please click on the following link to watch the lecture online:

https://www.youtube.com/watch?v=Fu49OrYxdlg

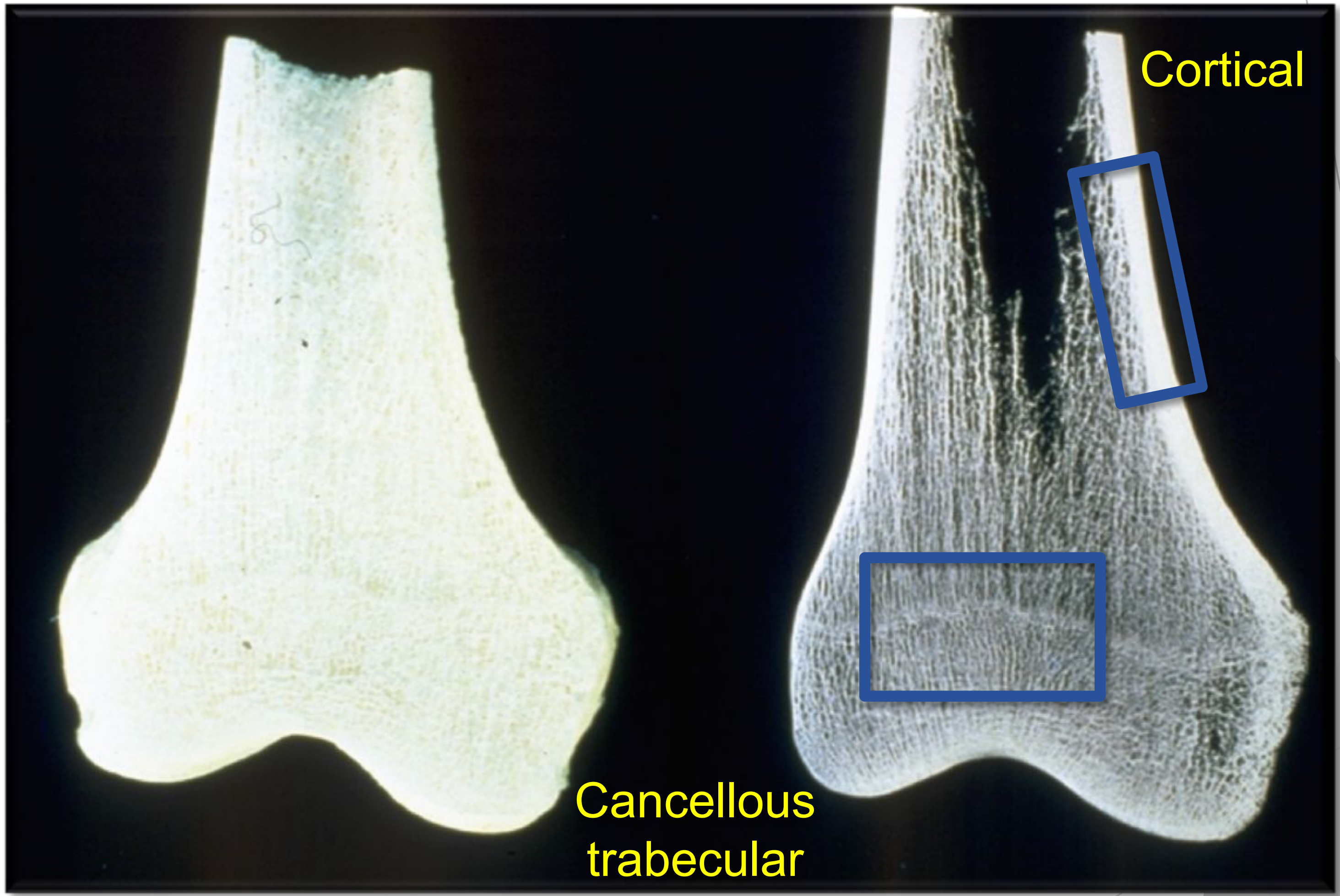
Biology Of Bone Healing

Dr Saad Al-Edwan

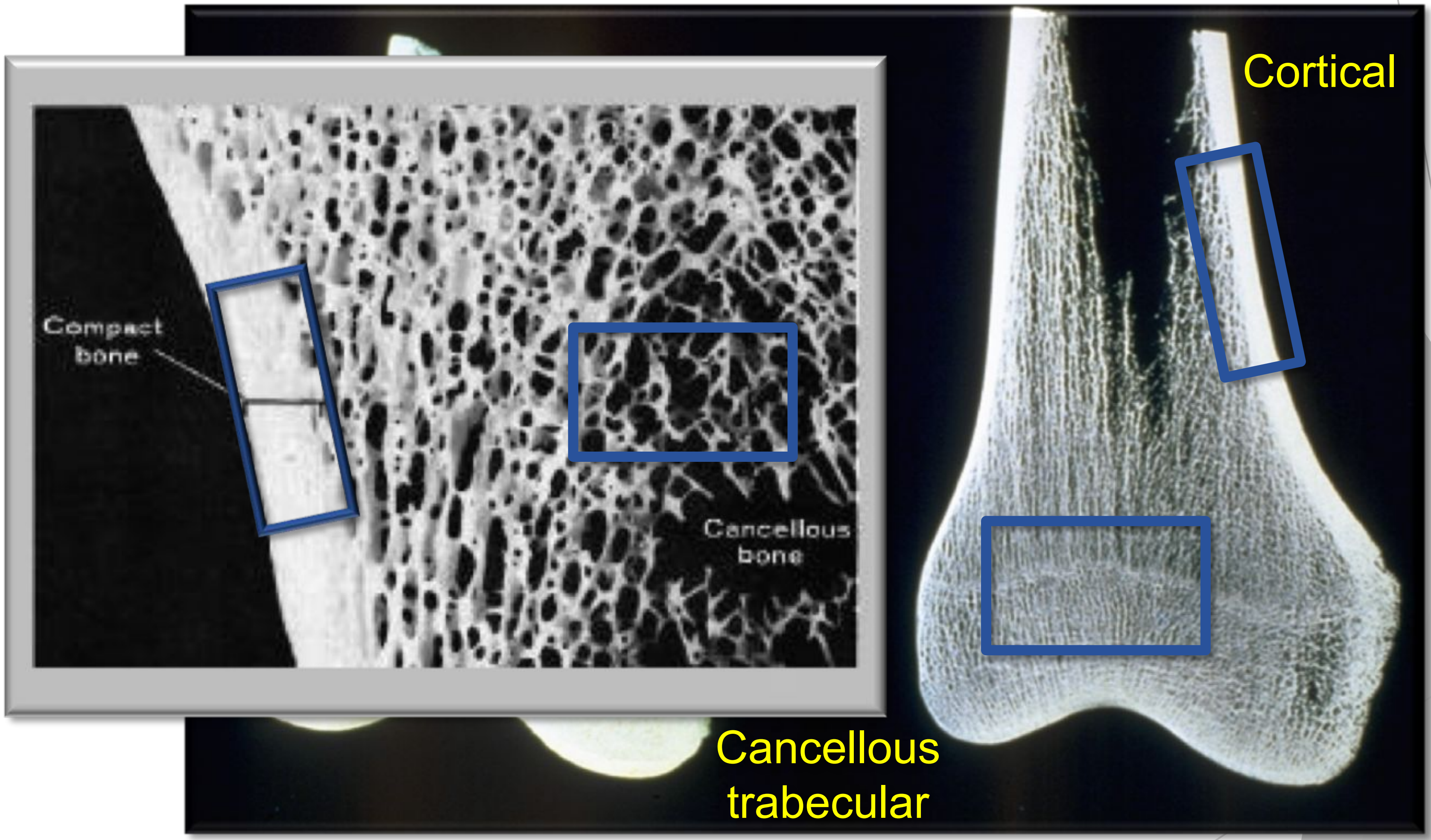
Learning objectives

- Explain the different processes of bone healing and review direct and indirect bone healing
- Describe the factors that influence the healing process and those that may lead to delayed union or nonunion
- Recognize the importance of soft tissues for bone healing
- Discuss the effects and influence of osteosynthesis on the bone and its healing process

