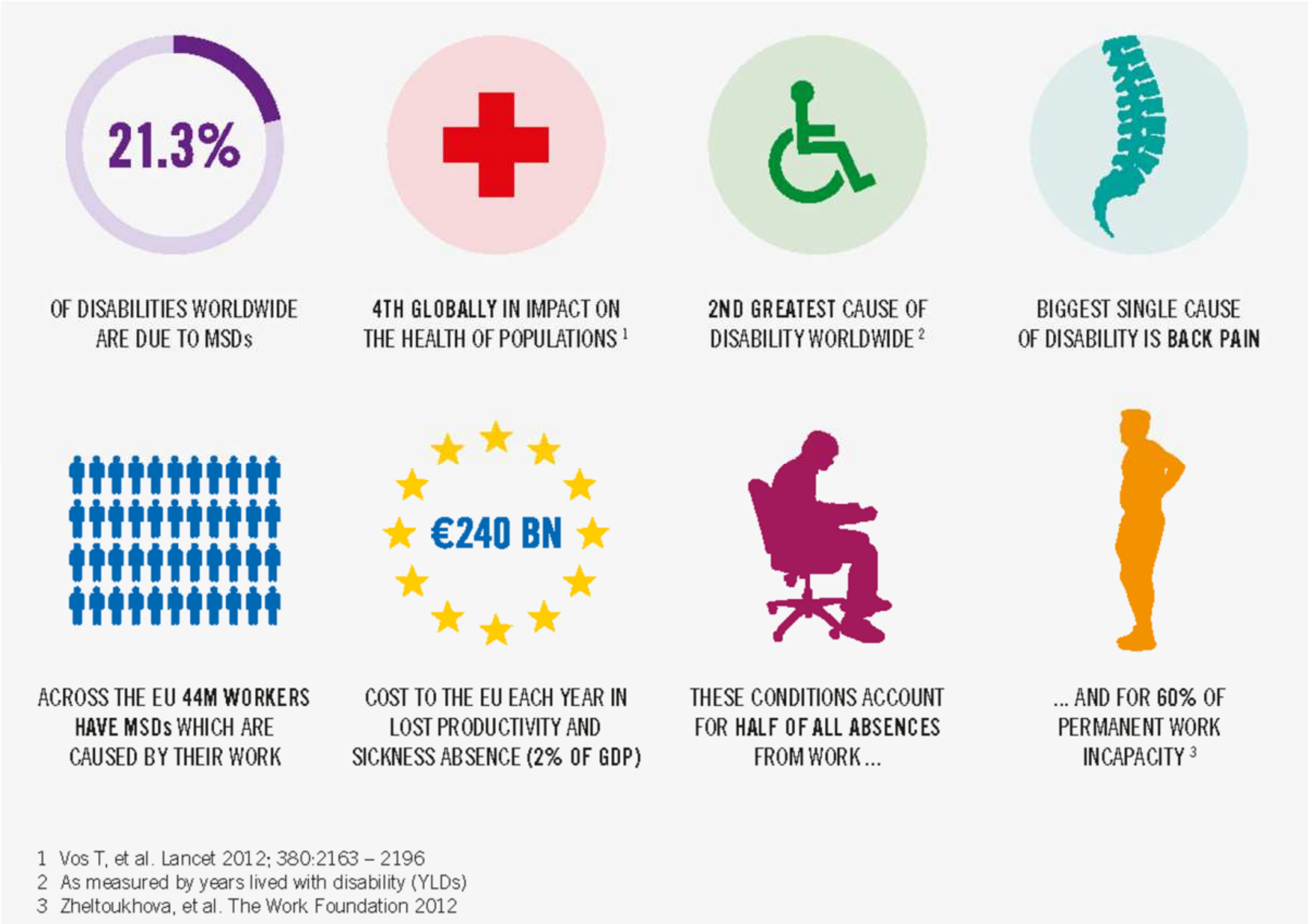
AO Research Institute Davos

Key facts about musculoskeletal disorders



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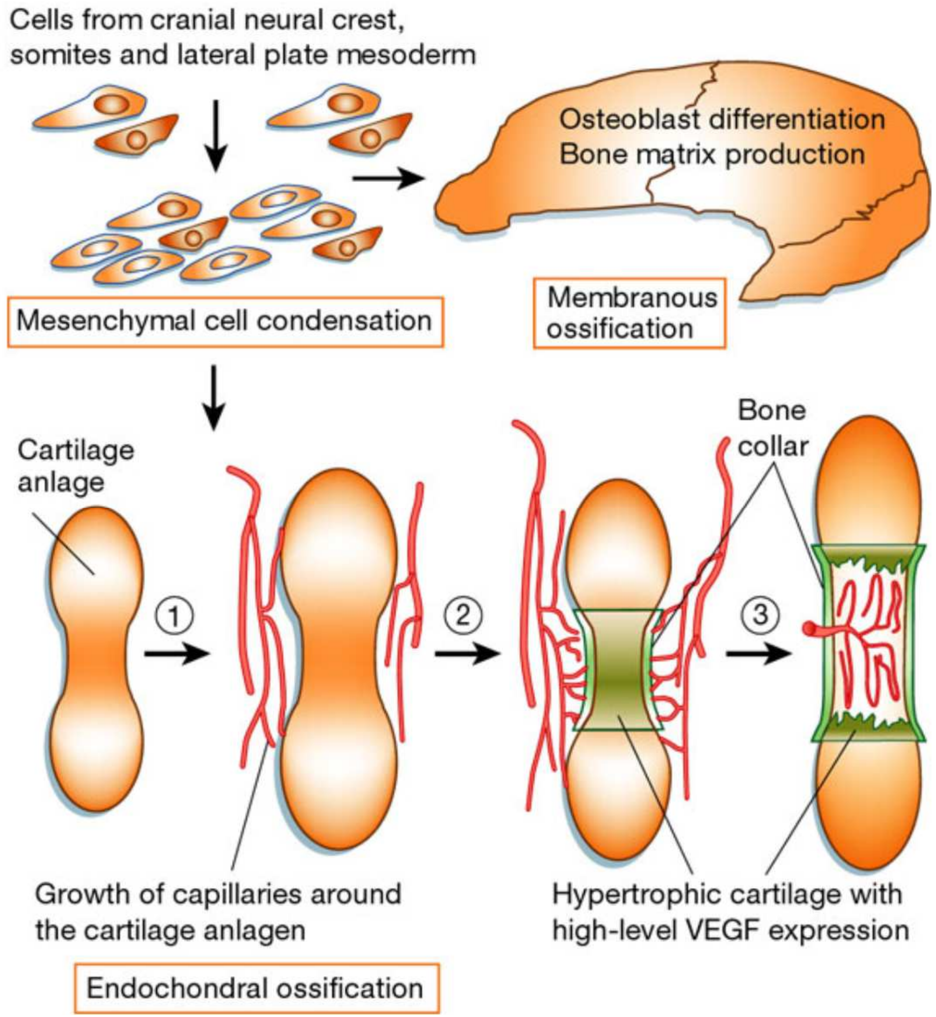
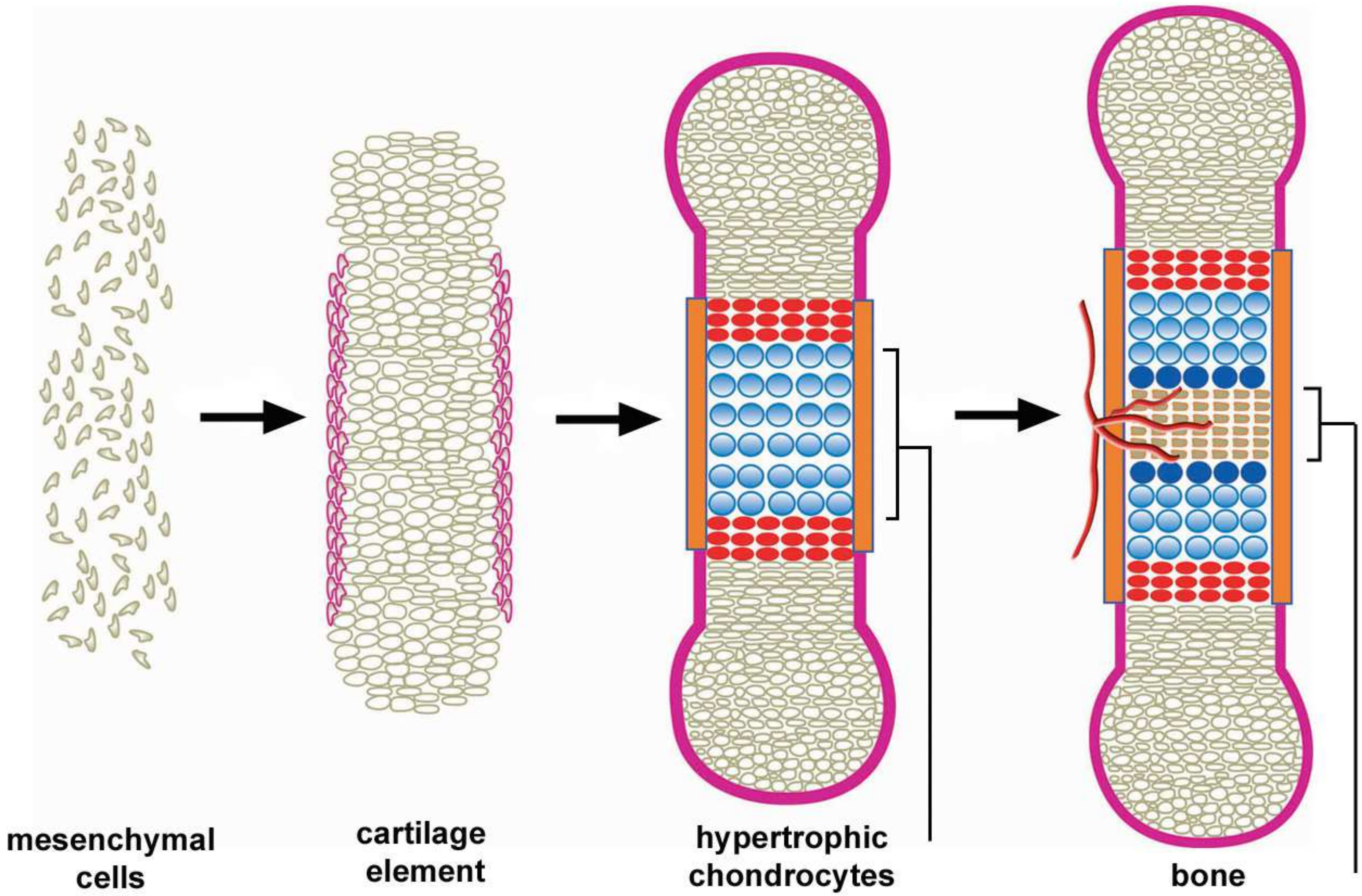
Bones

