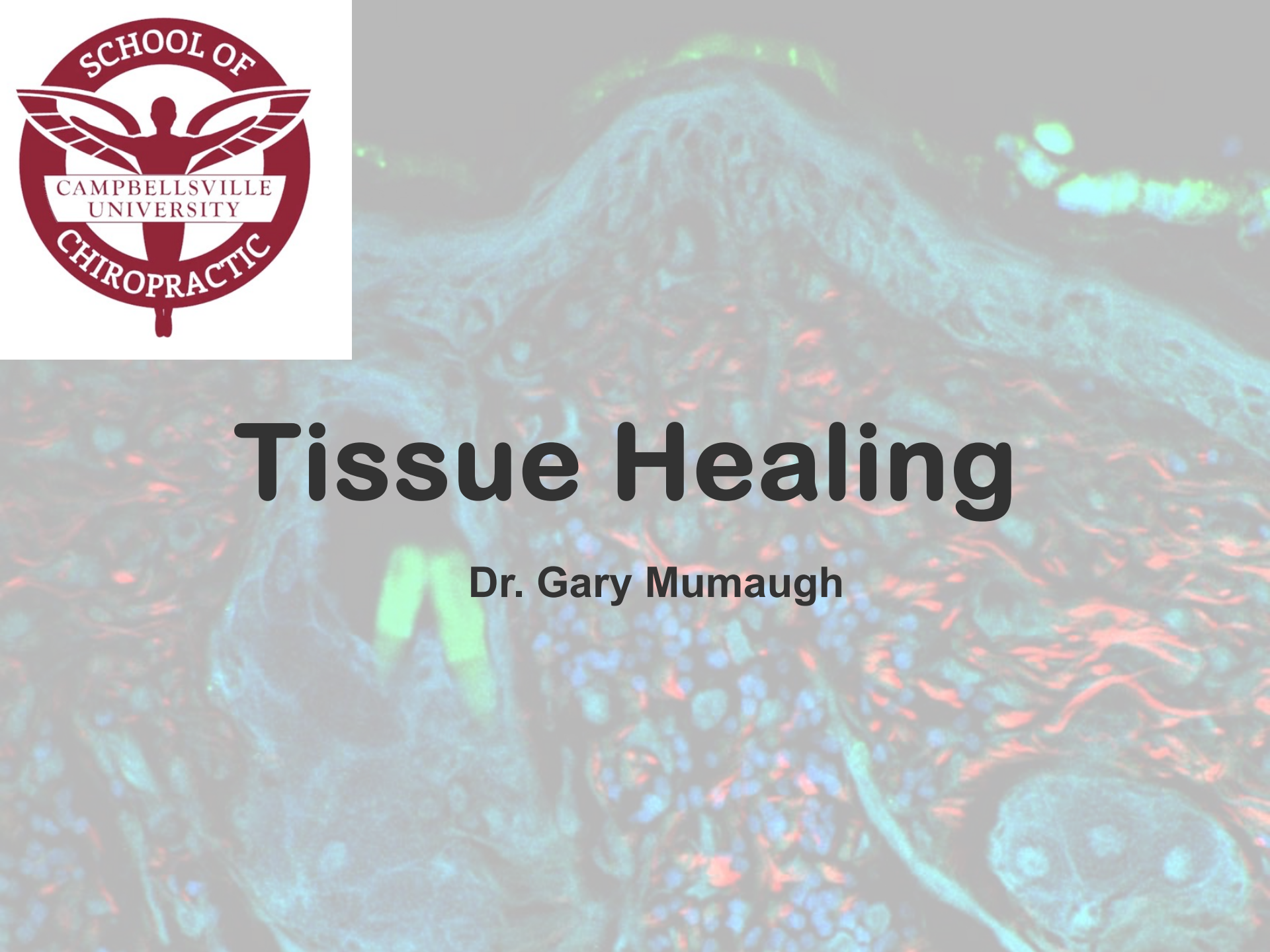


Tissue Healing

Dr. Gary Mumaugh

Healing

Healing

- Process of restoring damaged cells/ tissues
- Often involves restoration of structure and/or function of damaged tissues