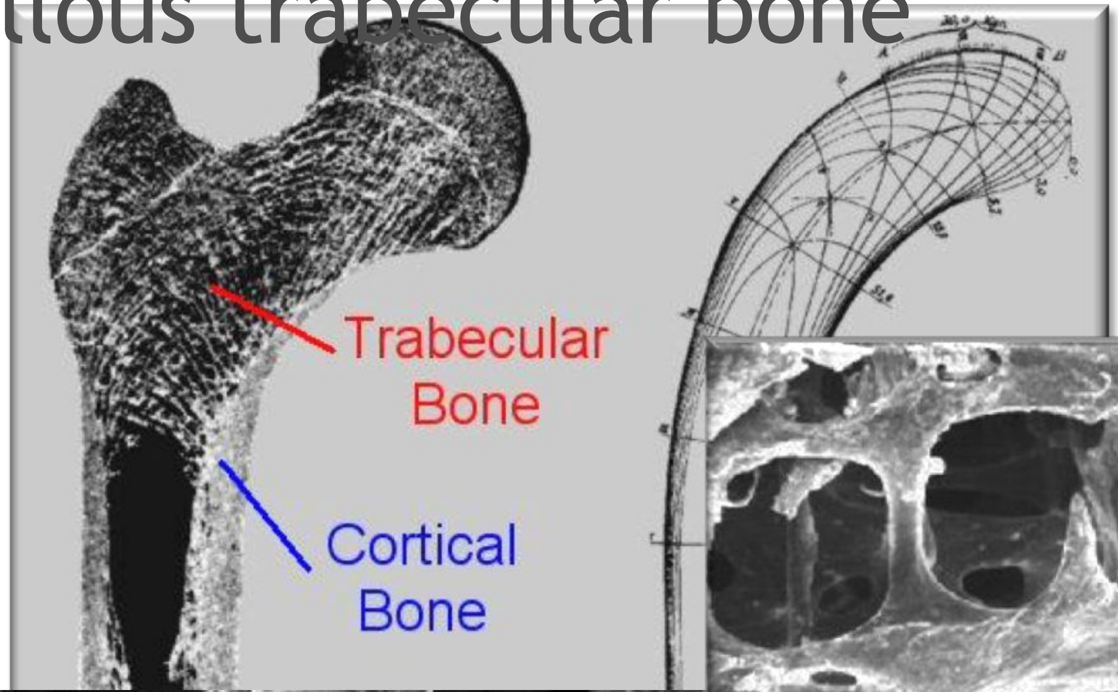
Bone structure

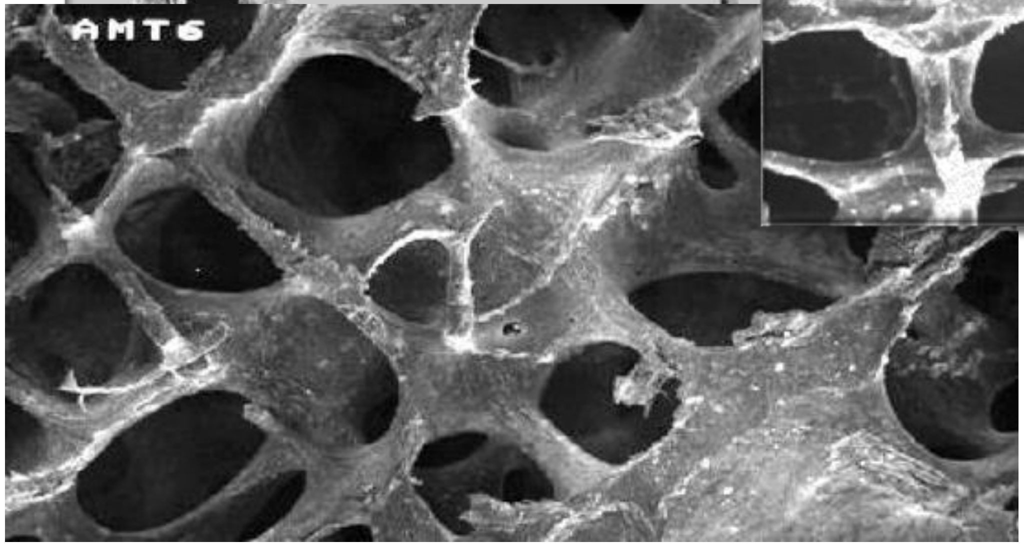


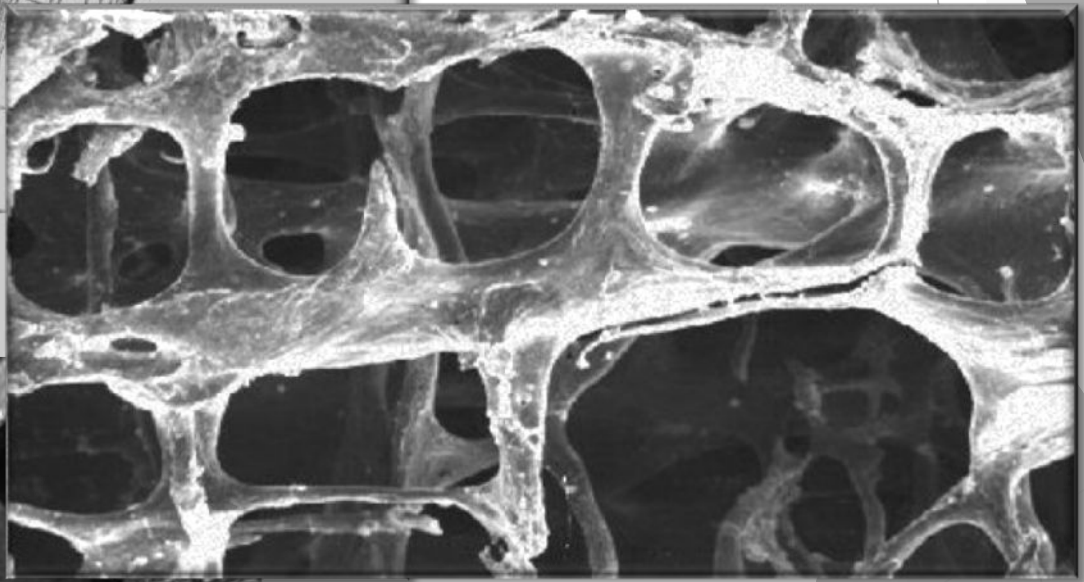
Bone structure



Cancellous trabecular bone

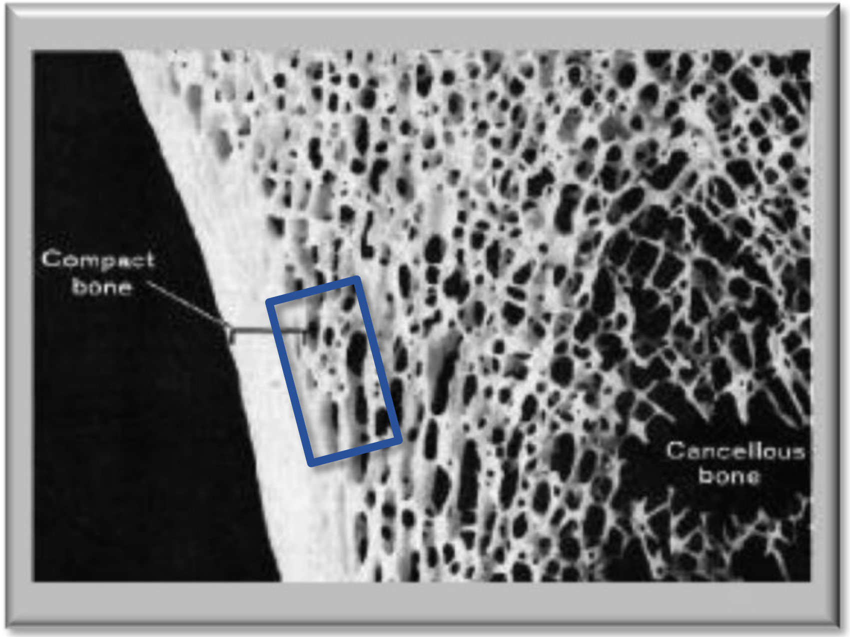


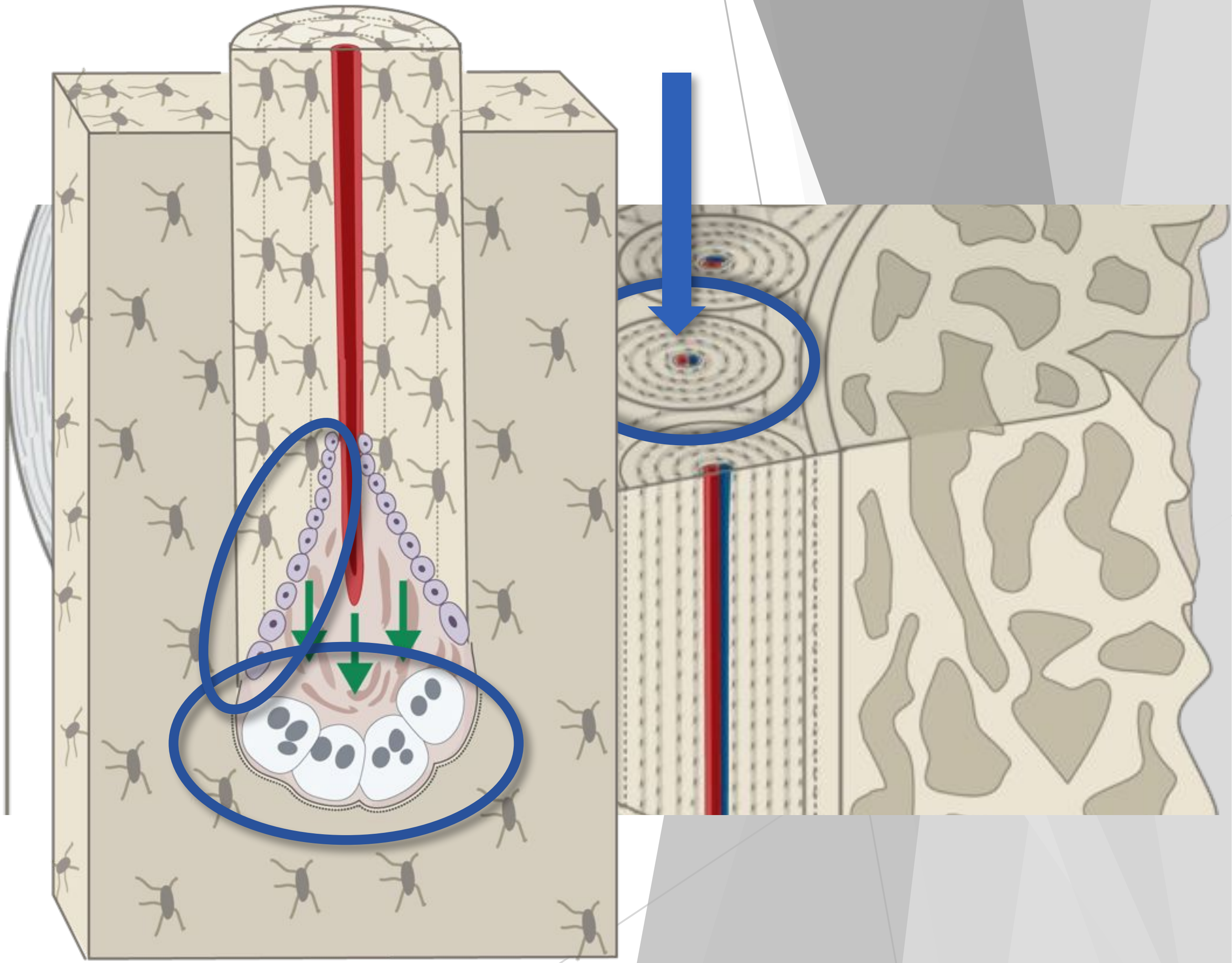




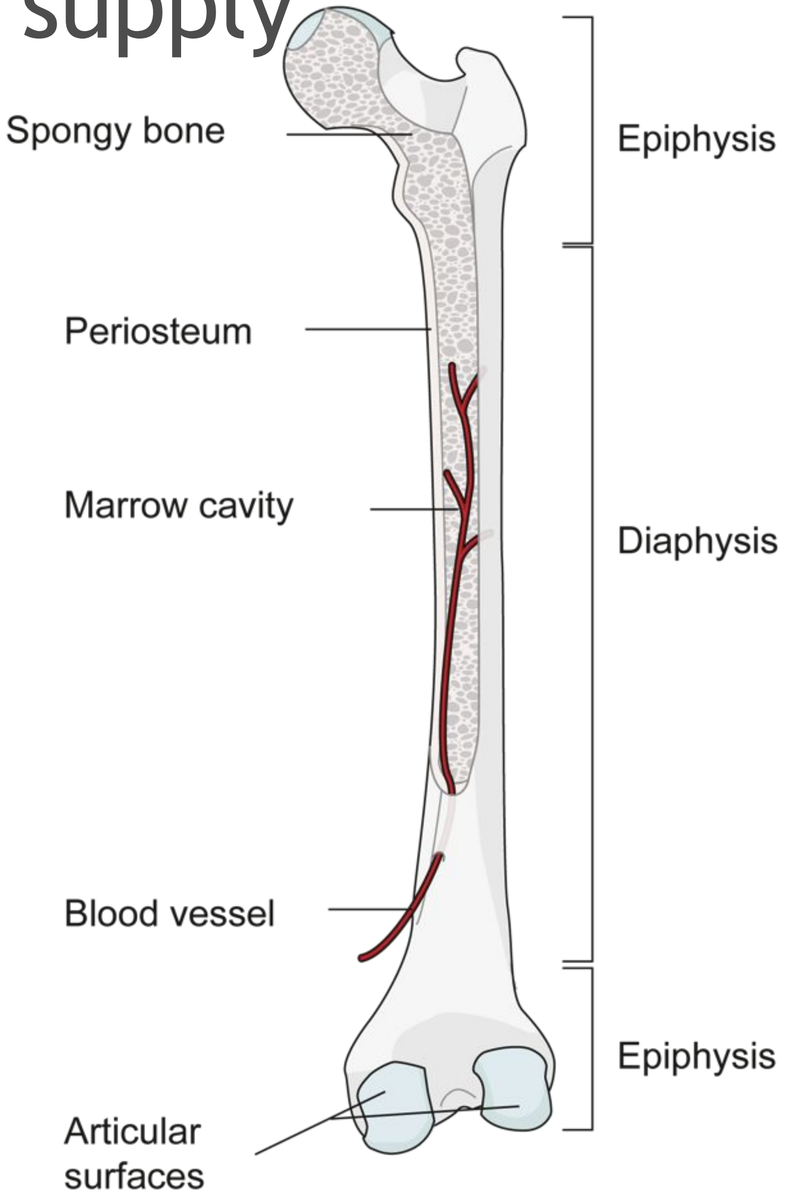
Cortical bone

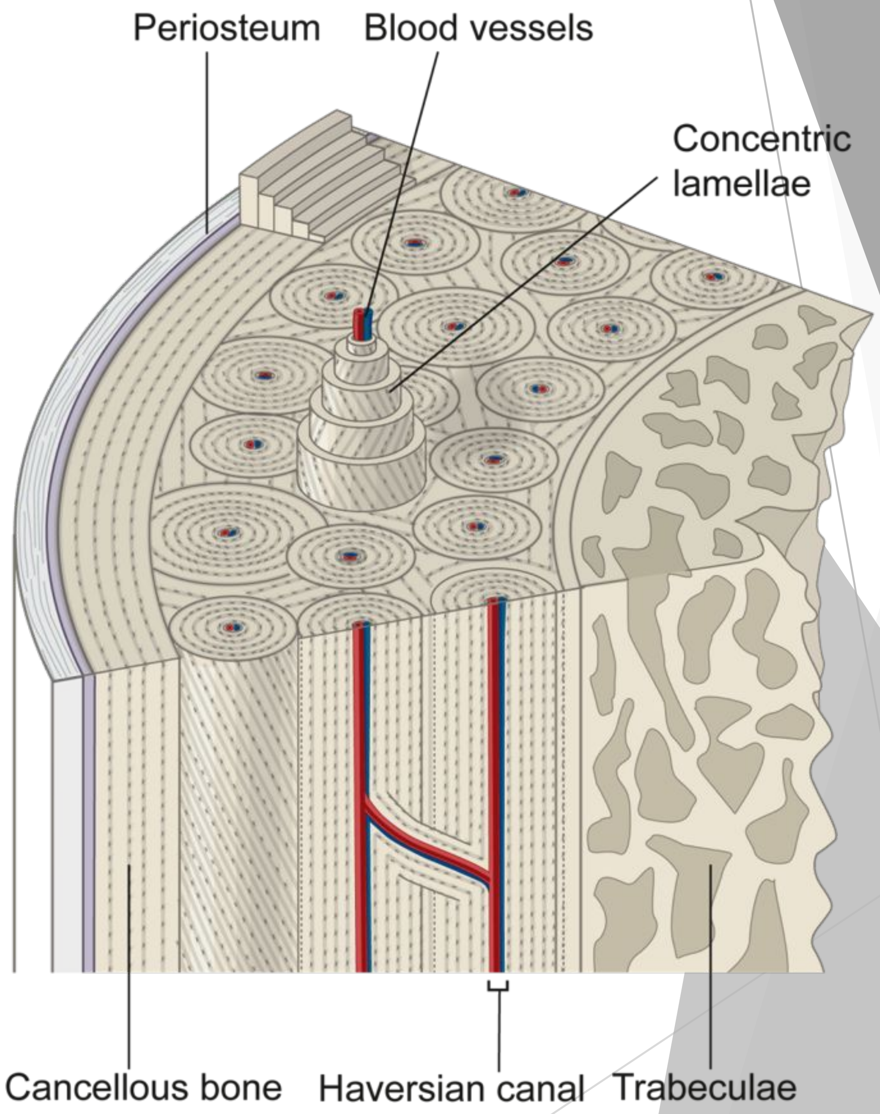
- Made up of osteons
- Continually remodelled by cutting cones



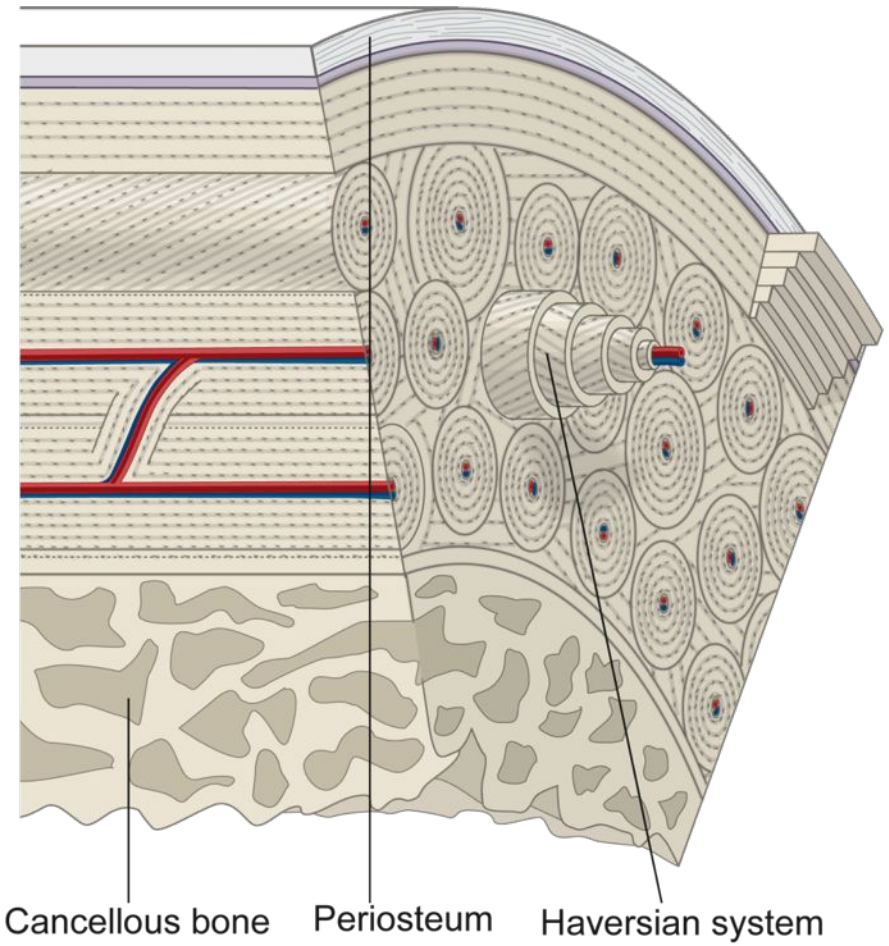


Blood supply