Endochondral vs. membraneous ossification

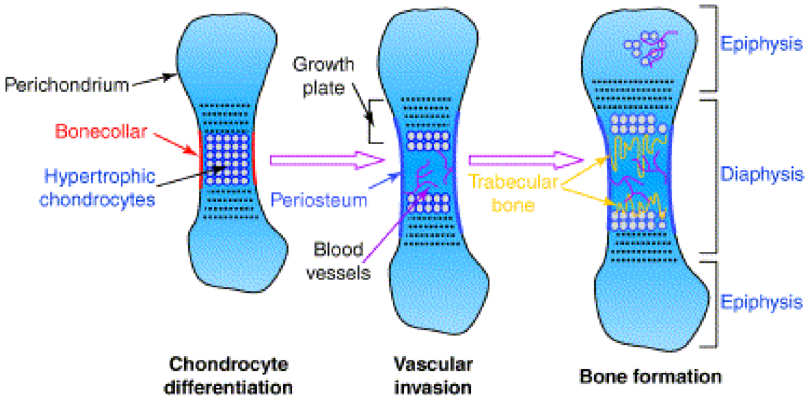


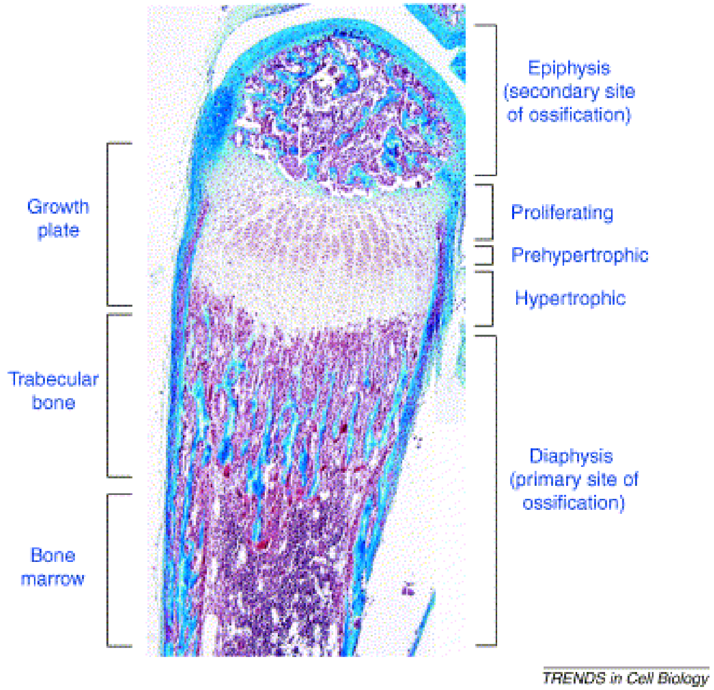
Zelzer et al. 2003

Cartilage Formation



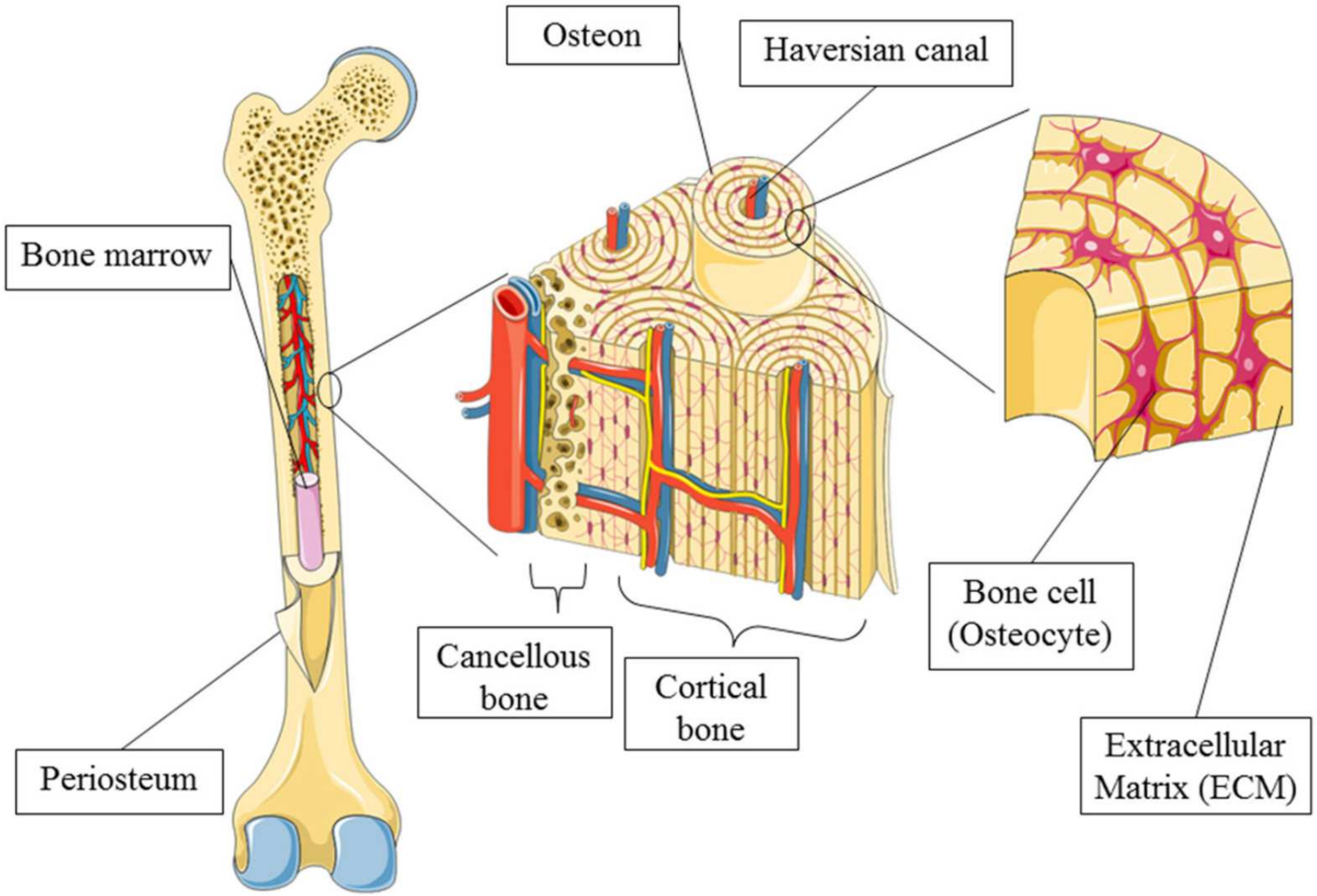
A. Vorkampf


Perichondrium
Bonecollar
Hypertrophic chondrocytes
Growth plate
Periosteum
Blood vessels
Trabecular bone
Epiphysis
Diaphysis
Epiphysis
Chondrocyte differentiation
Vascular invasion
Bone formation


Growth plate
Trabecular bone
Bone marrow
Epiphysis (secondary site of ossification)
Proliferating
Prehypertrophic
Hypertrophic
Diaphysis (primary site of ossification)
TRENDS in Cell Biology

L. Sandell

Bone structure



Bao et al. 2013

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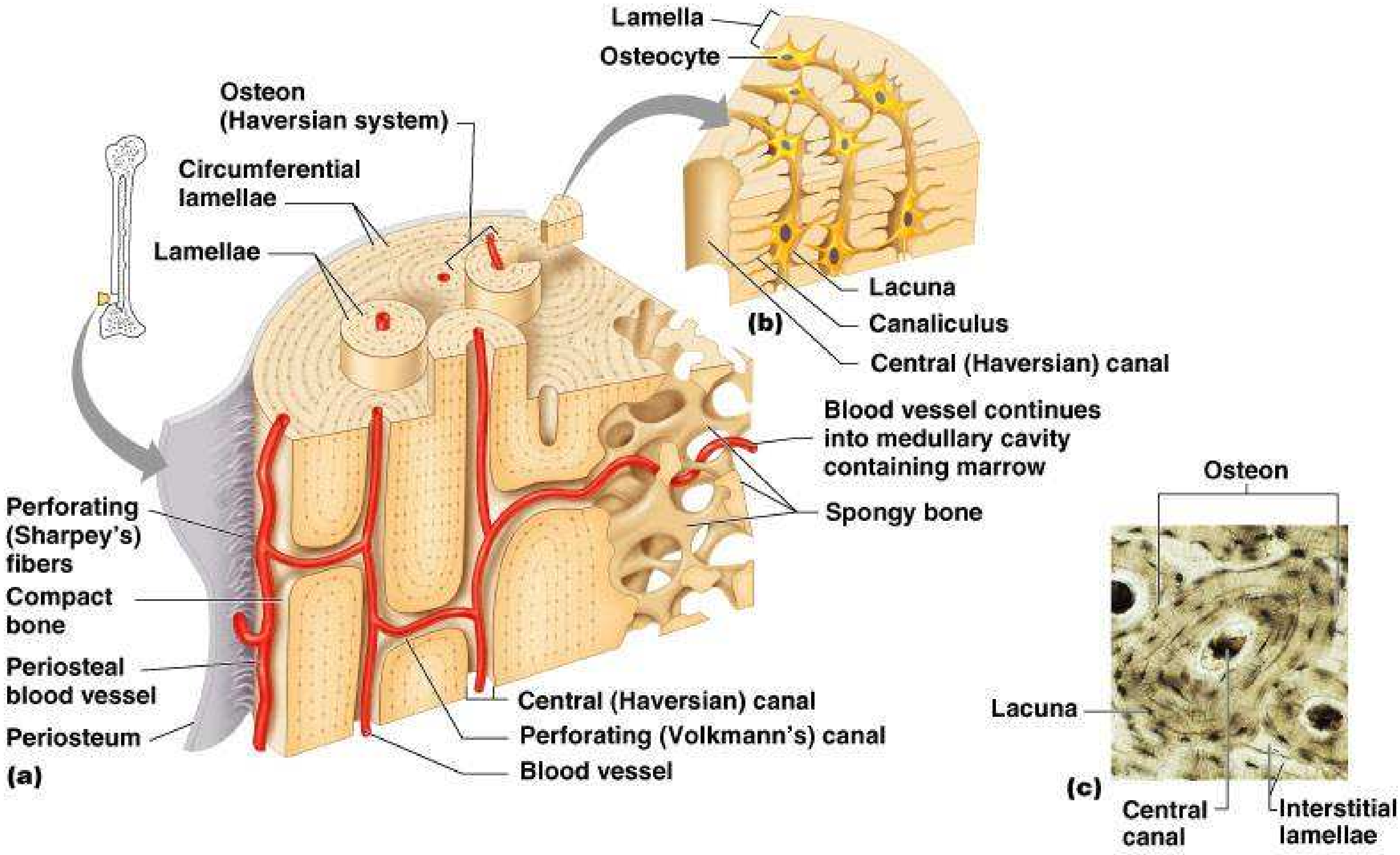
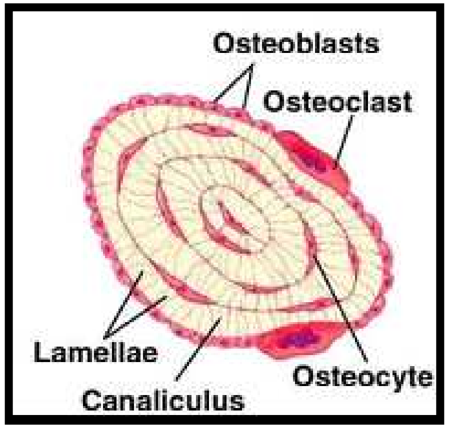
Structure of bone