Components of Healing

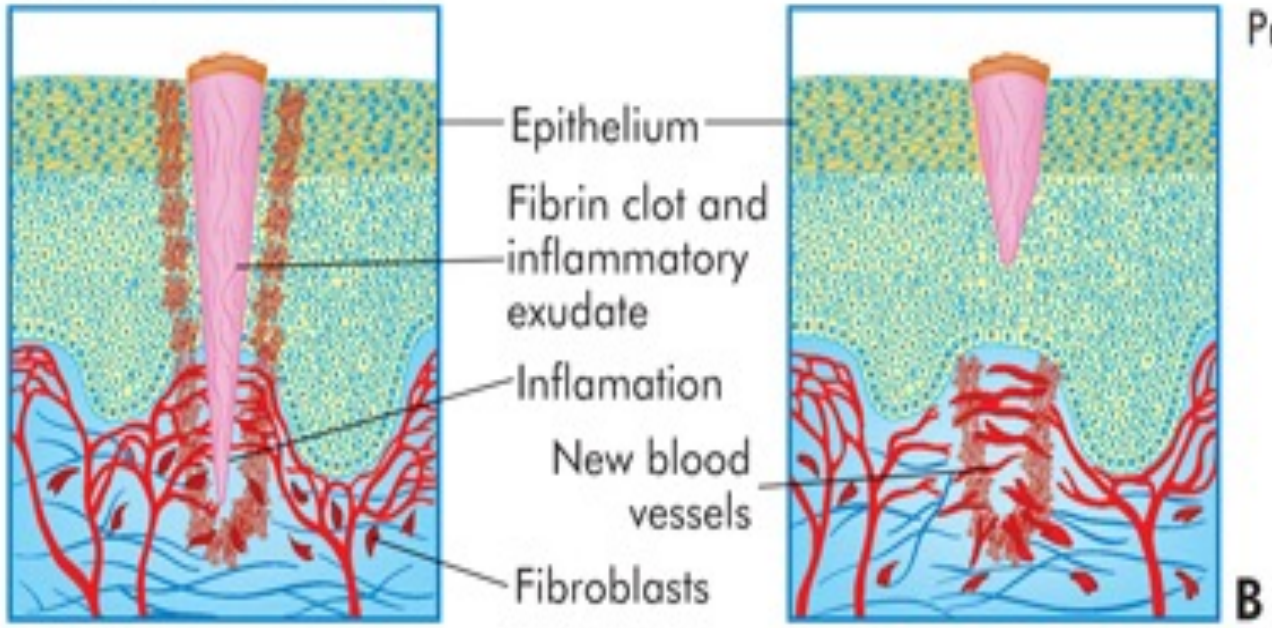
A. **Regeneration**- Damaged cells are replaced by **parenchymal cells** (neighboring functional cells)

B. **Repair**- Fibrous scar tissue fills gap left by damaged tissue

C. **Revascularization**- New vasculature must infiltrate new tissues

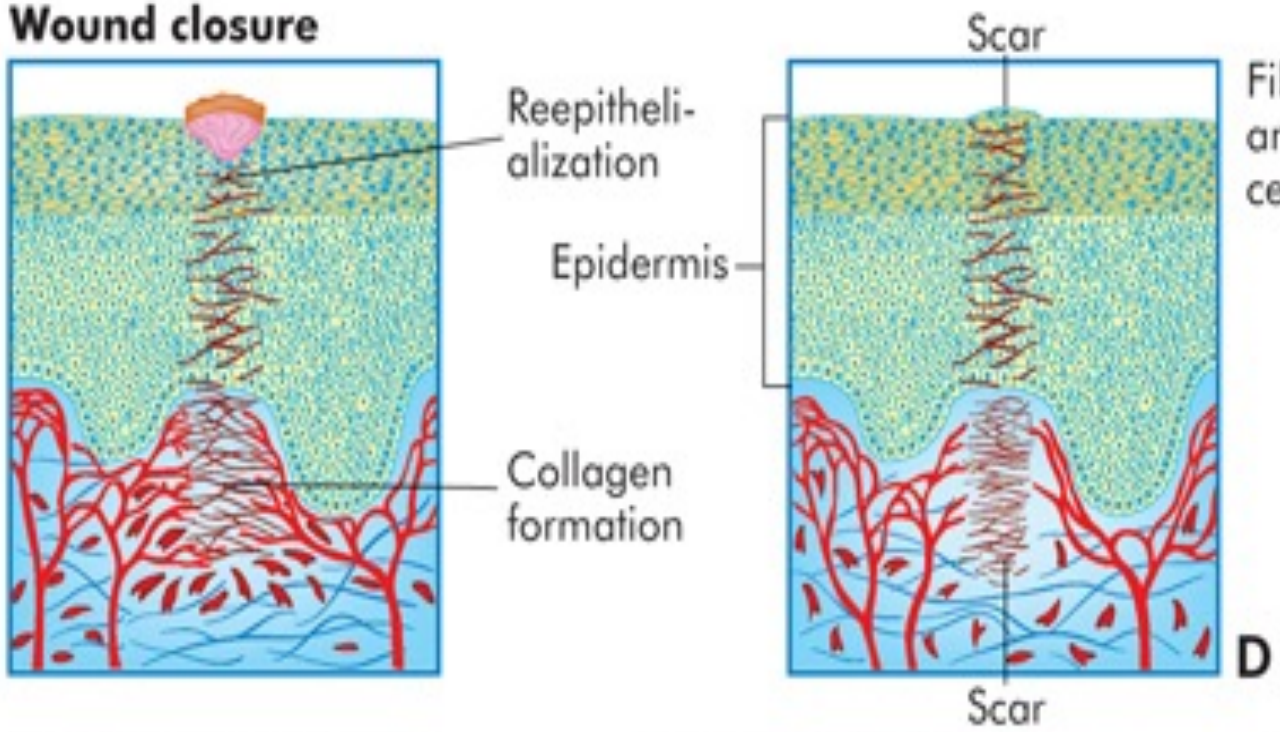
D. **Surface Restoration**- New epithelium often needs to form over damaged tissues/organs