Bony anatomy

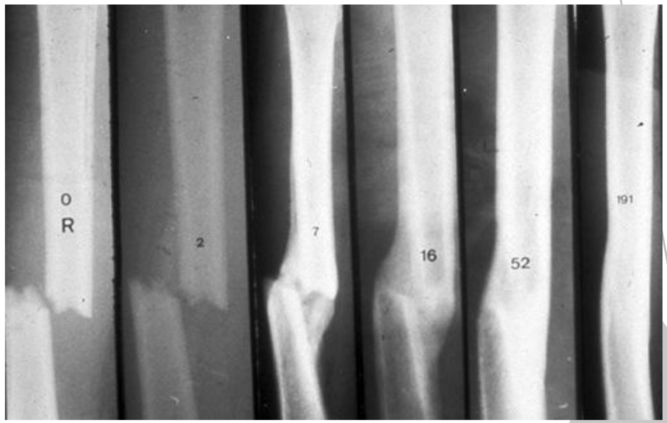


Different types of bone healing

Bone healing—definitions

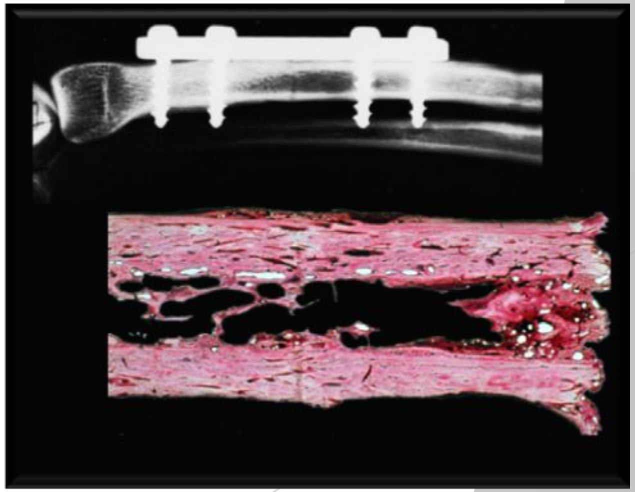
Radiological

Visible callus formation



Indirect healing

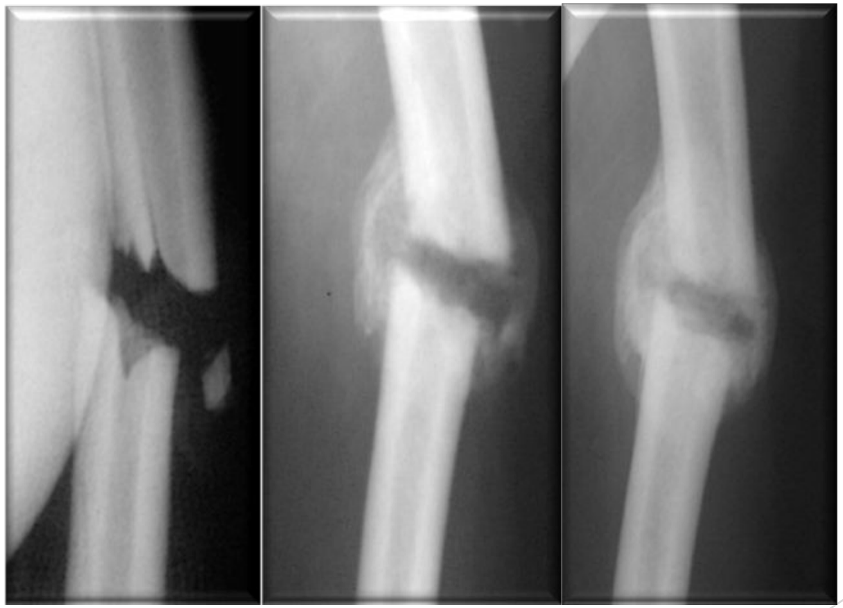
No visible callus formation



Direct healing

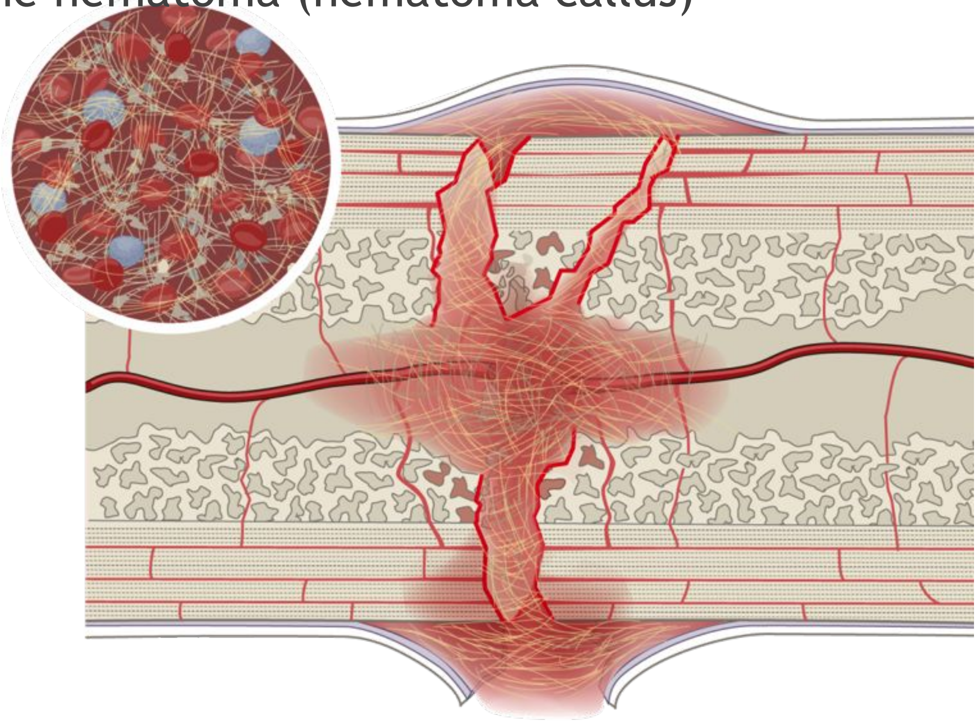
Bone healing—callus

- Left alone, a broken bone will heal by callus formation
- Callus is the natural response of living bone to interfragmentary movement