Basic Bone Cell Types

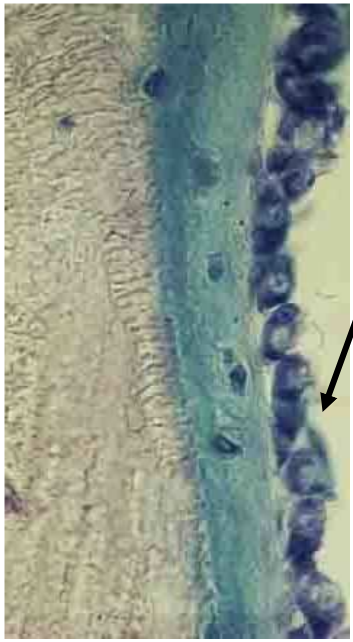
Osteon

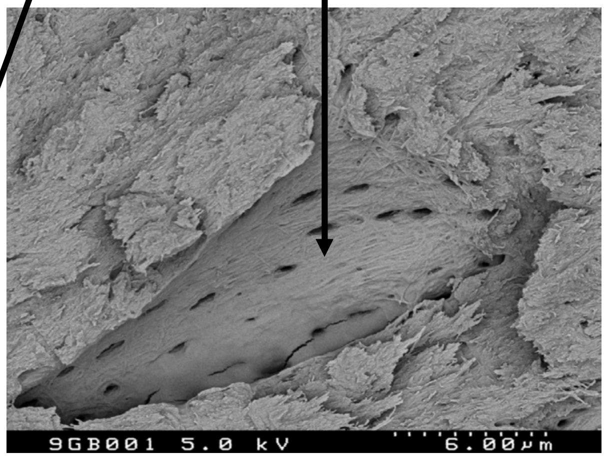


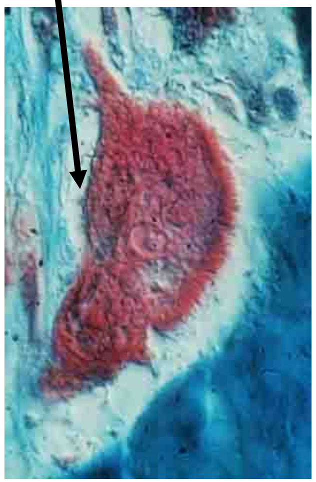
Osteoblasts - synthesis of bone proteins (collagen - 20%) & ecm osteoid. Matrix mineralisation - 10 days ~15% become trapped within the matrix as osteocytes

Osteocytes - regulate bone response to the mechanical environment . Bone remodeling controllers

Osteoclasts - resorption of bone matrix
Mineral Dissolution - acid microenvironment
Collagen degradation - lysosomal enzymes







Different origin

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Tubular vs. Flat Bones

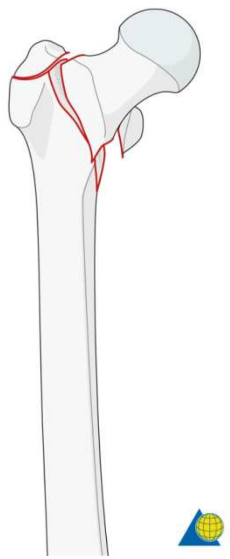
Tubular bones

Endochondral origin

Tubular shape

Thick cortex

Higher load



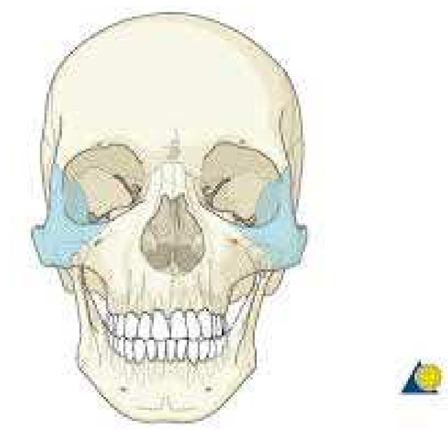
Craniofacial (flat) bones

Membraneous origin

Flat shape

Thin cortex

Smaller load



Origin no longer visible in mature bone

Healing patterns similar

Reaction pattern to circulatory injury similar

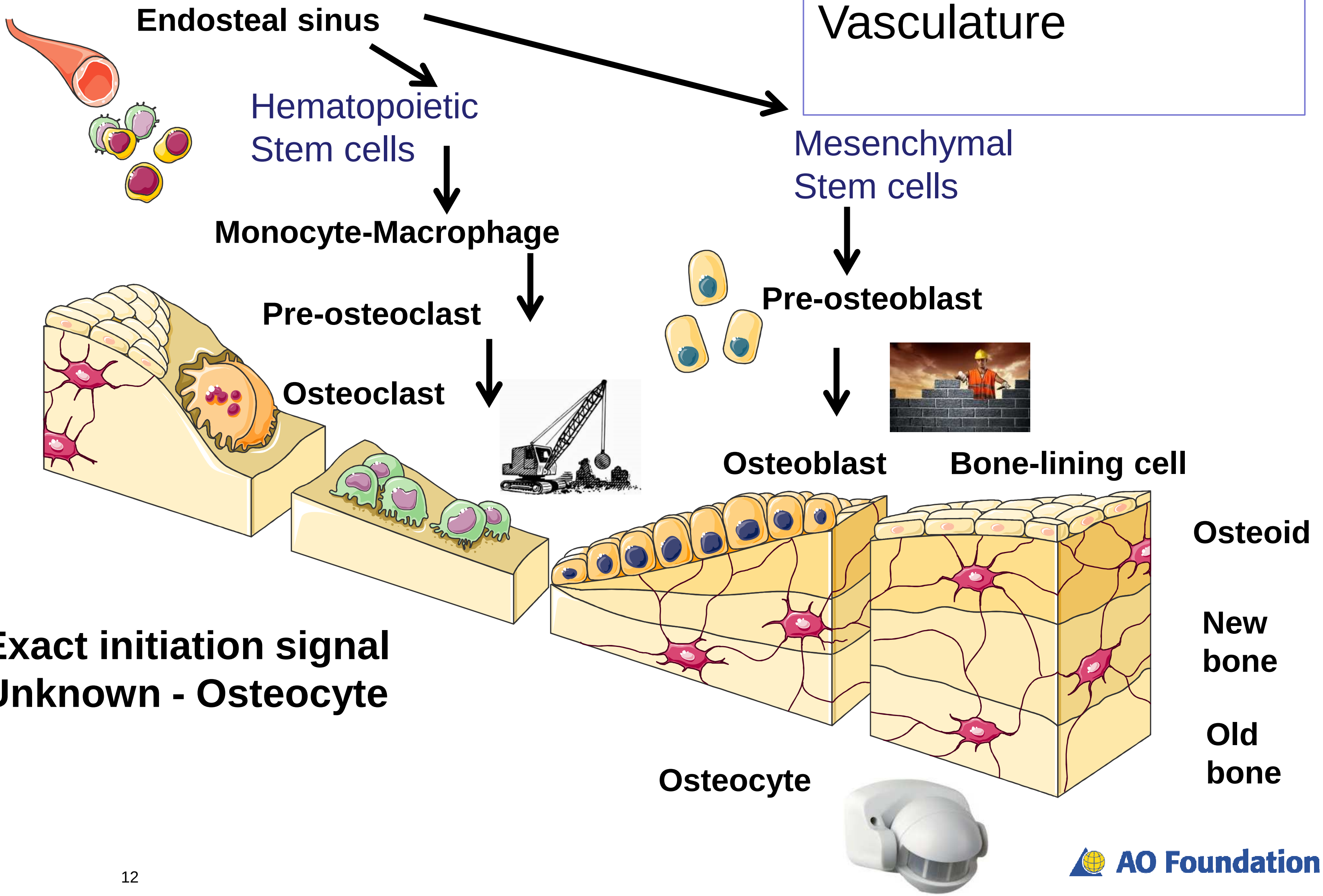
Structure of Bone

- Cancellous bone: direct vascularization → fast healing
- Compact bone: longer remodelling → slower healing
- Flat bones e.g. pelvis:
  2 layers of compact bone with cancellous between
  - behaves similar to cancellous bone
  (flat shape, thin cortexes, privileged access to blood supply)
- Mandible: behaves similar to long bones

Prein and Rahn,1998

Bone Remodelling

AO Principle
Preserve soft tissue/
Vasculature



Exact initiation signal
Unknown - Osteocyte

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Function of bone

Mechanical:

Protection (brain)
Gives structure (tendon)
Facilitates movement
Facilitates hearing

Synthetic and Metabolic

Bone marrow (hematopoiesis)
Stores Ca and P
Stores growth factors
Regulate the acid-base