Acute inflammation

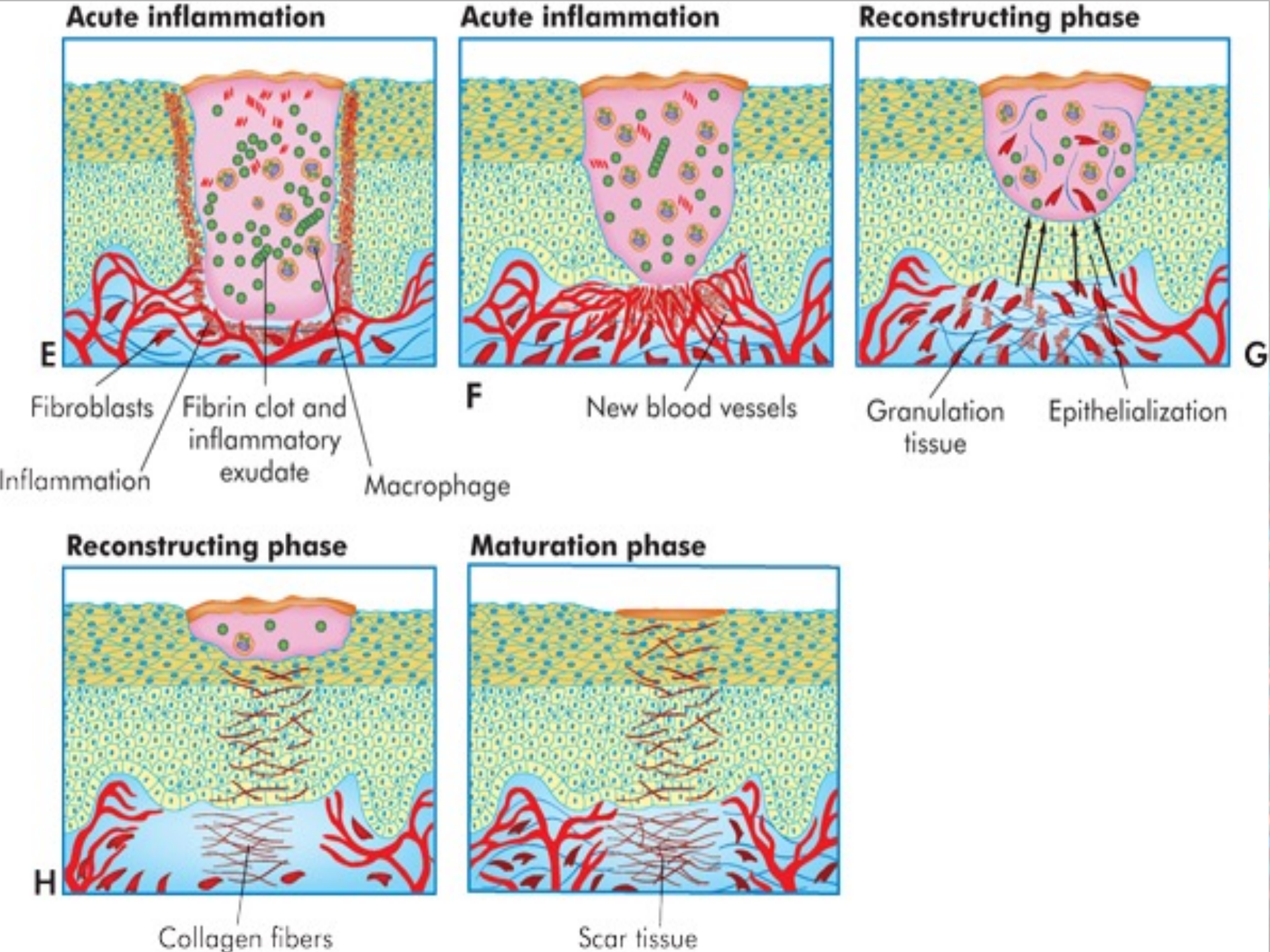


Present in inflammatory exudate:
- Neutrophils
- Macrophages
- Bacteria and dead cells
- Erythrocytes
- Fibrin

Wound closure



Fibroblast migration and collagen-producing epithelial cells recover surface


Acute inflammation
Acute inflammation
Reconstructing phase
E
F
G
Fibroblasts
Fibrin clot and inflammatory exudate
Inflammation
Macrophage
New blood vessels
Granulation tissue
Epithelialization
Reconstructing phase
Maturation phase
H
Collagen fibers
Scar tissue

Regeneration

Cells dividing (via mitosis) to replace dead/damaged cells.