Indirect bone healing—inflammatory phase

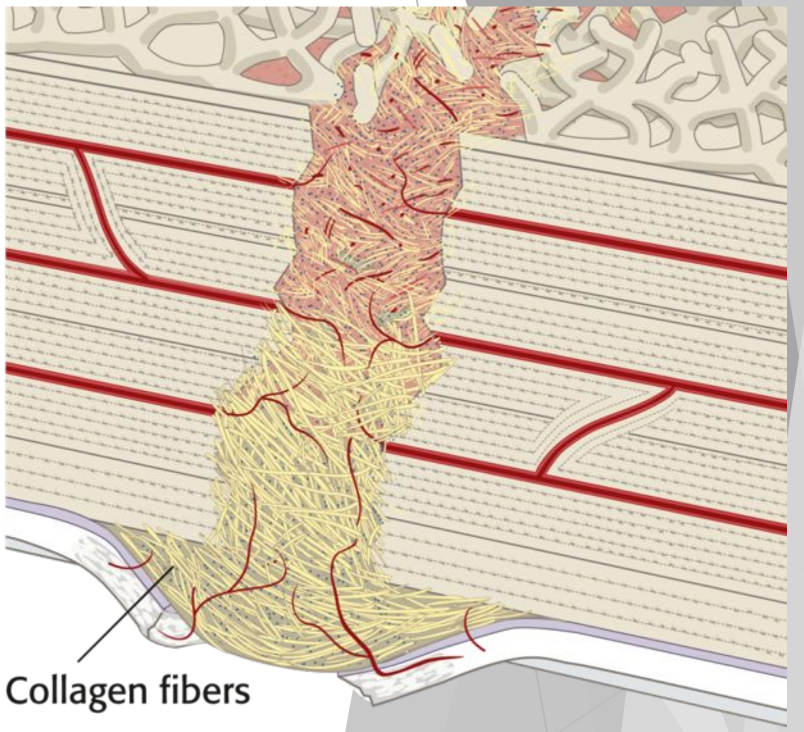
- Coagulation
- Fibrin fibers stabilize the hematoma (hematoma callus)



Indirect bone healing—granulation phase, soft callus

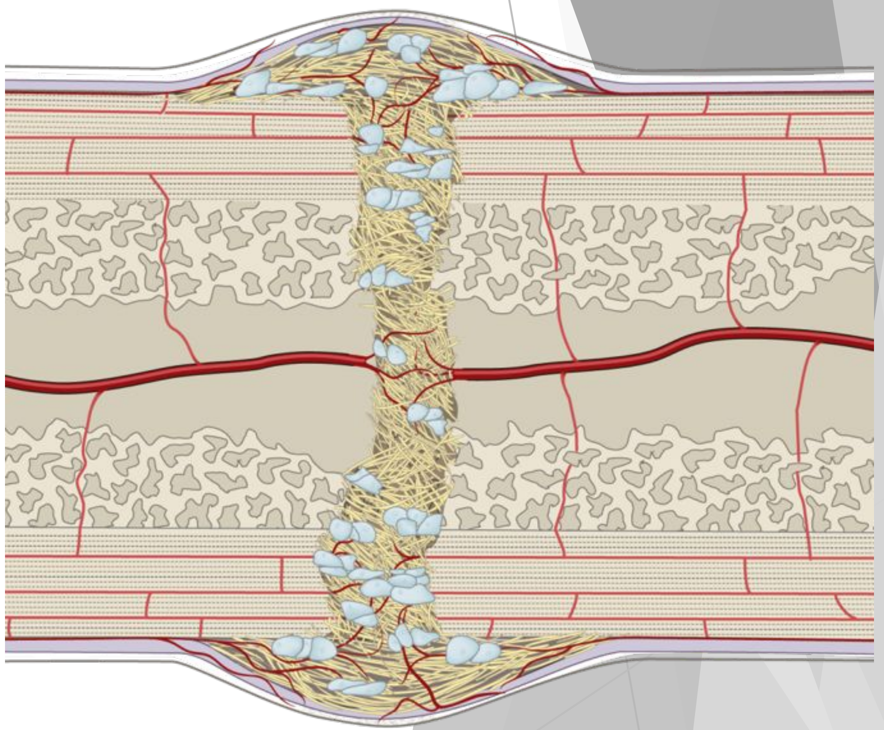
Natural bone healing process begins with soft callus:

- New blood vessels invade the hematoma
- Fibroblasts, derived from the periosteum, colonize the hematoma
- Fibroblasts produce collagen fibers (granulation tissue)
- Collagen fibers loosely link the bone fragments



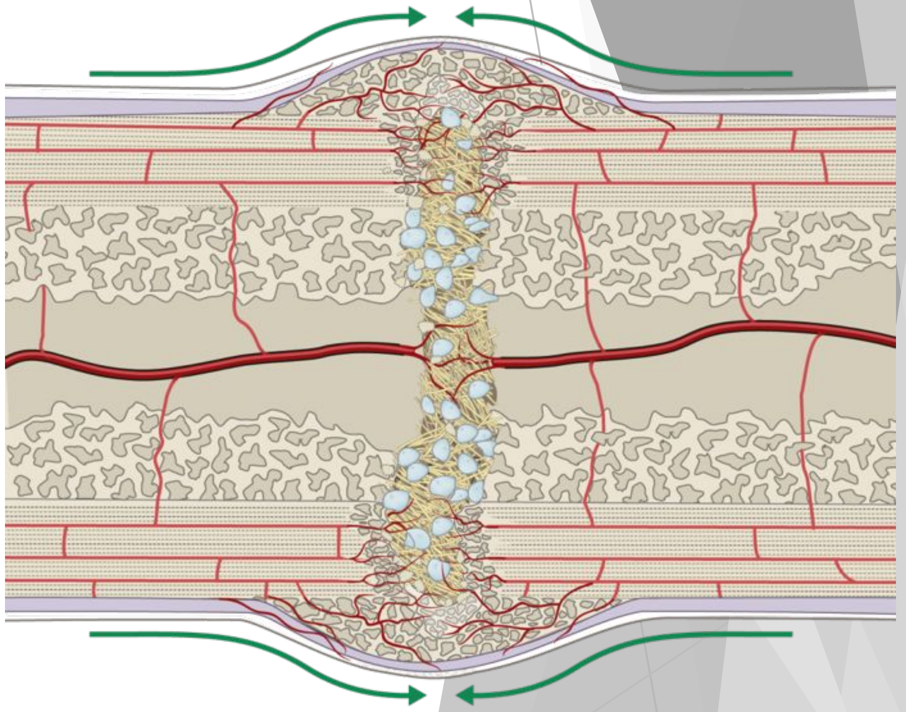
Indirect bone healing—granulation phase, soft callus

- Granulation tissue gradually differentiates into fibrous tissue, and subsequently fibrocartilage



Indirect bone healing—granulation phase, hard callus

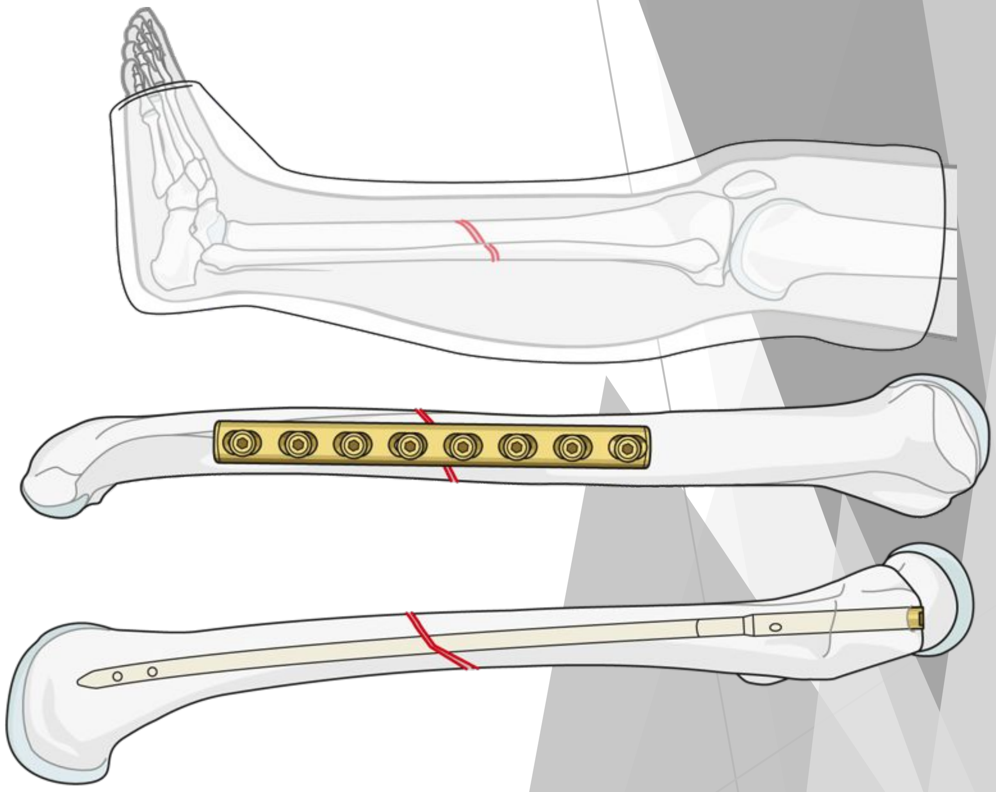
- Hard callus stage starts and lasts until the fragments are firmly united by new bone (3–4 months)
- Endochondral ossification forms spindle-shaped bone cuffs
- Starts at the periphery and moves toward the center, further stiffening the healing tissue



Micromotion—Strain theory

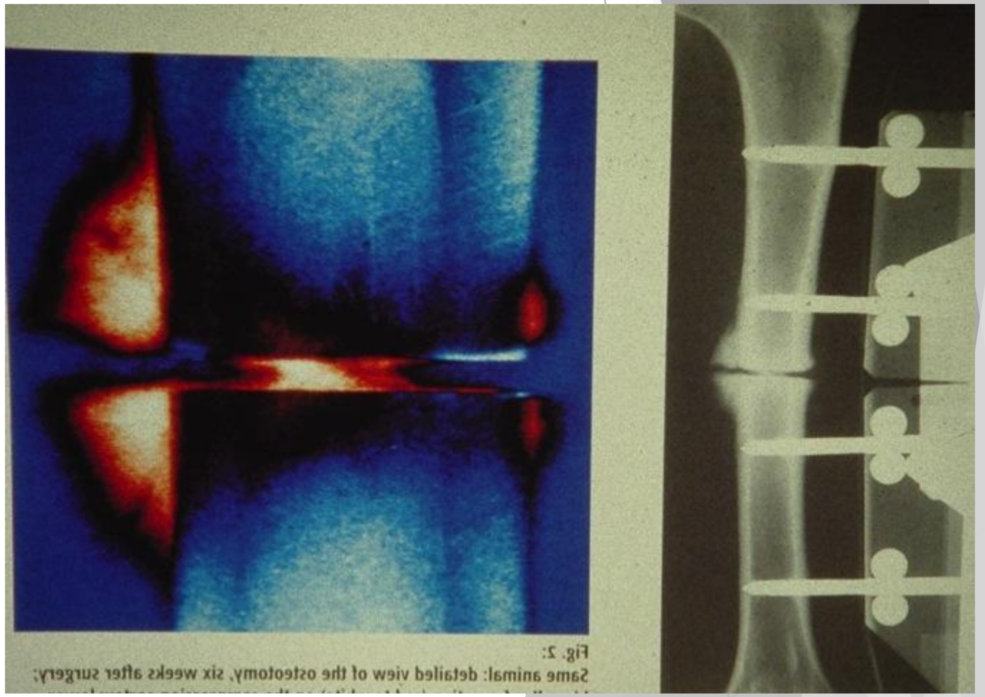
- Load applied to a material produces stress within the material and results in deformation (strain)