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Costs

1 US oil barrel = 159 L = $ 75.00

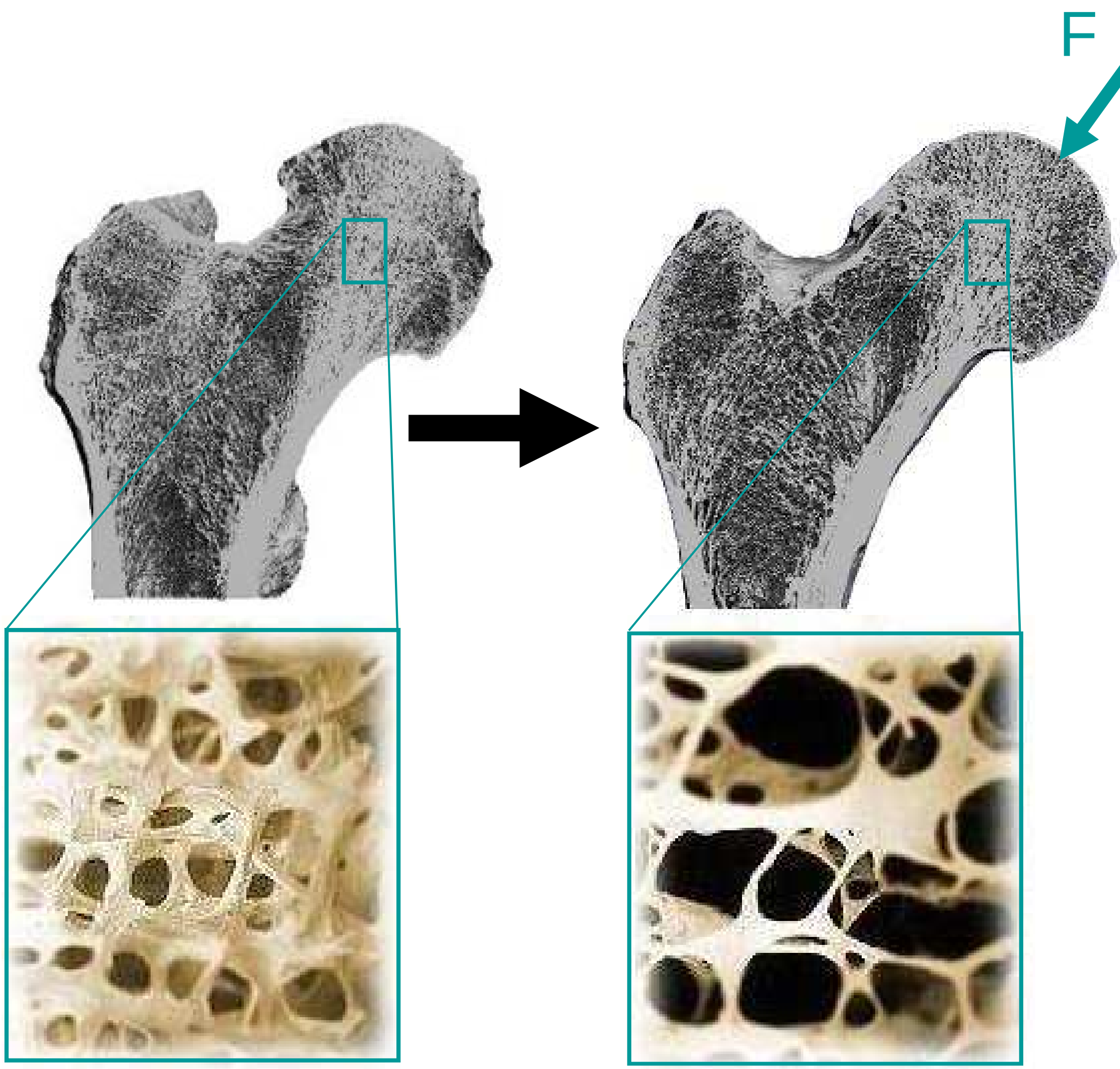
1Kg oil = $ 0.54 → 1mg = $ 0. 54 10^{-6}

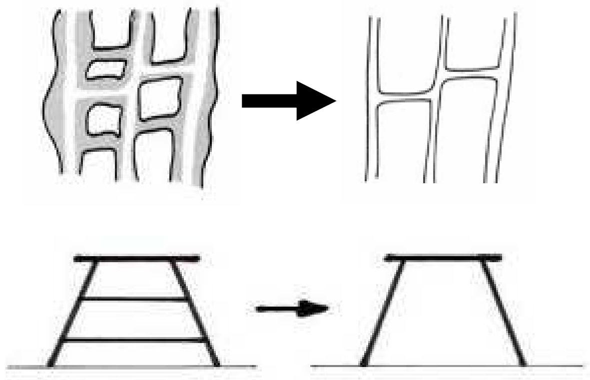
1Kg gold = $ 40’000 → 1mg = $ 0.040

1.5mg BMPs = $ 5’000 → 1Kg = $ 3’333 x 10^{6}

Diseases

Clinical problem: Osteoporotic fractures





Up to 8 x reduction in strength

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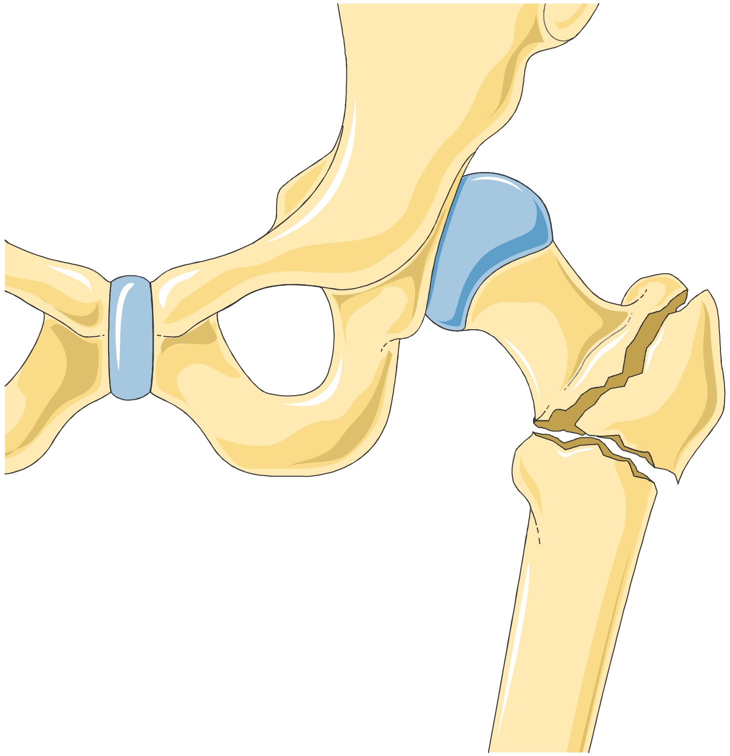
A fractured bone means ...

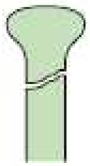
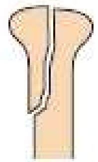
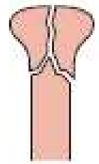
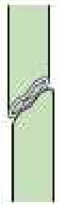
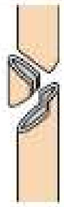
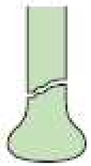
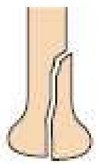
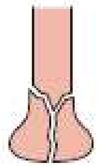


- Interruption of circulation
- Interruption to force transmission
- Damage to the bone & soft tissue
- Crack (gap / separation)
- Bony fragmentation
- Impaction of cancellous bone

Flat Bones

- Less circulatory damage and faster recovery
    - Depends heavily on size and location
- Smaller loads make stabilization less demanding

Bone fracture

Segment	Type		
	A	B	C
1 Proximal	 **Extraarticular** No involvement of displaced fractures extending into the articular surface	 **Partial articular** Part of the articular component is involved, leaving the other part attached to the meta-/diaphysis	 **Complete articular** Articular surface involved, metaphyseal fracture completely separates articular component from the diaphysis
2 Diaphyseal	 **Simple** One fracture line, cortical contact between fragments exceeds 90% after reduction	 **Wedge** Three or more fragments, main fragments have contact after reduction	 **Complex** Three or more fragments, main fragments have no contact after reduction
3 Distal	 **Extraarticular** No involvement of displaced fractures extending into the articular surface	 **Partial articular** Part of the articular component is involved, leaving the other part attached to the meta-/diaphysis	 **Complete articular** Articular surface involved, metaphyseal fracture completely separates articular component from the diaphysis

AO Principles of Fracture Management, AO Publishing, 2007

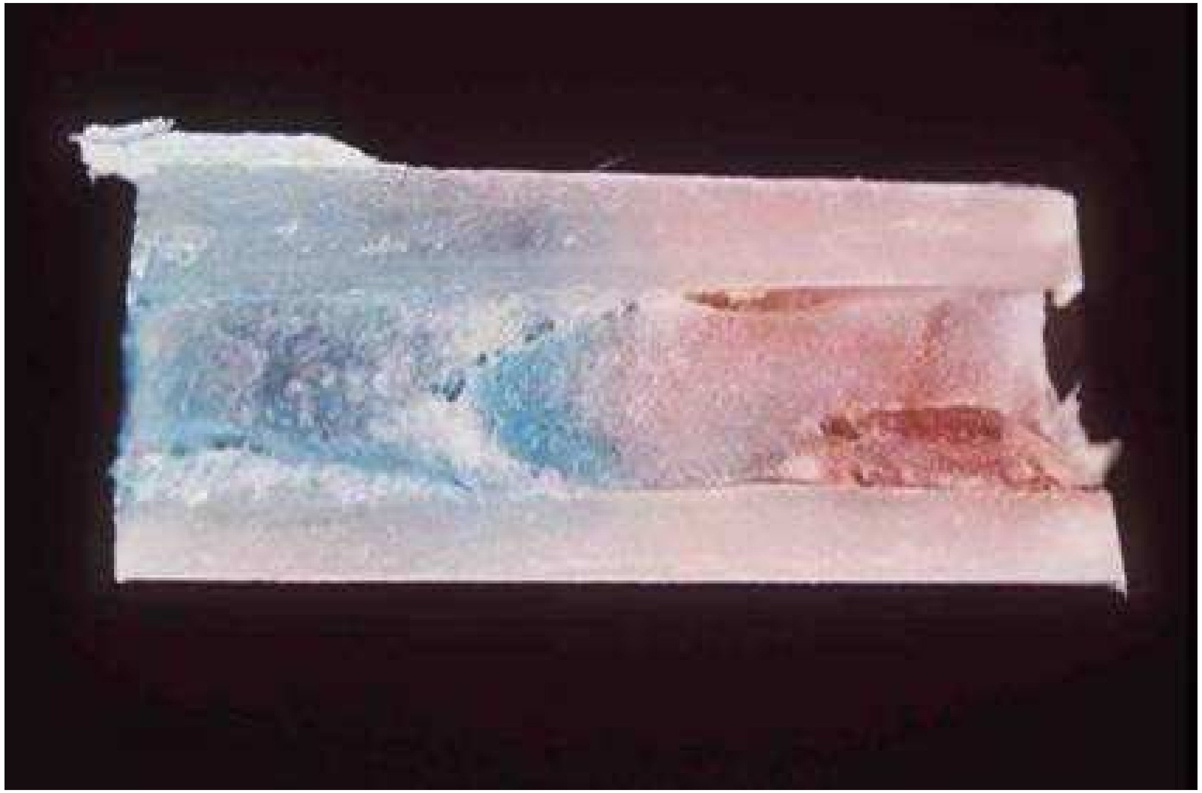
Clinical Problem: Nonunion

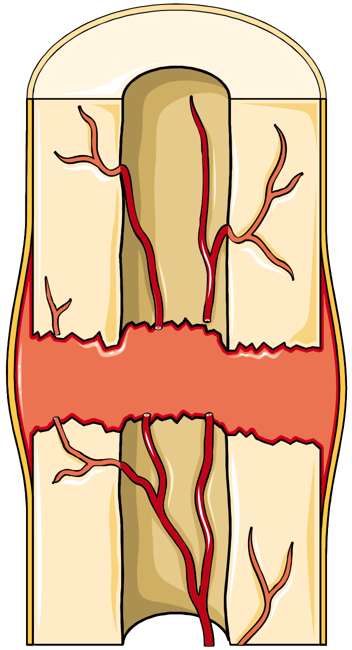
- Majority of fractures heal without difficulty.
- Nonunion rate: ~ 5-10%

Hypertrophic Nonunion	Atrophic Nonunion
• Callus formation but no bridging of fragments • Lack of mechanical stability -> stabilization	• No callus formation • Vascular or metabolic causes -> osteoinductive and osteoconductive graft -> stabilization

AO Principles of Fracture Management, AO Publishing, 2007

First reaction between fragment ends





1h after fracture, intravenous vital stain - absent in fragment ends.