Mitosis continues until new tissue approx. the volume of tissue lost to injury, assumes normal function, ideal response

1. **Labile Tissues**
   - **Constantly grow throughout life**
   - Consist of rapidly dividing cells
   - > 1.5% of cells are in mitosis
   - e.g. red bone marrow, skin, mucous membranes, etc.

2. **Stable Tissues**
   - **Cells multiple and divide when needed**
   - Cells divide more slowly (more functional)
   - < 1.5% of cells are in mitosis
   - e.g. many organs, especially liver and kidney tubules, fibroblasts, smooth muscle, etc.
   -

3. Permanent Tissues

- No “real” regeneration- no mitosis - often replaced by scar tissue → functional loss
- e.g. neurons, cardiac and skeletal muscle cells

Repair

Depositing strong, fibrous (scar) tissue to replace damaged cells/tissues that can't regenerate

1. **Fibrosis**- Fibroblasts lay down much collagen that forms a scar
2. **Procollagen**- fundamental subunit enzymatically altered to be linked to form collagen
3. **Collagen**- Protein complex that contributes to many load-bearing structures in the body
   - Great **tensile strength**- ability to resist being pulled apart

4. Ground Substance + Collagen = Scar Tissue

5. Clot- Mass of fibrin (fibrous protein) and RBCs (and other tissue debris)

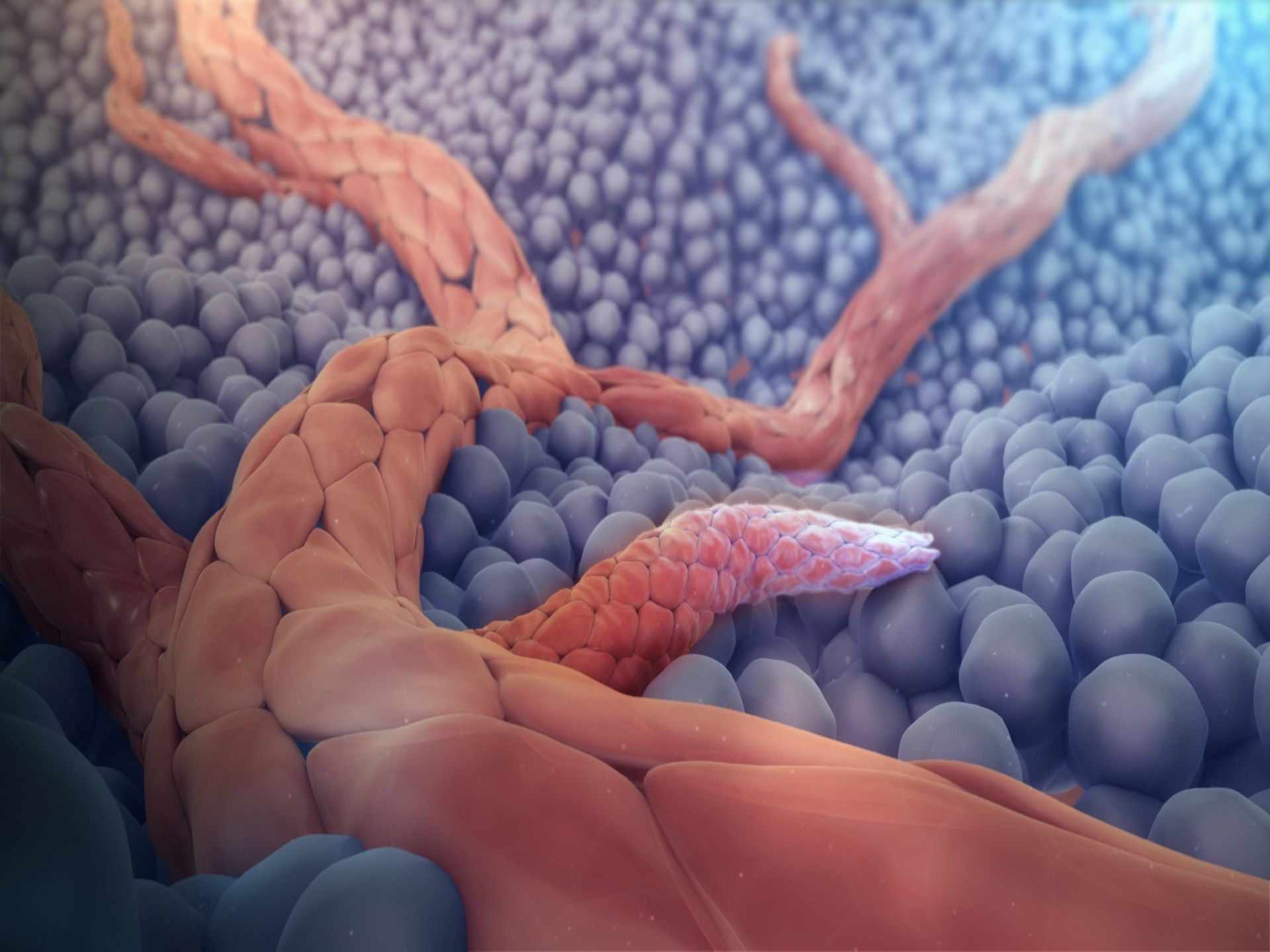
6. Organization- Process of clot being broken down (via phagocytosis) and replaced by scar