- Following a fracture, any motion of one main fragment relative to the other is projected to the fracture zone



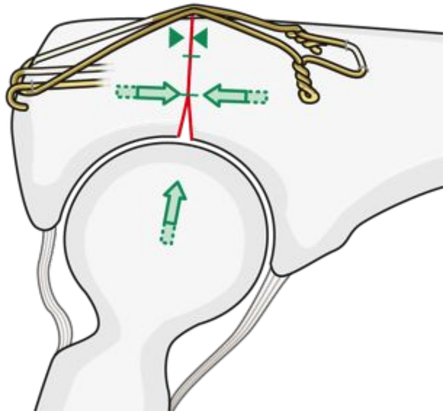
High strain in small gaps

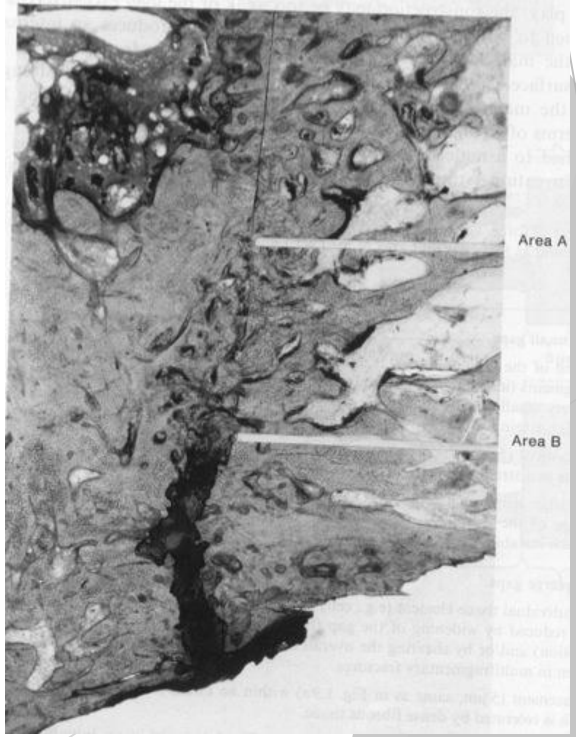
- If only two fragments are involved, the sum of all motion will be projected into the single fracture gap
- Motion amplitudes will limit the capacity of the soft repair tissue (hematoma ¤ collagen ¤ soft callus) to withstand shear and dislocation forces
- If the “strain” on the tissue is too great, tissue integrity is disrupted



Strain

- Strain itself is considered to be an inductor of callus formation (compare embryologic tissue growth)
- With the formation of tissues of increasing stiffness, the overall stability increases
- Different healing qualities may exist simultaneously

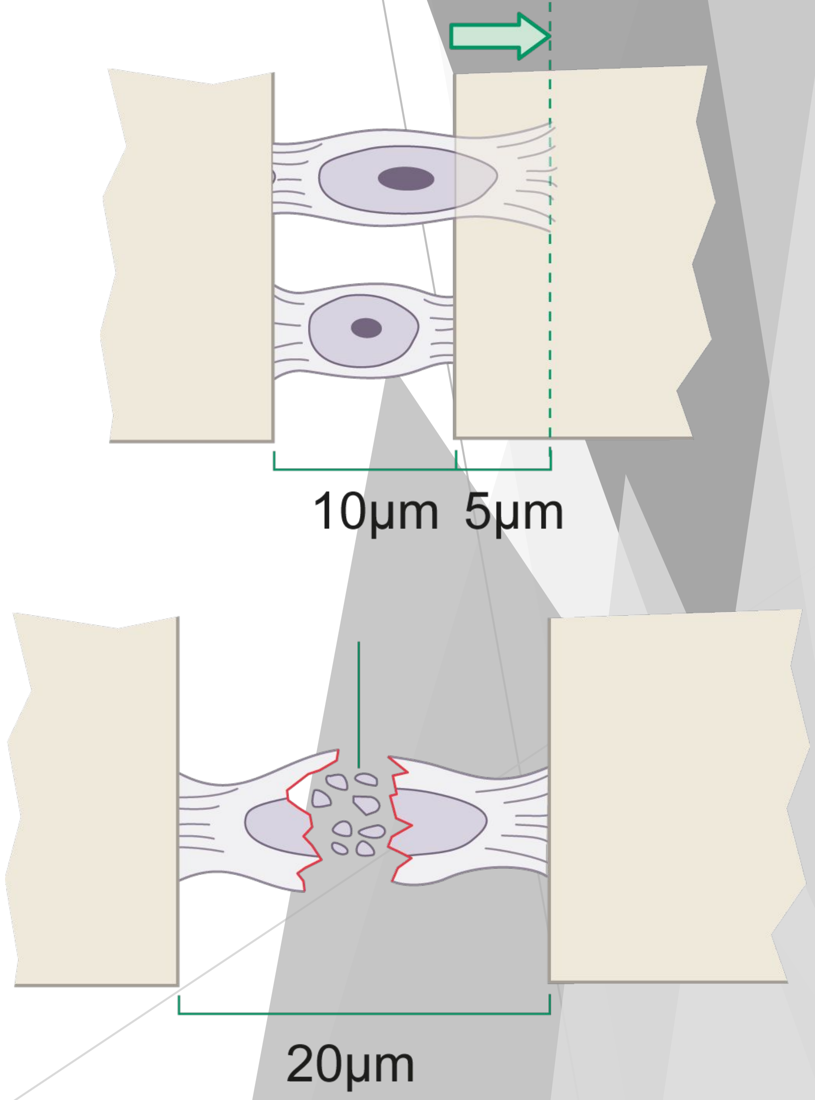




High strain in small gaps

- In a minute gap with only few bridging cells, any micromotion not contained by absolute stability will exceed strain tolerance of the tissues involved and the cell structure is destroyed

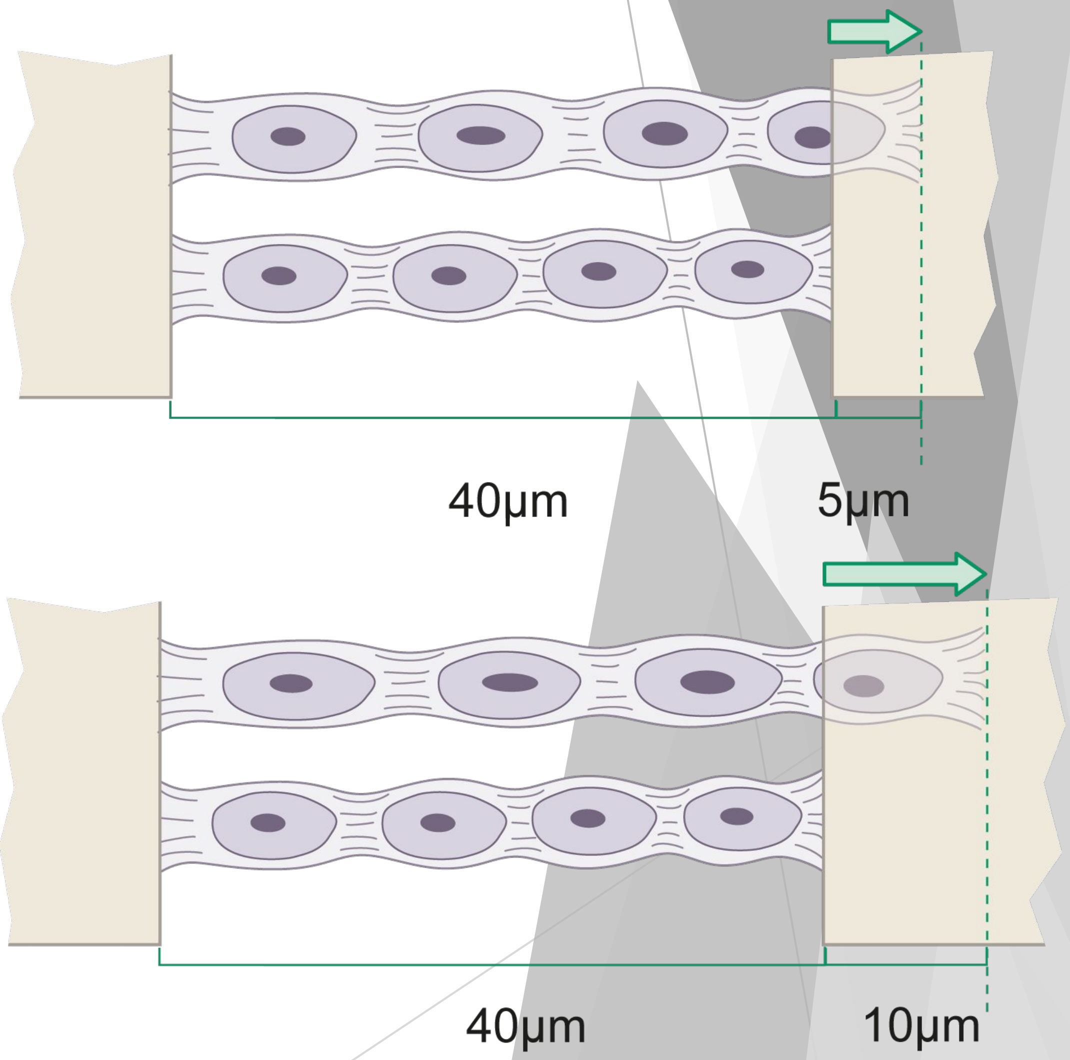
- Tissue specific strain tolerances:
  - Granulation tissue: 100%
  - Lamellar bone: 2%



Low strain in large gaps

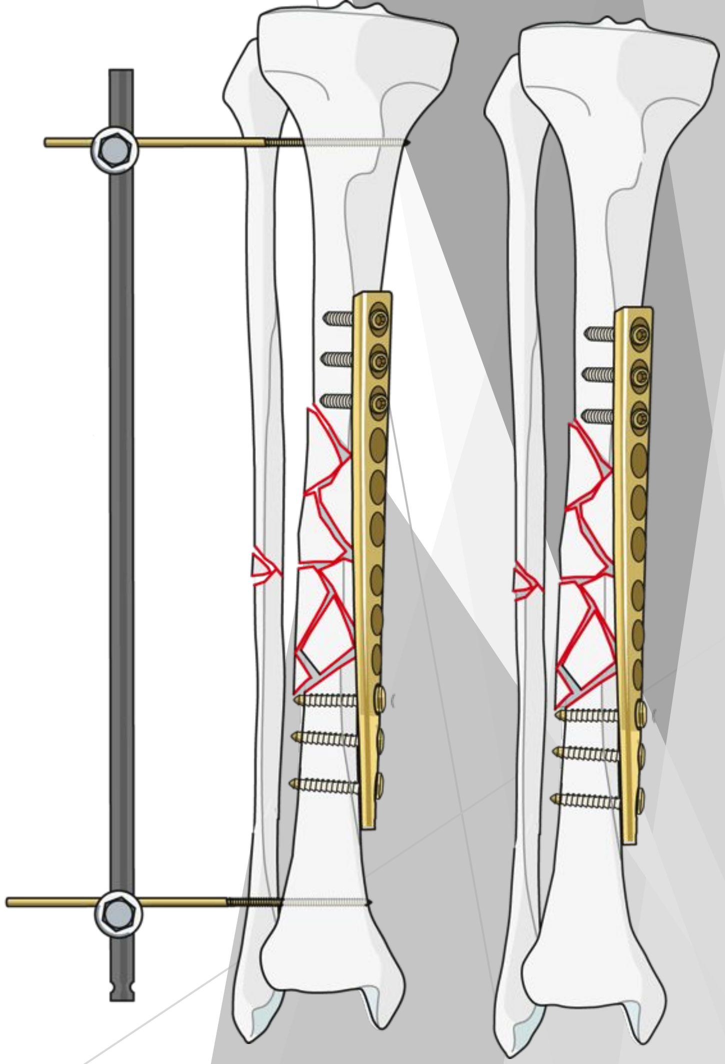
- If the gap is widened (by bone surface resorption), the strain is shared by many more bridging soft-tissue elements and fragment motion does not create an intolerable strain on individual cells