Blood vessels dilate, local tissue temp. rises.
Local release of cytokines –cause inflammation - accumulation of macrophages, neutrophil granulocytes, **Mesenchymal stem cells**.

Progenitor cells arrive **from periosteum**

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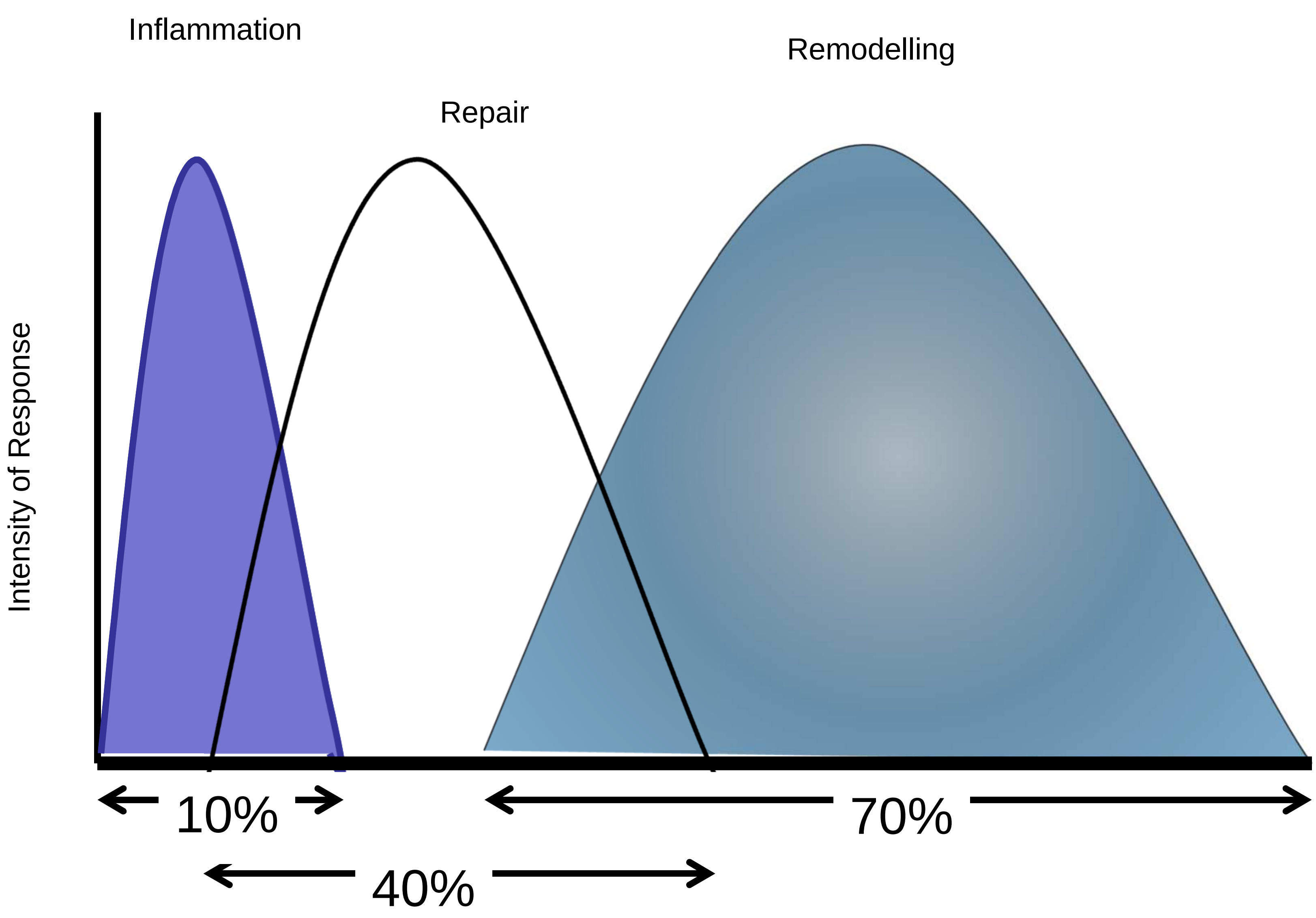
Bone Healing Response



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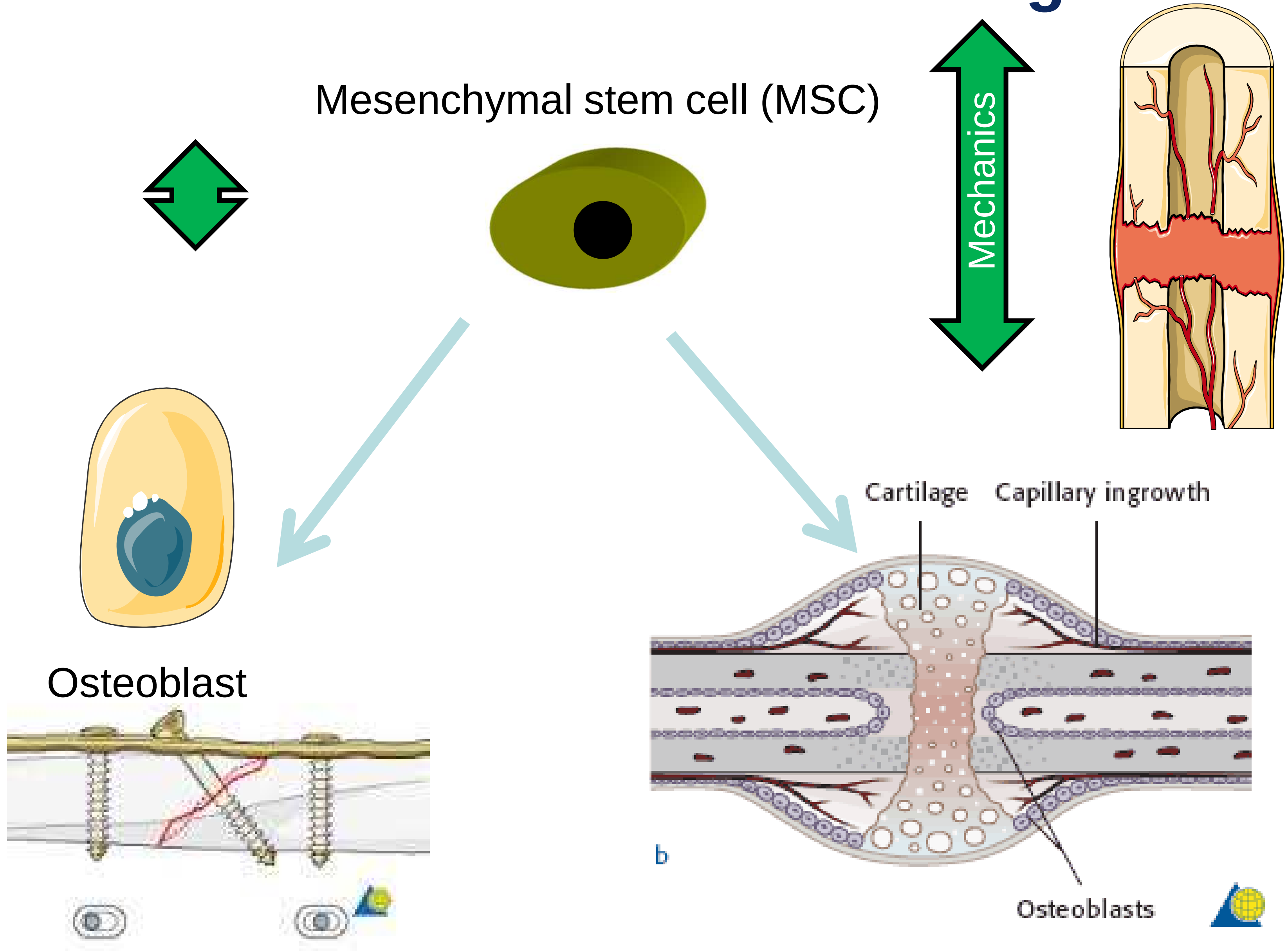
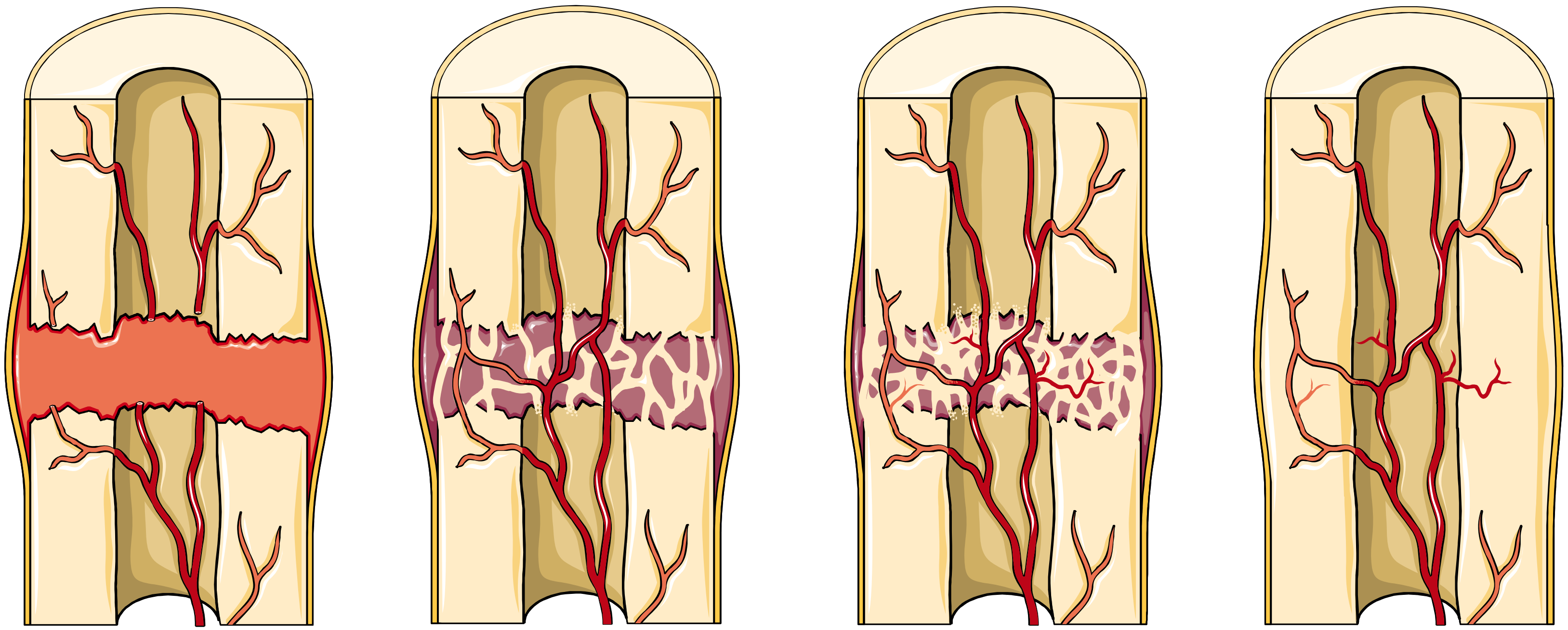
Direct versus indirect bone healing