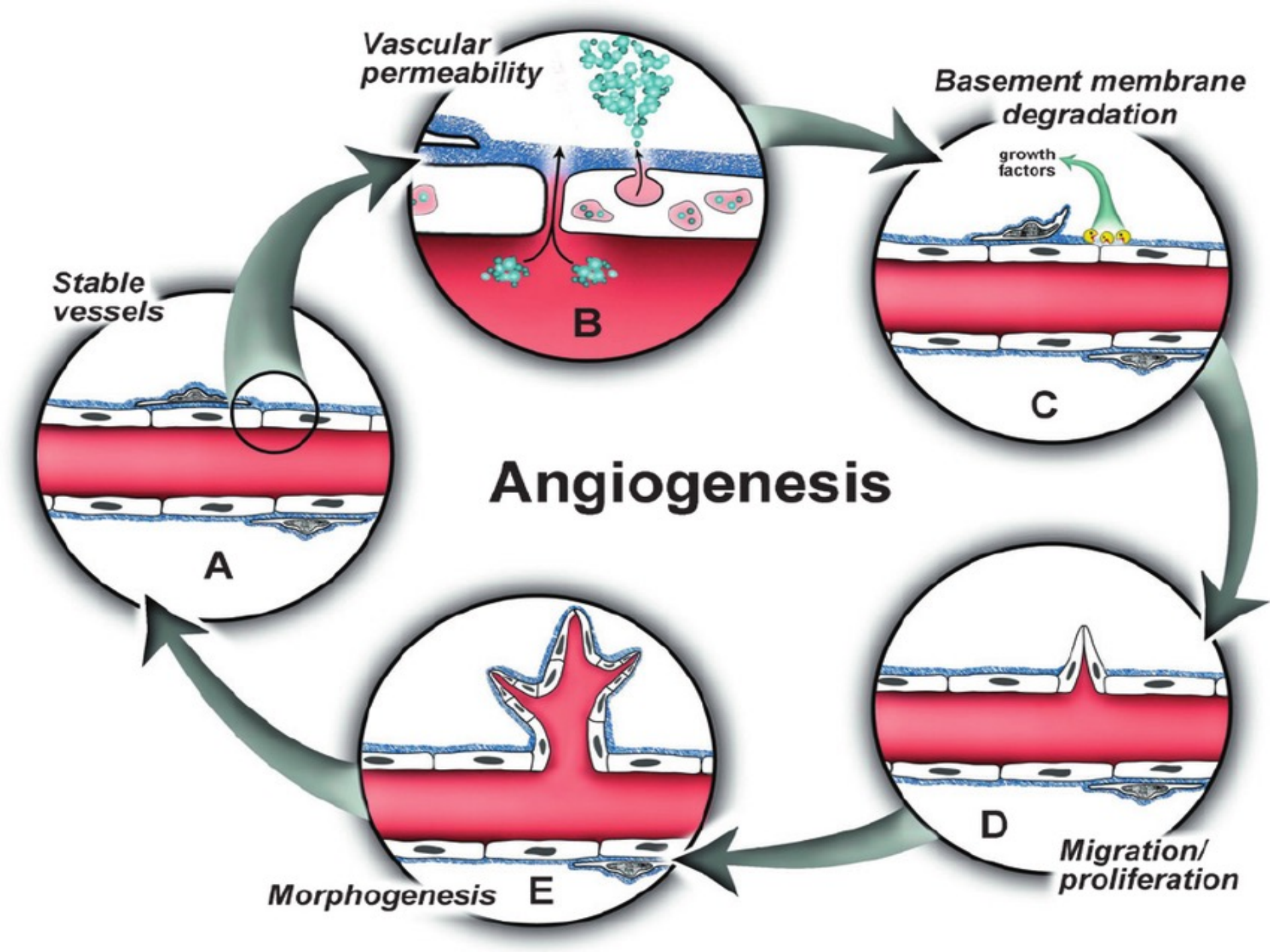
Revascularization

Restoration of blood supply to damaged tissue (a.k.a. **Angiogenesis**)

1. **Granulation Tissue**

- Pink, granular looking tissue
- Infiltrates exudate at site of injury
- Newly developing capillaries forming from uninjured vessels near injury (chemotaxis)