- In larger gaps, **the strain on individual cells is reduced**

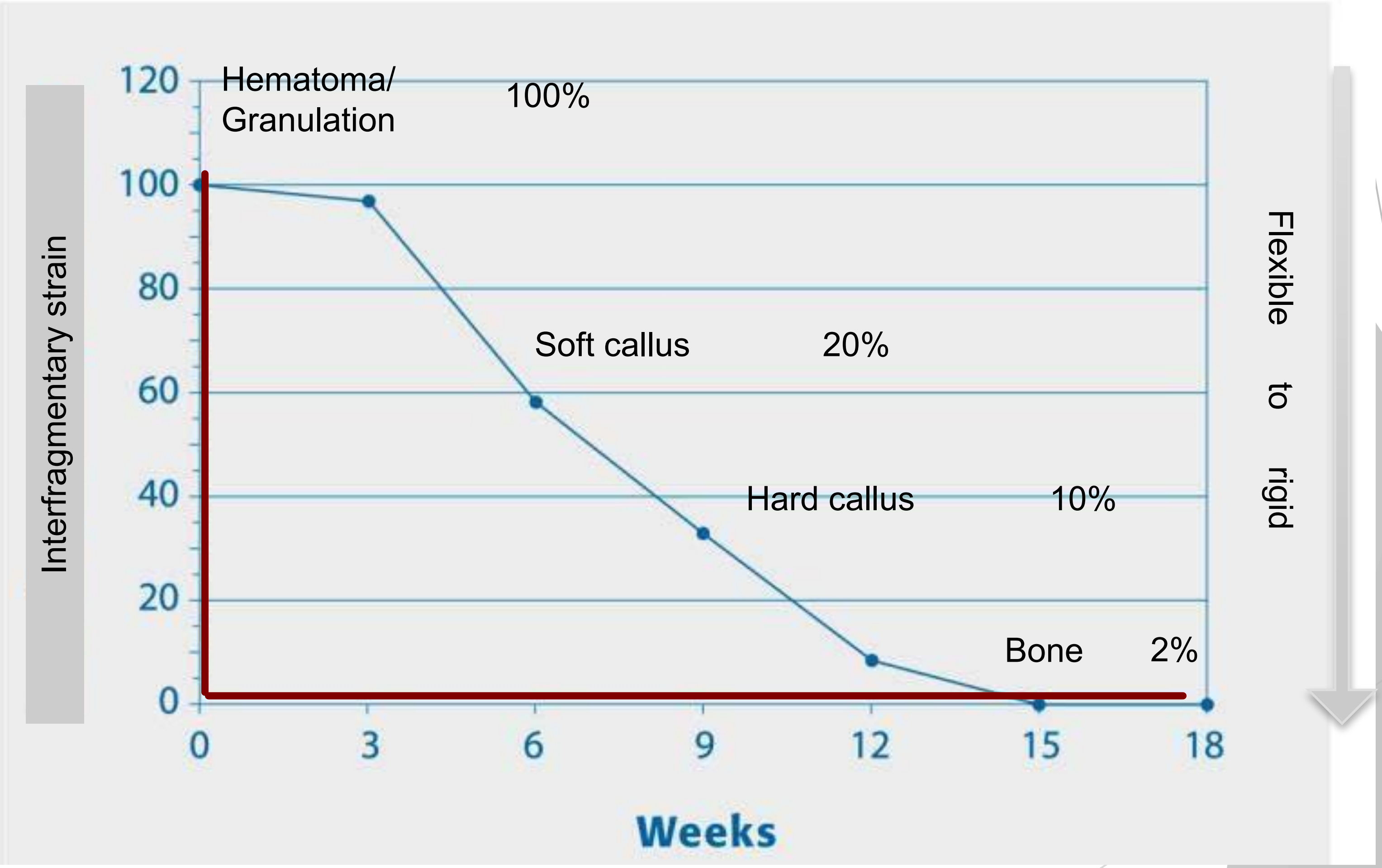


Strain

- This phenomenon explains why strain sharing permits multifragmentary fractures to heal well
- Multiple serial gaps share the overall displacement, and callus induction occurs despite relatively high total motion
- Different strains in different gap sizes also explain why various tissues, ranging from loose connective and fibrocartilage tissue, may exist simultaneously



Mechanobiology of bone healing



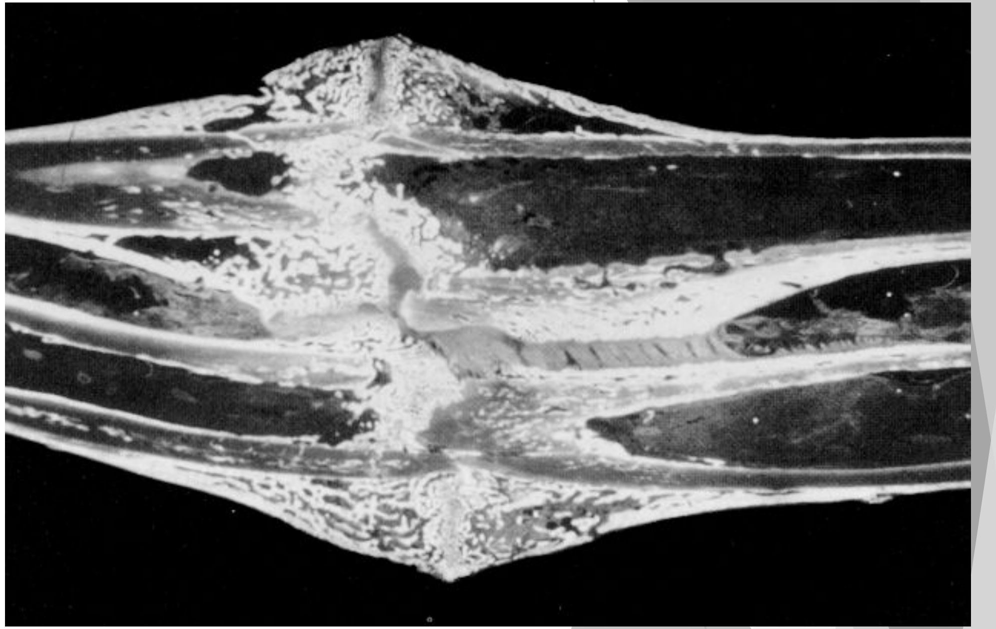
Indirect bone healing
Direct bone healing

Indirect bone healing

Gap > 2 mm

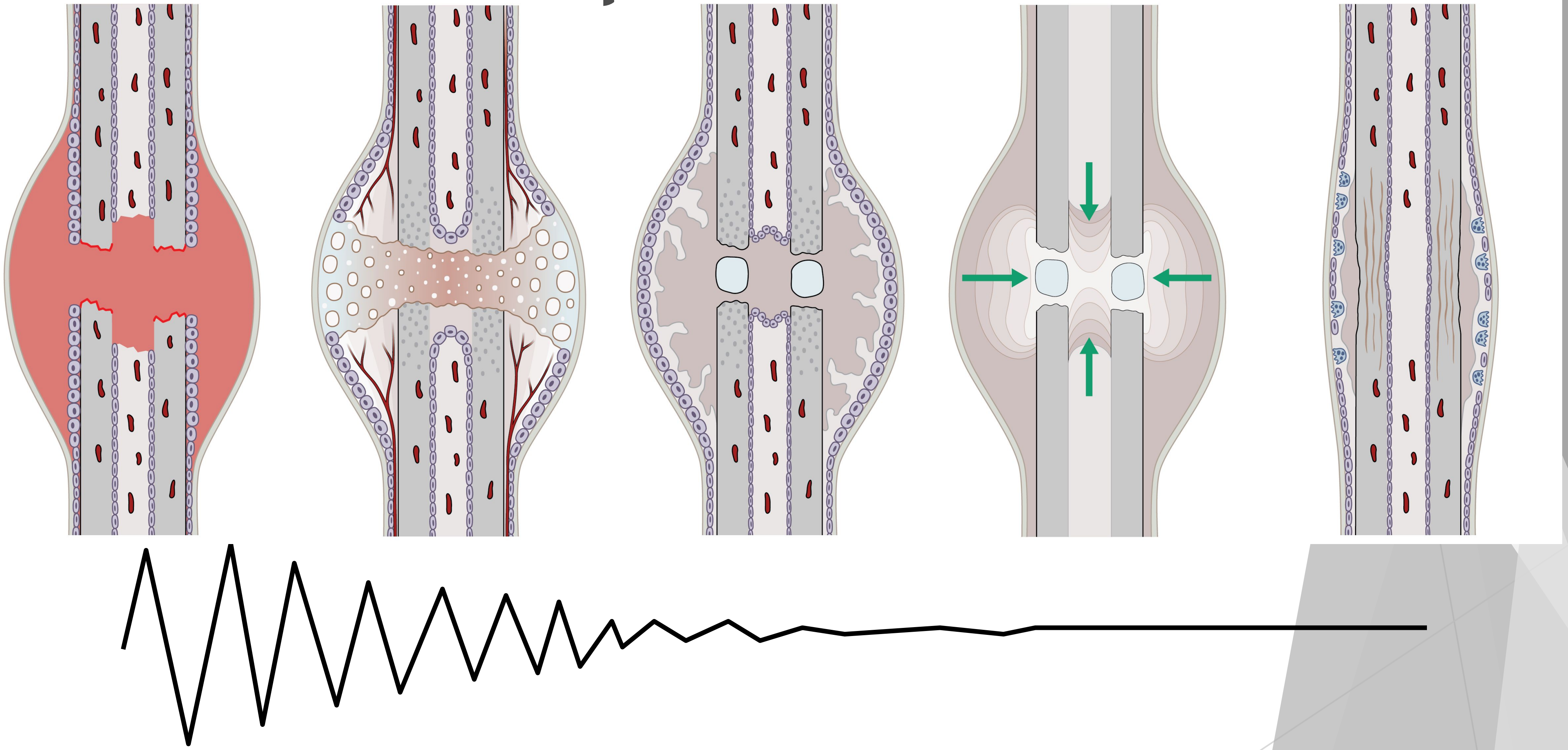
Controlled motion

Living bone



- Granulation tissue
- Ingrowth of vessels
- Fibrocartilage → calcification
- Calcified cartilage → woven bone
- Woven bone → lamellar bone
- Osteonal remodelling