Intramembraneous

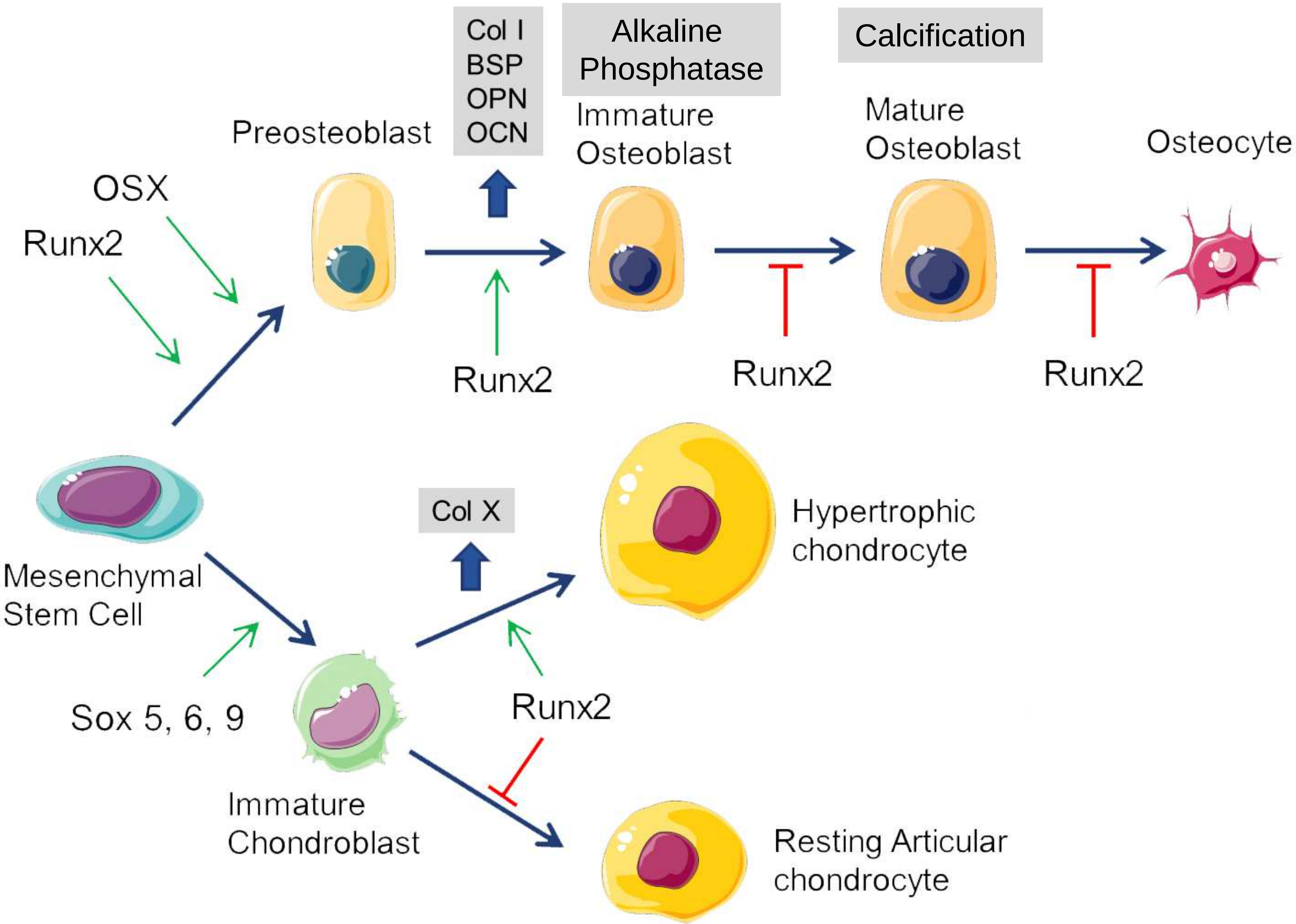
Endochondral

Indirect bone healing
Endochondral ossification



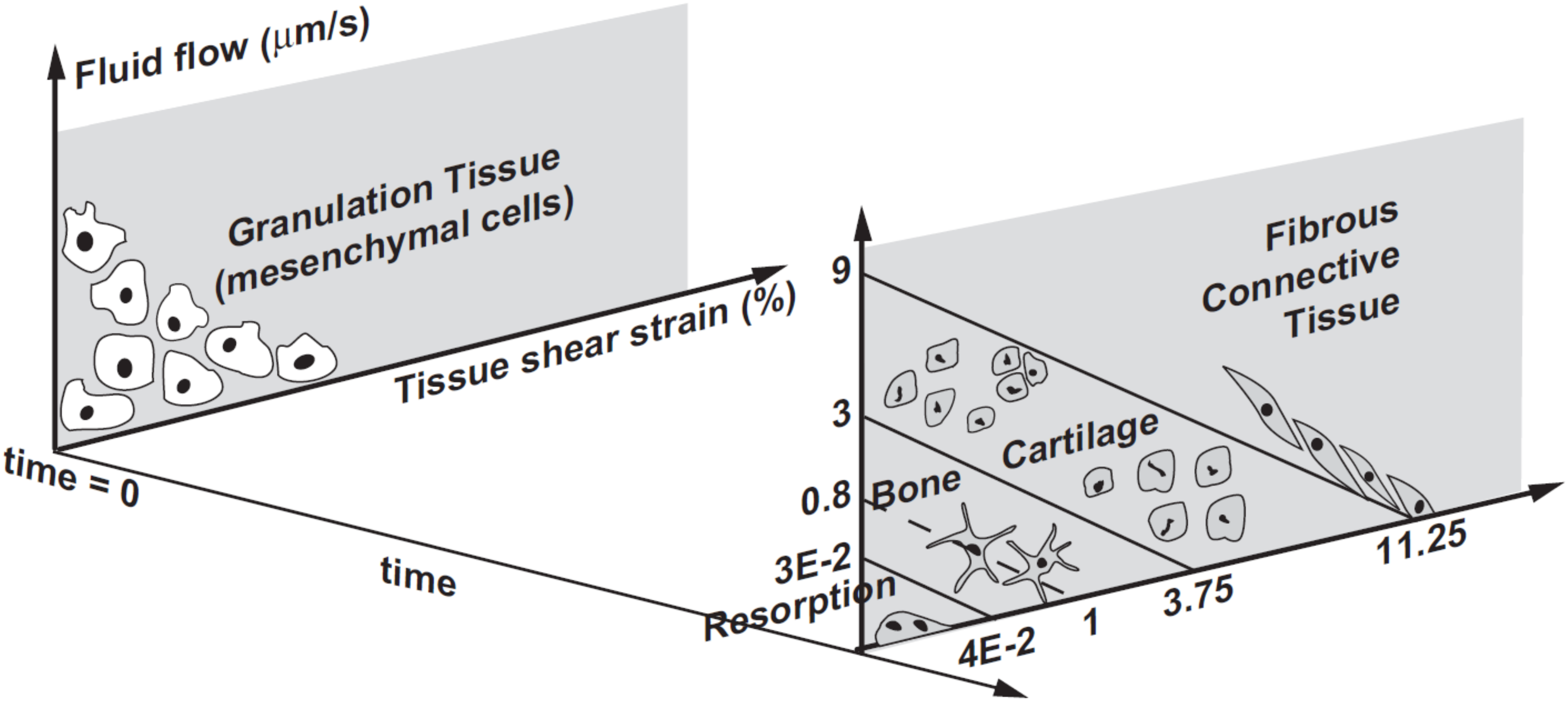
Hematoma   Cartilage callus   Calcified callus   Bony remodeling