Vascular permeability
B
Basement membrane degradation
growth factors
C
Stable vessels
A
Angiogenesis
D
Migration/ proliferation
Morphogenesis
E

- **Buds**- Projections from endothelial cells lining undamaged vessels, form blood and lymphatic vessels
- May differentiate into venules or arterioles
- Eventually “scaled back” following repair

2. May also involve re-infiltration of other types of tissue (e.g. nervous, lymphatic, etc.)

New scar tissue initially pick appearance (increased blood supply); old scar more pale after vascularization decreased

Surface Restoration

Re-establishment of epithelial tissue “coverings”

- Zone of active mitosis develops near wound edge
- Newly formed cells “migrate” over damaged surface while secreting new basement membrane
- Migration continues until edges migrating over the damaged tissue have come together
- Become anchored to basement membrane once wound is closed
-

Skin Injuries: Primary Healing

Primary Healing

- Involves wounds where edges can come together (i.e. incisions)
- Clotting stops initial blood loss and prevents infections and dehydration
- Repair, revascularization, and surface restoration starts "under" clot → scar tissue
- Melanocytes are NOT replaced (so new skin looks lighter in color)
- Scar tissue usually never reaches original skin's strength

Skin Injuries: Secondary Healing

- Involves wounds whose edges are NOT close together (e.g. ulcers)
- Usually larger and more debris than incision wounds
- Much granulation tissue must form to cover the wounded area → takes longer
- **Wound Contraction**
  - Process of the edges of a wounded area closing over a wound to reduce size
  - Mediated by **myofibroblasts**

Healing Major Tissues

Major Tissues

A. Connective Tissue

B. Epithelial and Glandular Tissue

C. Nervous Tissue

D. Muscle Tissue

Connective Tissue Healing

- Some connective tissues have a limited blood supply
- Prolonged healing allows for re-injury→ may be more severe than initial injury
- *Tendon/Ligament*
  - Usually successful repairs when straight edges can be tightly sutured; scar tissue when irregular edges
  - Fibroblasts produce collagen- restore tensile strength

- *Cartilage*
  - Fibroblast produce scar tissue on surface- protective
  - Can lose some function
- *Adipose*
  - Adipocytes are replaced by special precursor cells when damaged/removed
  -

Bone Healing

- Breaks must be **reduced**- bones positioned at (or close to) original position
- Movement restricted to allow healing (3 stages):
- **1**. Clots and bone fragments must be removed from break area; **osteoblasts** (bone-forming cells) activated **(4-5 days)**
- **2.** Osteoblasts lay down collagen-rich **osteoid tissue** in break area- the **soft callus;** Osteoid tissue is eventually "ossified" to form **hard callus (3 weeks)**

3. Hard callus is broken and re-formed by **<u>osteoclasts</u>** (bone-dissolving cells) to restore bone to its normal structure **(months-years)**

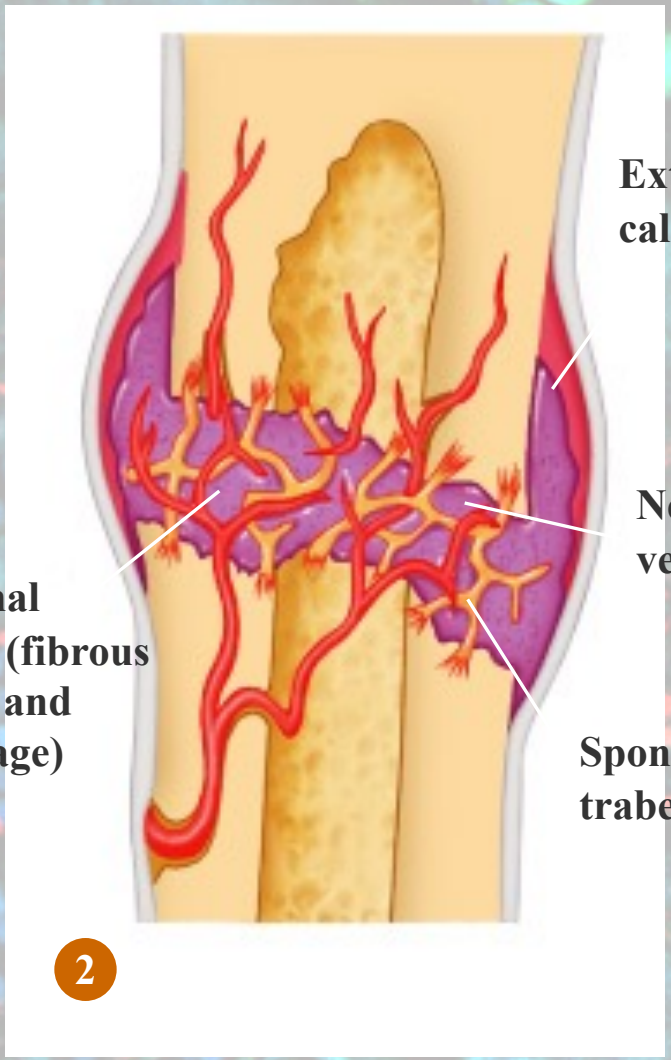
Stages in the Healing of a Bone Fracture