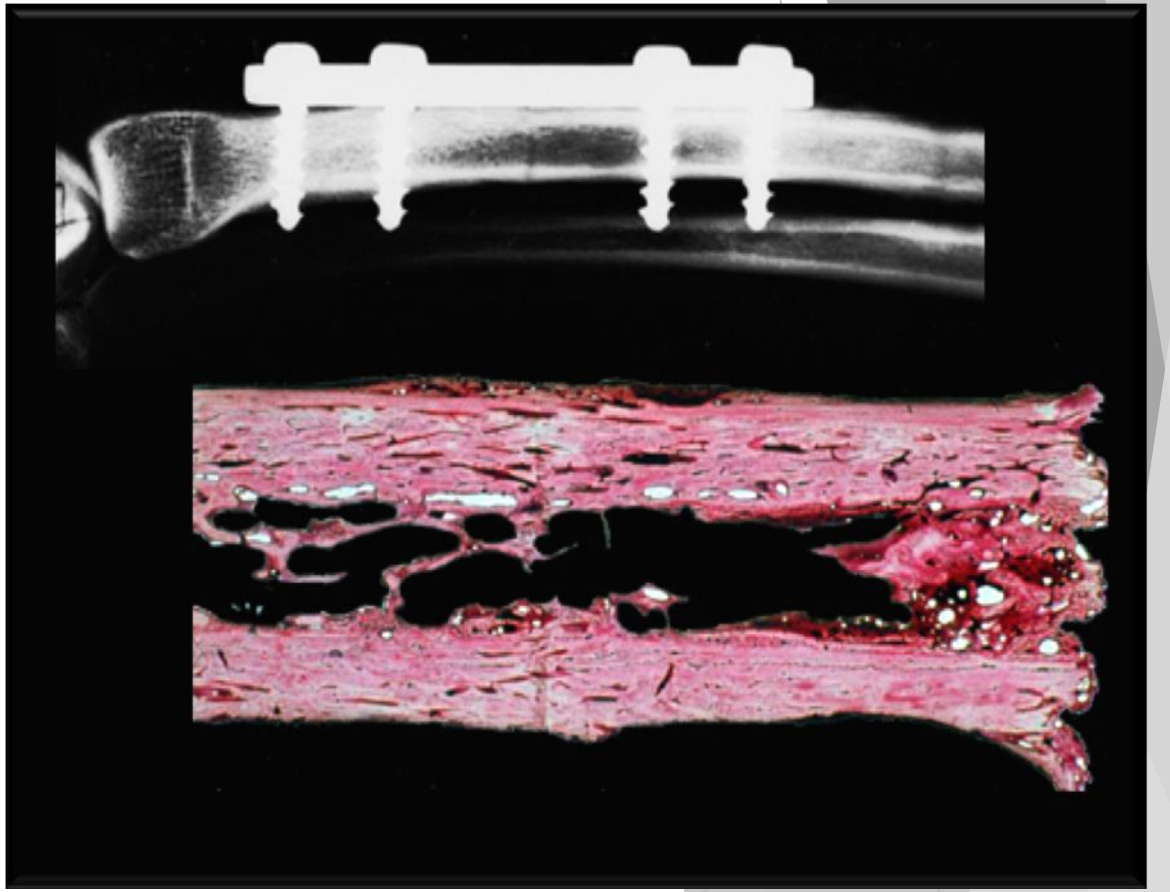
Indirect bone healing—mechanical effect



As the callus forms and stiffens, movement is abolished and normal osteonal remodeling can occur

Direct bone healing

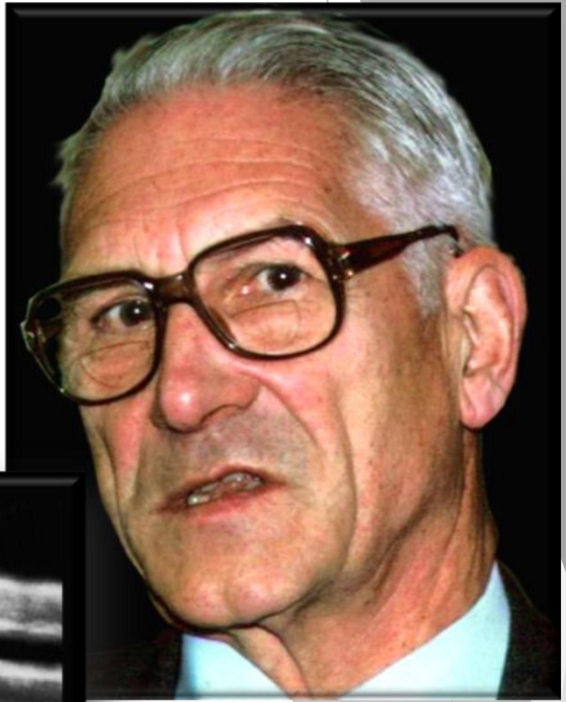
- No visible callus formation
- Direct healing