Stem cell differentiation



Bruderer *et al,* 2014

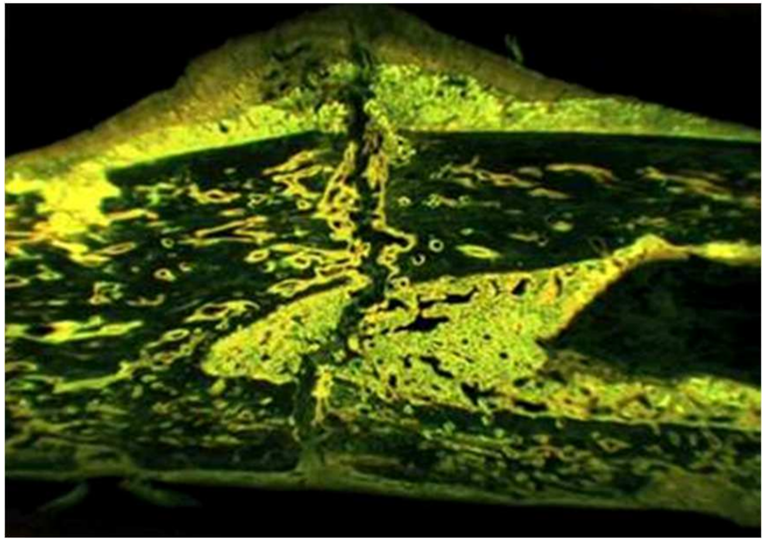
Mechanical Load- Cellular behavior

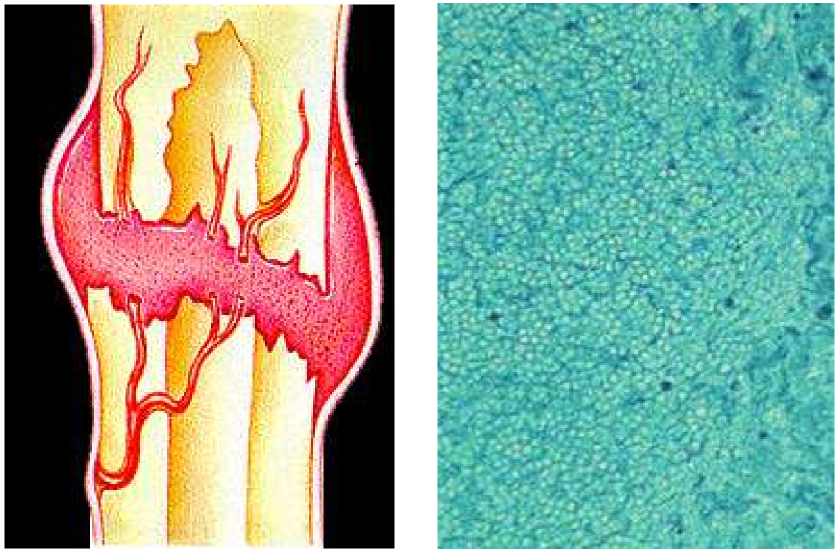


Lacroix Prendergast 2002

Indirect Fracture Healing

Differentiation cascade of interfragmentary tissues





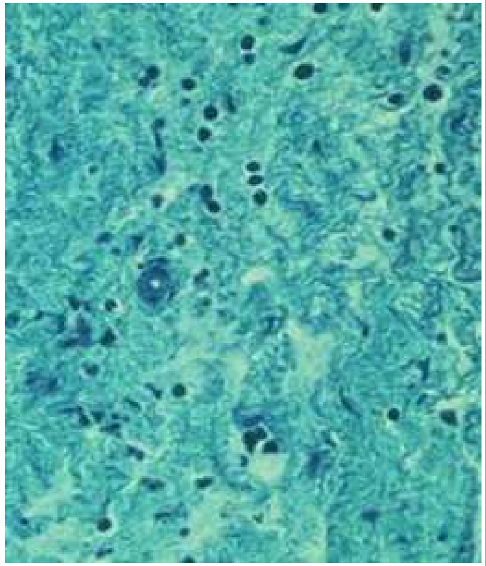
Haematoma

- Initially haematoma between fragment ends
- Negligible mechanical properties.
- Inflammatory exudation from ruptured blood vessels
- After 1 week forms granulation tissue
- Osteoclasts remove necrotic bone at fragment ends.

Indirect Fracture Healing

- Entrance of new blood vessels & initiation of trabeculae
- Matures to form connective tissue - collagen fibres & fibrin
- pain & swelling decrease
- granulation tissue differentiates to form fibrocartilage (callus) increase in stiffness

Fibrous Callus

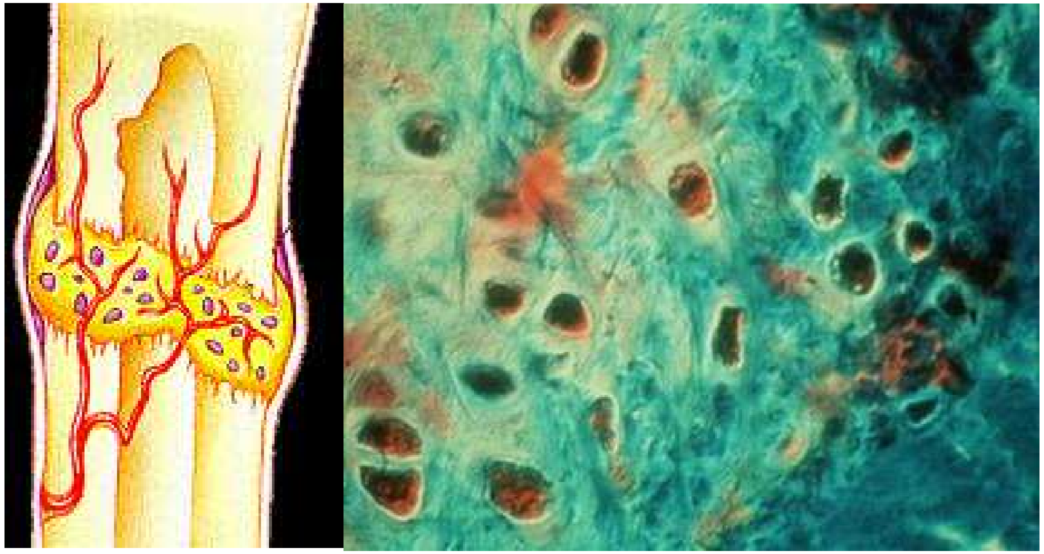


Granulation tissue

- resist interfragmentory motion ~2-3 weeks post fracture
- stability adequate to prevent shortening although angulation at fracture site may still occur.

Indirect Fracture Healing

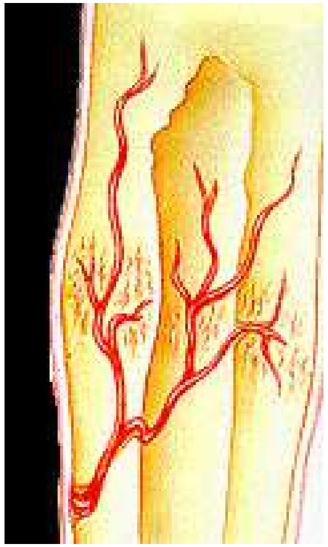
Bony Callus



- Capillary ingrowth into callus
- MSC's proliferate & migrate through callus differentiating into fibroblasts & chondrocytes producing ECM.
- Fracture ends linked together by soft callus - hard callus stage starts & lasts until fragment ends are firmly united by new bone (3-4 months).

Indirect Fracture Healing

Bone remodelling



- Fibrocartilage mineralizes (converts callus to woven bone)
- Remodeling begins once fracture solidly united with woven bone (no interfragmentary motion) .
- Woven bone slowly replaced by lamellar bone through surface erosion & osteonal remodeling (few months to years).
- Further bone deposition combined with local resorption leads to trabeculae reshaping until the bone returns to original morphology.

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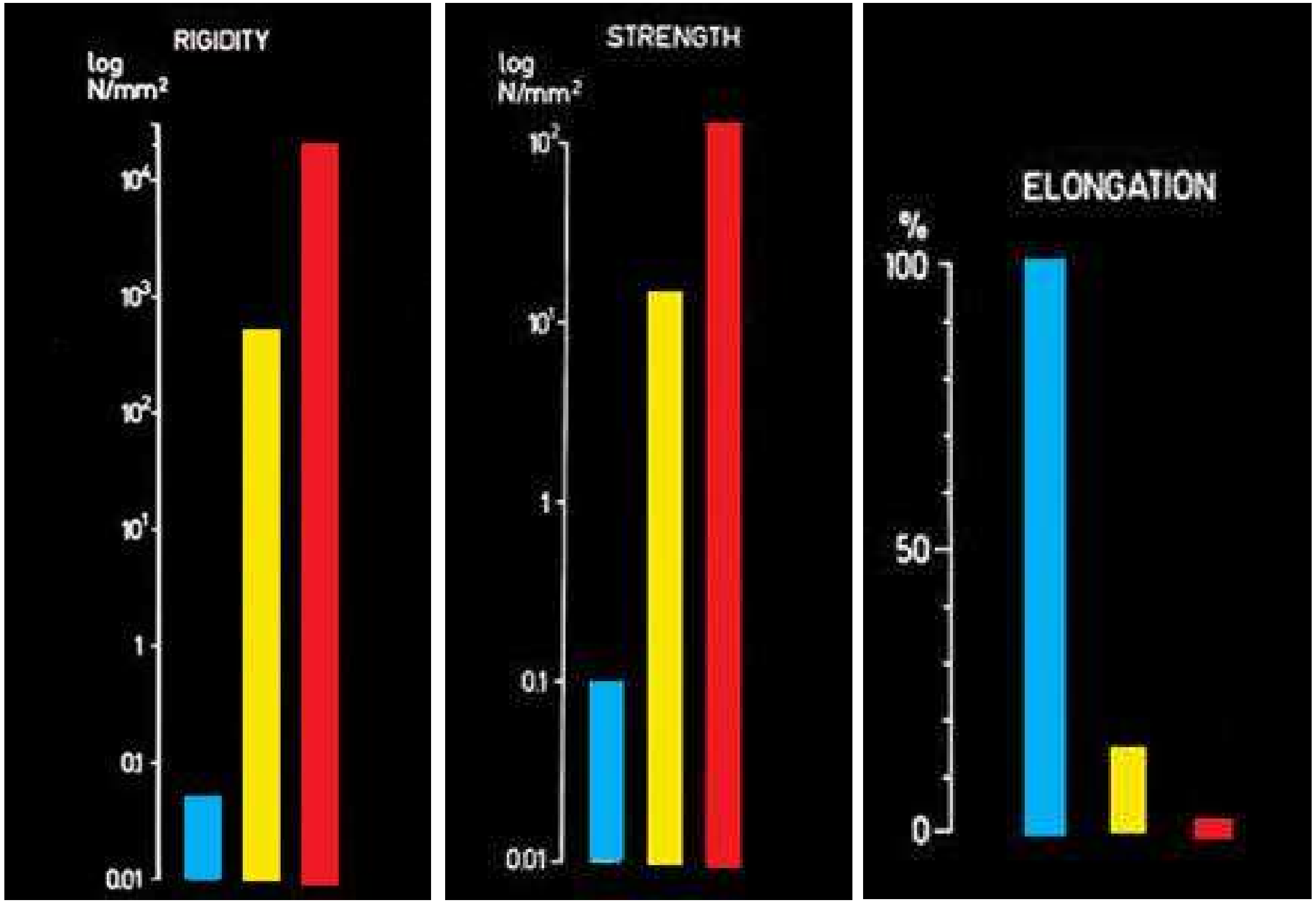
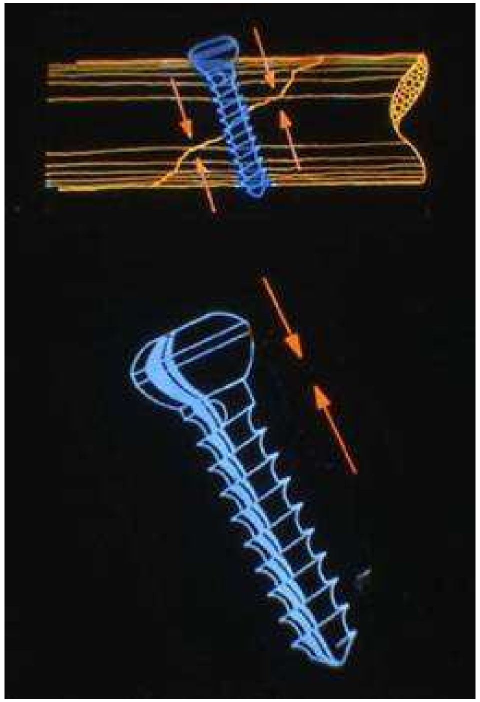
Changes of mechanical properties during maturation