- Hematoma formation
  - Torn blood vessels hemorrhage
  - A mass of clotted blood (hematoma) forms at the fracture site
  - Site becomes swollen, painful, and inflamed

See Notes Page 39

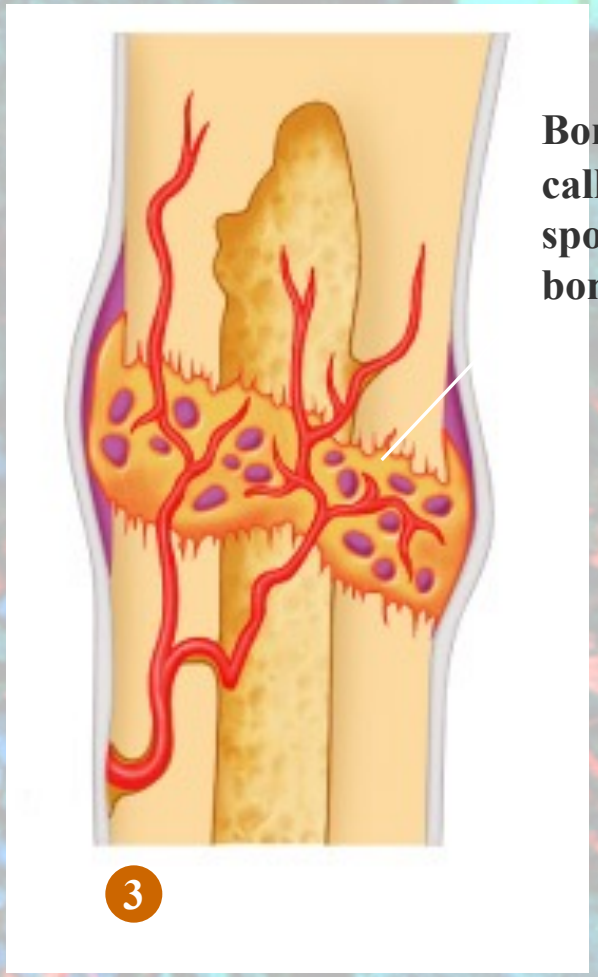
Stages in the Healing of a Bone Fracture

- **Fibrocartilaginous callus forms**



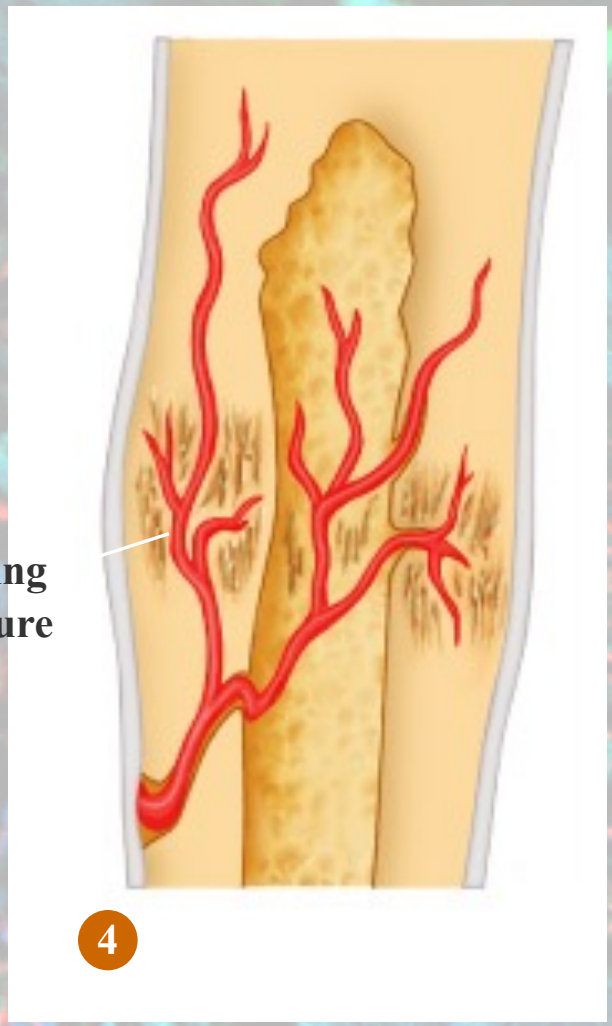
Stages in the Healing of a Bone Fracture