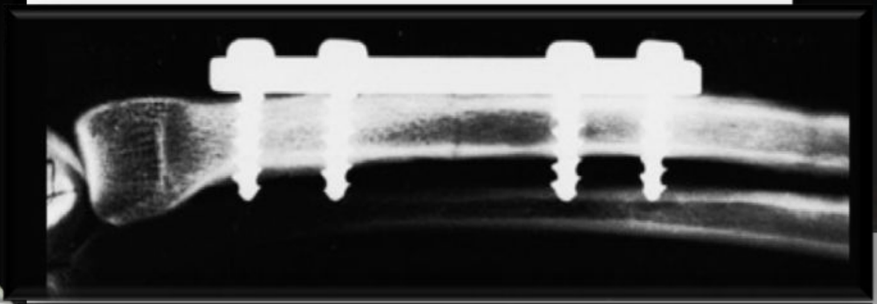


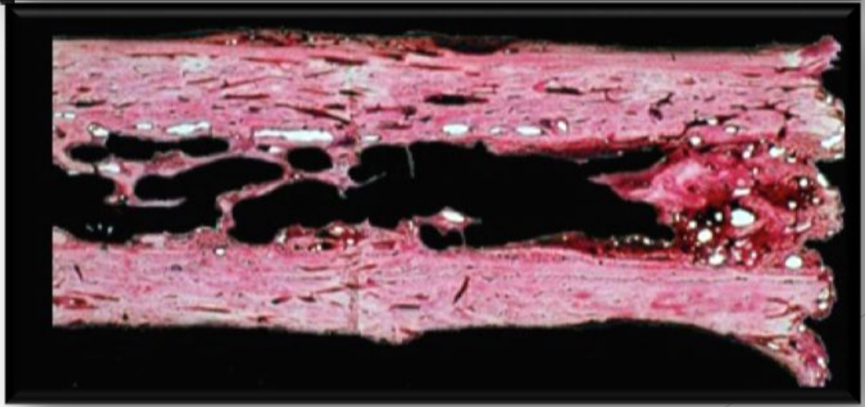
Direct bone healing

Schenk and Willenegger

1958

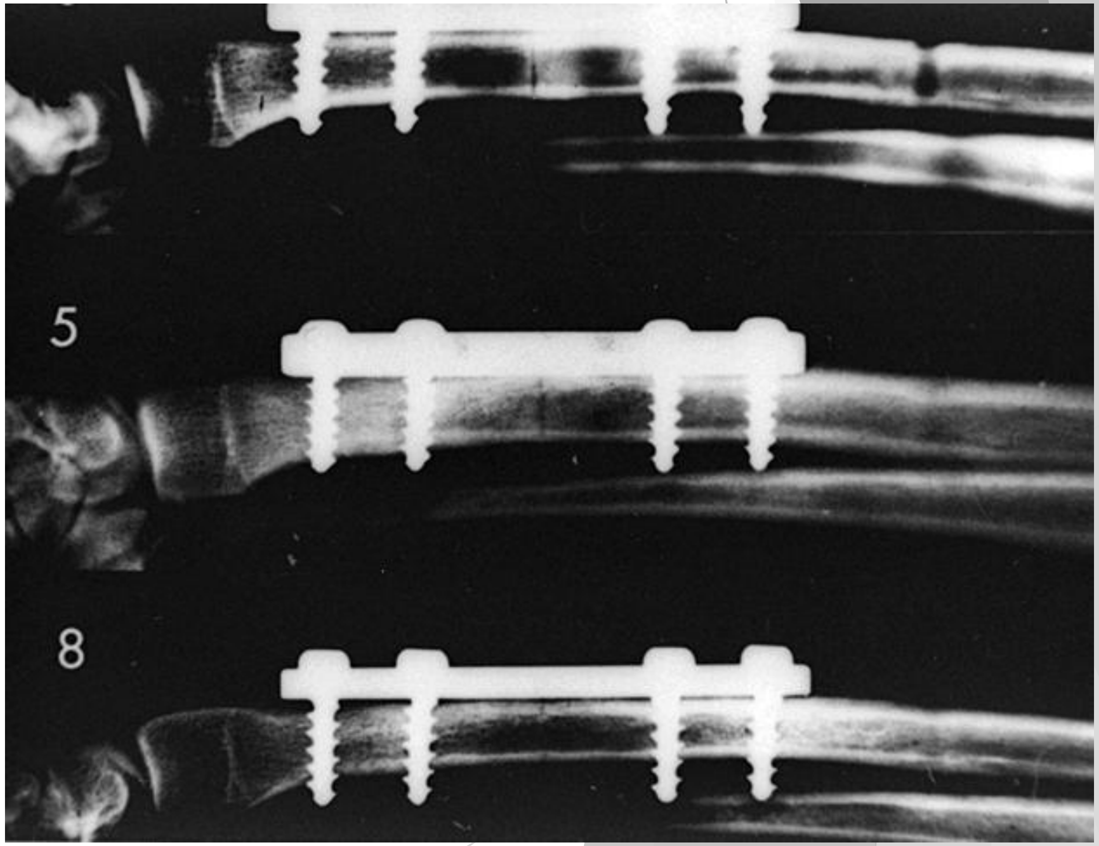






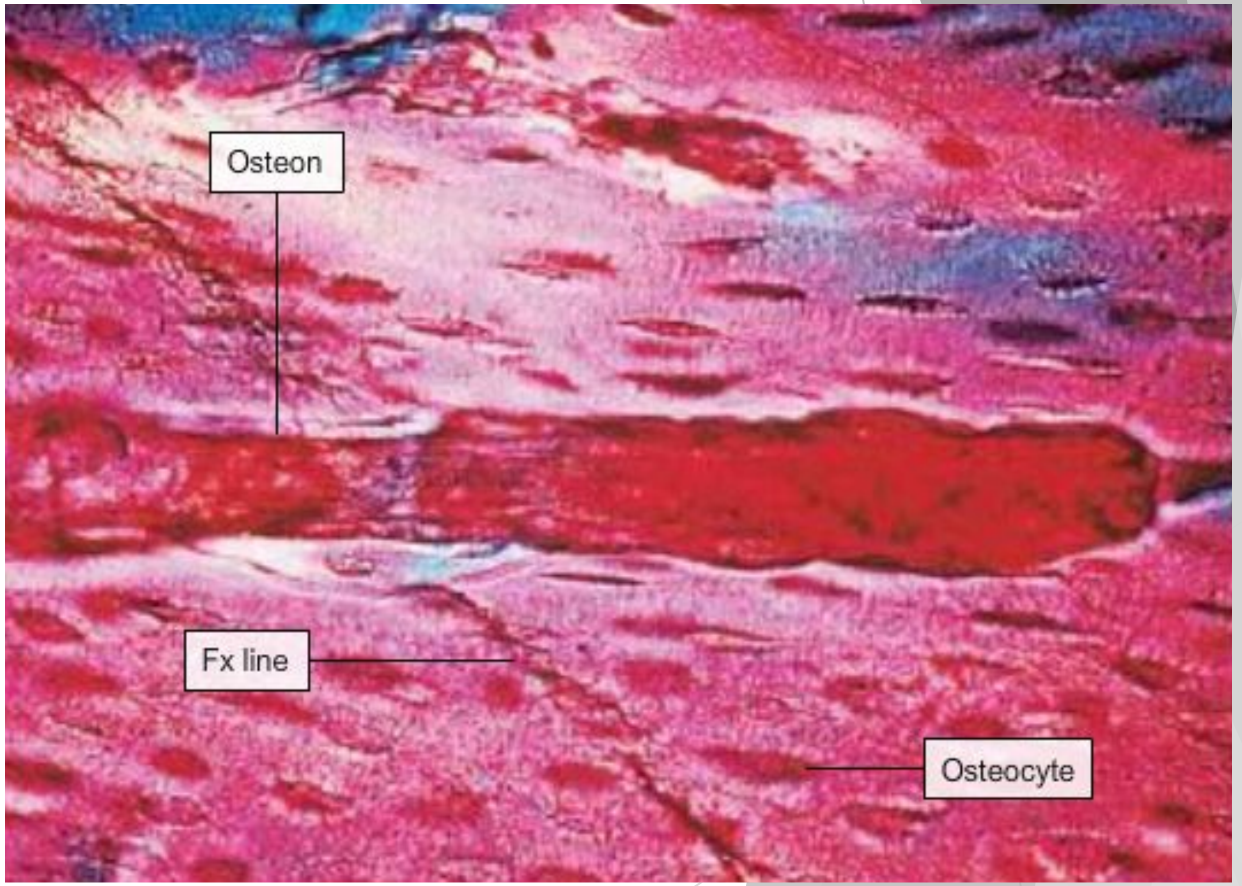
Direct bone healing

- Gap < 2 mm
- No intermediate fibrous tissue

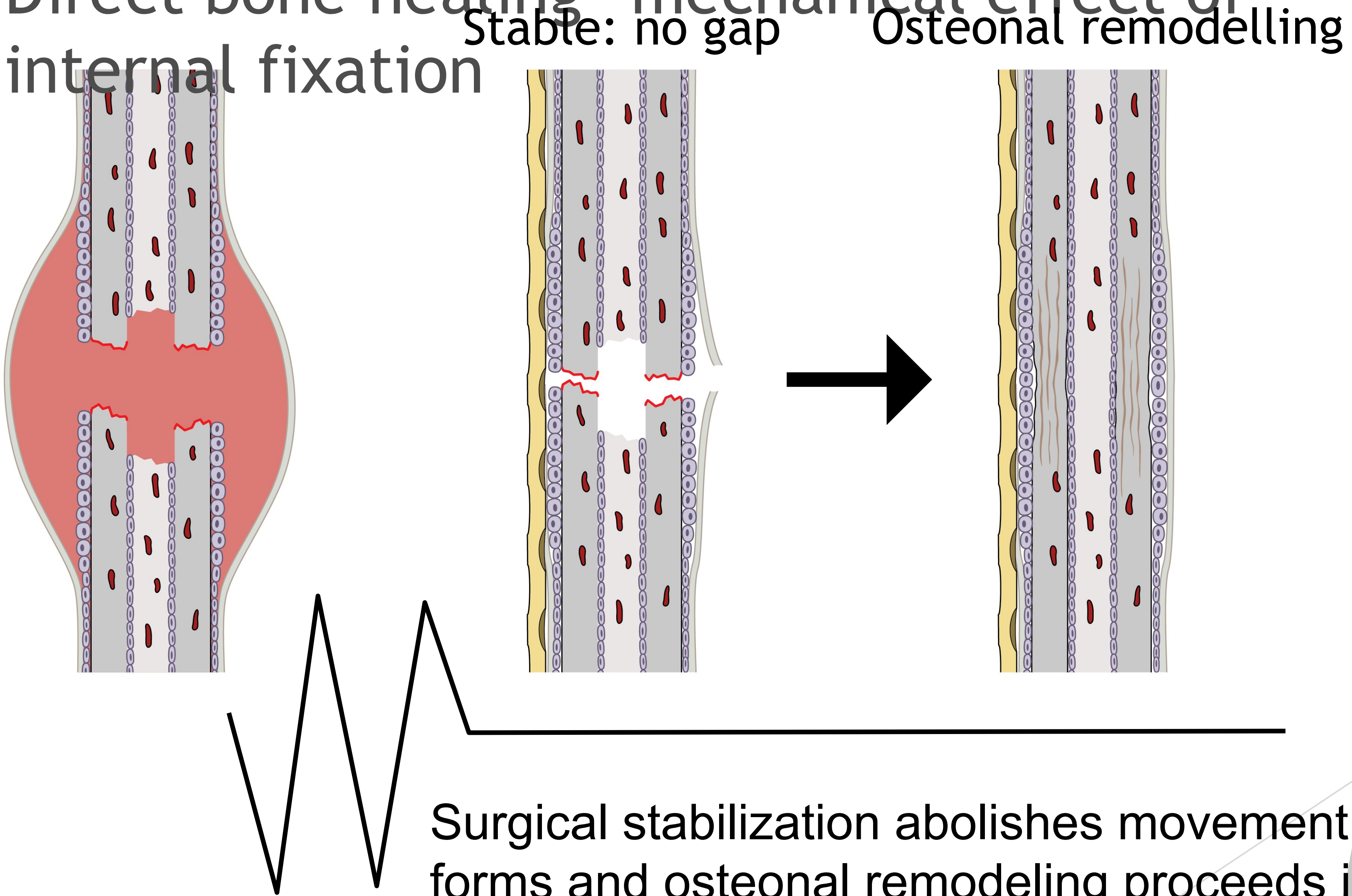


Direct bone healing—osteonal remodeling

- Osteoclasts cut tunnel into cortical bone
- Behind osteoclasts, osteoblasts lay down concentric lamellae of bone, the osteon
- This process relies on absolute stability



Direct bone healing—mechanical effect of internal fixation



Surgical stabilization abolishes movement, so no callus forms and osteonal remodeling proceeds immediately

Take-home messages

- Complex structure heals by replication and remodelling
- Bone is programmed to heal:
  - Must be living
  - Controlled movement
- Type of healing varies with mechanical environment

Take-home messages

- Bone healing is a cascade of biological events leading to restoration of the continuity and mechanical properties of the bone
- Healing is dependent on mechanical and biological factors that are closely associated with bone blood supply
- Fracture stability dictates the biologic response:
  - Absolute stability = direct healing
  - Relative stability = callus healing

Take-home messages

Spectrum of stability

Direct healing

Indirect healing

Absolute stability

Relative stability

Direct

- 2 mm
- No movement
- Good blood supply

Indirect hea

- Gap > 2 mm
- Controlled movem
- Good blood supply

ROYAL MEDICAL SERVICES

ORTHOPEDIC DEPARTMENT

BONE HEALING

Biological and Mechanical Principles

CLINICAL IMPORTANCE

Bone healing underpins all fracture management

Determines:

- Choice of fixation
- Timing of weight bearing
- Need for biologic augmentation

Failure leads to delayed union, non-union, and implant failure

CLASSIFICATION OF BONE HEALING

Based on Mechanical Environment:

- **Primary (Direct) Bone Healing**
- **Secondary (Indirect) Bone Healing**

INTERFRAGMENTARY STRAIN THEORY

Mechanical stability governs the mechanical strain

Healing tissue depends on strain environment:

- $<2\%$ → primary bone healing
- 2–10% → secondary bone healing
- 10% → fibrous tissue / non-union

Guides fixation strategy selection

PRIMARY (DIRECT) BONE HEALING
(HAVERSIAN REMODELING)

Requires:

- Absolute stability (<2% strain)
- Anatomical reduction (<0.1 mm gap)

Achieved by:

- Compression plating
- Lag screws

Vulnerable to fixation failure if stability is lost

PRIMARY (DIRECT) BONE HEALING (MECHANISIM)

- “cutting cones” consisting of osteoclasts can cross the fracture.
- These cones generate cavities that are then filled by bone produced by osteoblasts at the rear of the cutting cone.
- This reestablishes bridges of osteons across the fracture line which then remodel into normal lamellar bone.
- This will result in fracture healing without the formation of periosteal callus.

SECONDARY (INDIRECT) BONE HEALING

Occurs under relative stability (2–10% strain)

Seen with:

- Intramedullary nailing
- External fixation
- Functional bracing

Characterized by:

- Endochondral ossification
- Callus formation

More tolerant to imperfect reduction

PHASES OF SECONDARY BONE HEALING

1. Inflammatory phase
2. Soft callus formation
3. Hard callus formation
4. Remodeling

INFLAMMATORY PHASE

Duration: 1–7 days

Fracture hematoma:

- Acts as biologic chamber which provides a source of hematopoietic cells capable of secreting growth factors
- Contains MSCs, cytokines, growth factors

Key mediators:

- IL-1, IL-6, TNF-α
- May be detected as early as 24 hours post-injury

Red lines

- Inhibition of COX-2 (ie NSAIDs) causes repression of runx-2/osterix, which are critical for differentiation of osteoblastic cells

- Excessive surgical stripping disrupts this phase

SOFT CALLUS FORMATION

Granulation tissue → fibrocartilage

Mesenchymal stem cells differentiate into:

- Chondrocytes
- Fibroblasts

Type II collagen (cartilage) is produced early in fracture healing and then followed by type I collagen (bone) expression

Hypoxic environment favors chondrogenesis

Cartillage provides initial mechanical stability

HARD CALLUS FORMATION

- Endochondral ossification
- Cartilage replaced by woven bone
- Increased vascularity
- Radiographic evidence of union appears

REMODELING PHASE

- Woven bone → lamellar bone
- Proteases degrade the extracellular matrix
- Cartilaginous calcification takes place at the junction between the maturing chondrocytes and newly forming bone
- Medullary canal reconstitution
- Follows Wolff's law and mechanostat theory
- Duration: months to years
- Influenced by functional loading

LAWS

Wolff's law:

bone remodels in response to mechanical stress

Piezoelectric charges:

bone remodels is response to electric charges: compression side is electronegative and stimulates osteoblast formation, tension side is electropostive and simulates osteoclasts

Mechanostat theory

Bone maintains a "set point" or "lazy zone" of mechanical strain; loads above this cause bone formation, while loads below it lead to resorption.

CELLULAR PLAYERS

- **Osteoblasts** – bone matrix synthesis
- **Osteoclasts** – bone resorption
- **Chondrocytes** – cartilaginous callus
- **Endothelial cells** – angiogenesis
- **Mesenchymal stem cells** – differentiation pool

  periosteum and endosteum are the two major sources

MOLECULAR REGULATION

- **BMPs (2, 4, 7)** – osteoinduction
- **VEGF** – angiogenesis
- **TGF-β** – MSC proliferation
- **PDGF** – chemotaxis and cell recruitment
- Targeted in biologic therapies

VARIABLES THAT INFLUENCE FRACTURE HEALING

Internal variables

- blood supply (most important)
- head injury may increase osteogenic response
- mechanical factors

1. bony soft tissue attachments
2. mechanical stability/strain
3. location of injury
4. degree of bone loss
5. pattern (segmental or fractures with butterfly fragments)

VARIABLES THAT INFLUENCE FRACTURE HEALING

External variables

- Low Intensity Pulsed Ultrasound (LIPUS)
  healing rates for delayed unions/nonunions has been reported to be close to 80%

- bone stimulators
  four main delivery modes of electrical stimulation
  - direct current
  - capacitively coupled electrical fields (alternating current, AC)
  - pulsed electromagnetic fields
  - combined magnetic fields
- COX-2
  promotes fracture healing by causing mesenchymal stem cells to differentiate into osteoblasts
- radiation (high dose)
  long term changes within the remodeling systems

VARIABLES THAT INFLUENCE FRACTURE HEALING

Patient factors

- diet
- diabetes mellitus
- nicotine
- HIV

medications affecting healing

- bisphosphonates
- systemic corticosteroids
- NSAIDs
- quinolones

THANK YOU