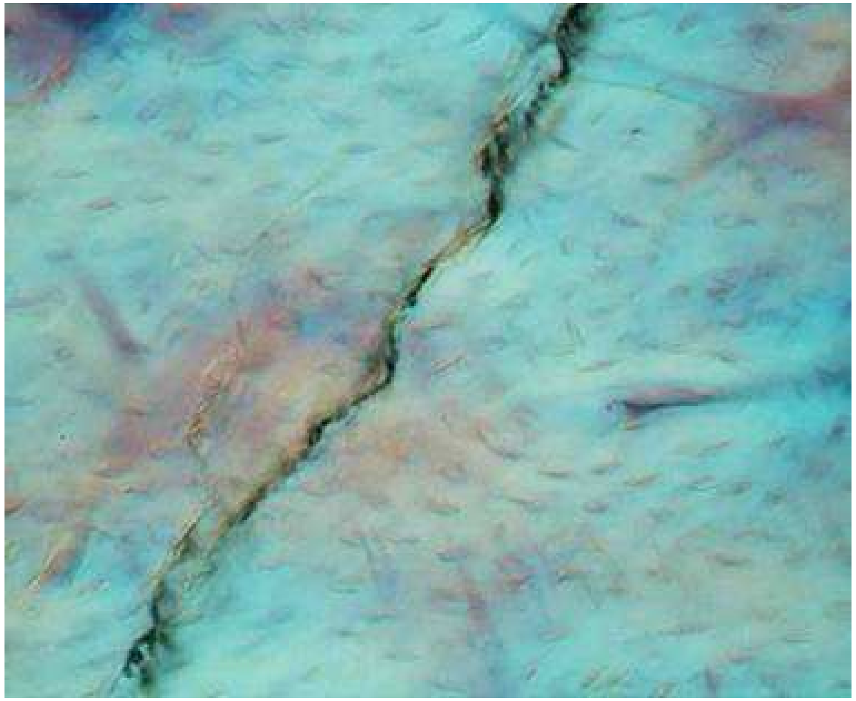


Bone
Cartilage
Granulation tissue

During healing different tissues replace each other over time gradually increasing in stiffness & strength & reducing in tolerance to deformation

Direct Fracture healing
Alignment of fragment ends

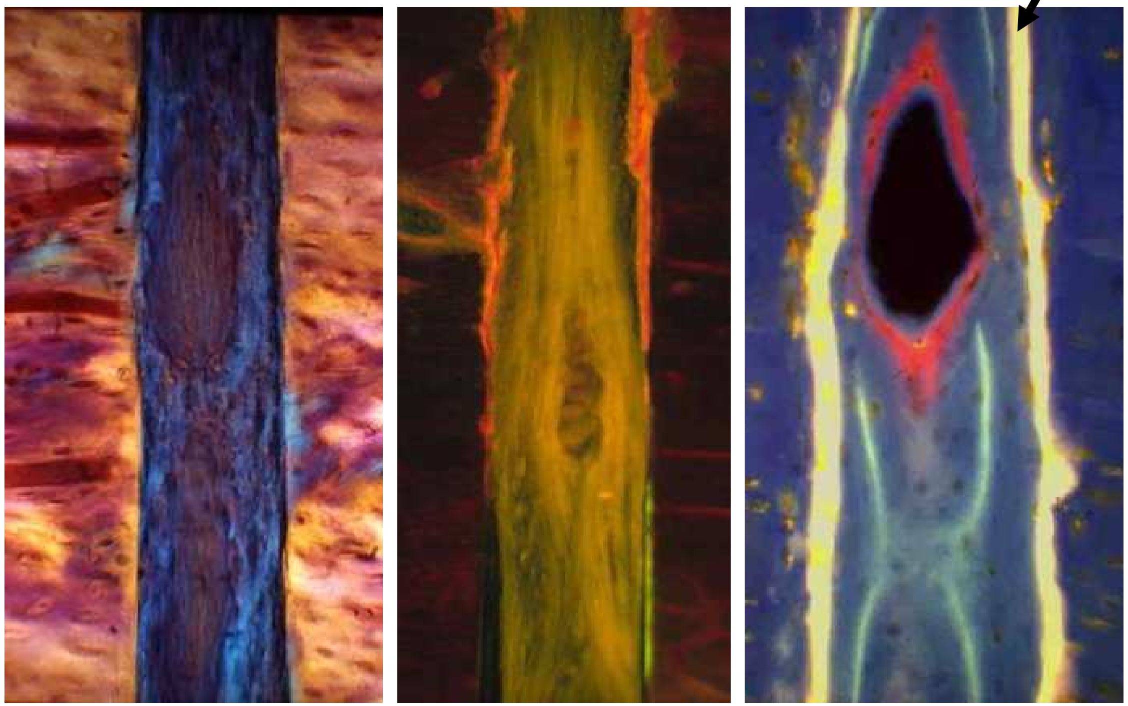


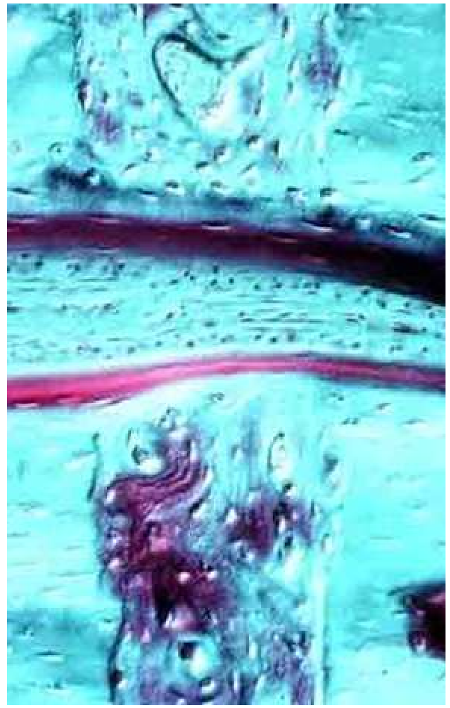


Anatomical alignment of fragment ends –aims to heal in a good position with minimal displacement of fragments.

Direct formation of lamellar bone in immobilised gap

High remodeling of fragment ends
initial disturbed blood supply

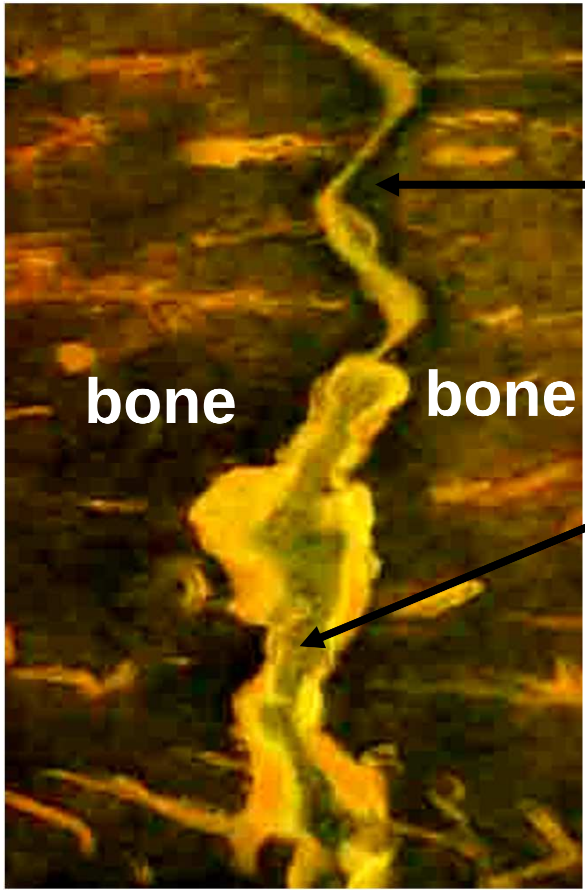


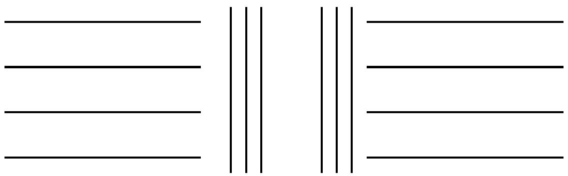


Capillary ingrowth into gap
Bone formation at capillary
yellow- new bone

- Osteon crossing filled gap,
- Remodels the 90° axis bone
- Connects fragments with lamellar bone at correct axis

Contact and gap zones





Even a **perfectly reduced fracture** has irregular surfaces and this creates gaps between fragments.

- Gap immobilized
- Capillary ingrowth into gap
- Deposition of lamellar bone on fracture ends at 90˚ to bone axis
- Gap fills -cutter cone remodels to correct orientation.
- No 2˚ healing –no fibrocartilage etc.

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Direct healing

SLOW!!

If you rigidly fix with too large a gap = risk of non union/ plate failure

Fixation	Healing method
Compression	Direct
Splinting	Indirect

Rigidity

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Summary

- Pattern of fracture healing depends upon mechanical situation at fracture site.
- Healing passes through different tissue stages with decreased deformability & increased stiffness & strength.
- If no stability provided by treatment, healing has to undergo all stages of tissue differentiation.
- If treatment provided stability, callus formation is minor & healing stages abbreviated.


16.08.2013
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Spirit of Davos

Conference Chair: R. Geoff Richards
Conference Program Chair: Mauro Alini

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Thank You