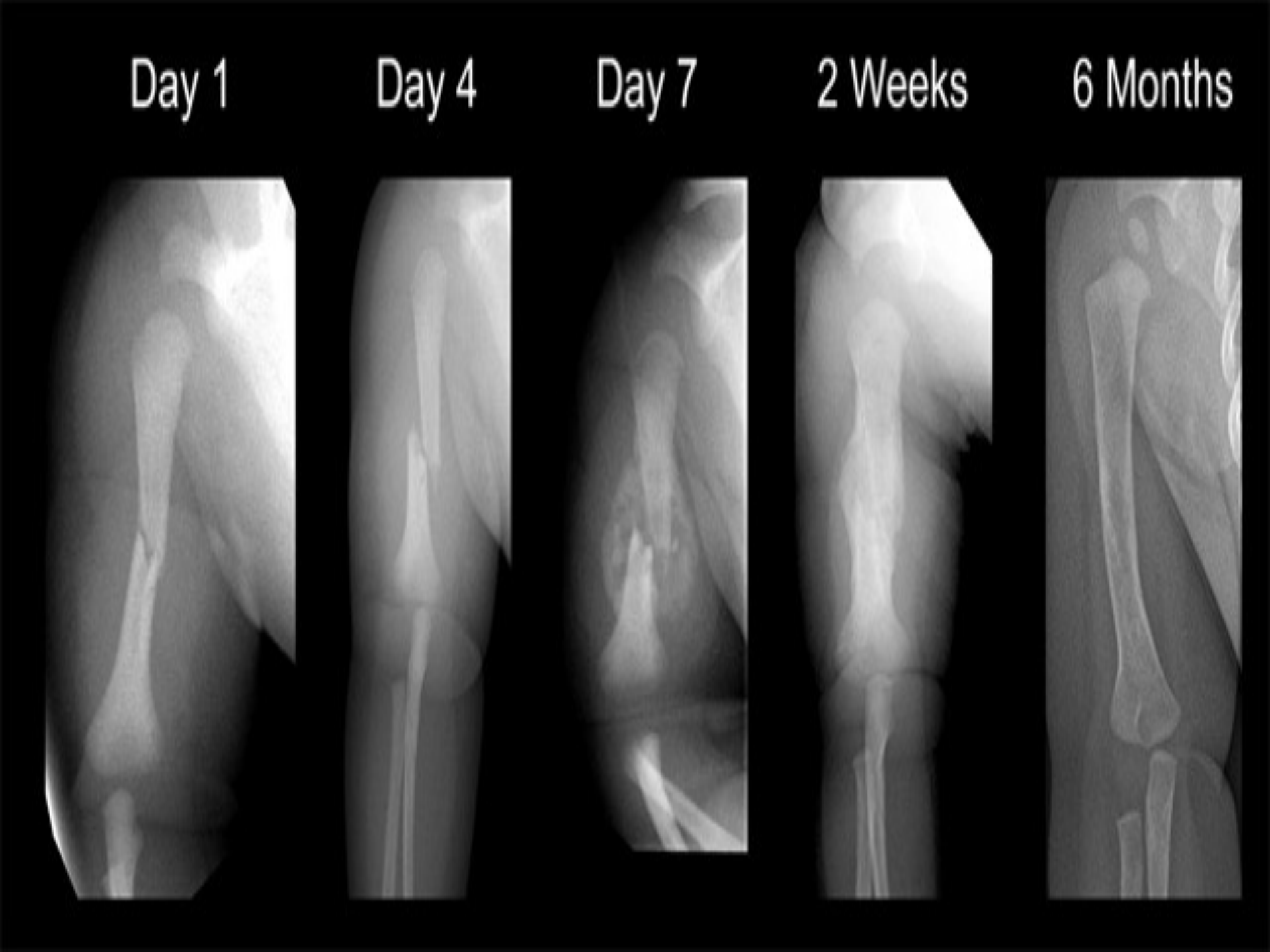
- **Bony callus formation**
  - **Bone callus begins 3-4 weeks after injury, and continues until firm union is formed 2-3 months later**



Stages in the Healing of a Bone Fracture

- Bone remodeling
  - Excess material on the bone shaft exterior and in the medullary canal is removed
  - Compact bone is laid down to reconstruct shaft walls




Day 1
Day 4
Day 7
2 Weeks
6 Months

Epithelial and Glandular Tissue Healing

Epithelial Tissue

- Labile tissue is able to regenerate, except respiratory surface

- **Glandular Tissue**
  - Ability to replaced with functional tissue varies by gland
    - Almost complete regeneration: liver
    - Limited regeneration: kidneys, parathyroid, adrenal medulla, and post. pituitary

Nervous Tissue Healing

- Neurons themselves do NOT go through mitosis after birth
- CNS:
  - **Gliosis**- Mitosis of neuroglial (supporting) cells
  - If cell body intact- initial regeneration of axons
  - May form scar-like masses in nervous tissue
- PNS:
  - Partial regeneration of axon if supporting tissue and **Schwann cells** (produce myelin) remain intact along neural pathway

Muscle Tissue Healing

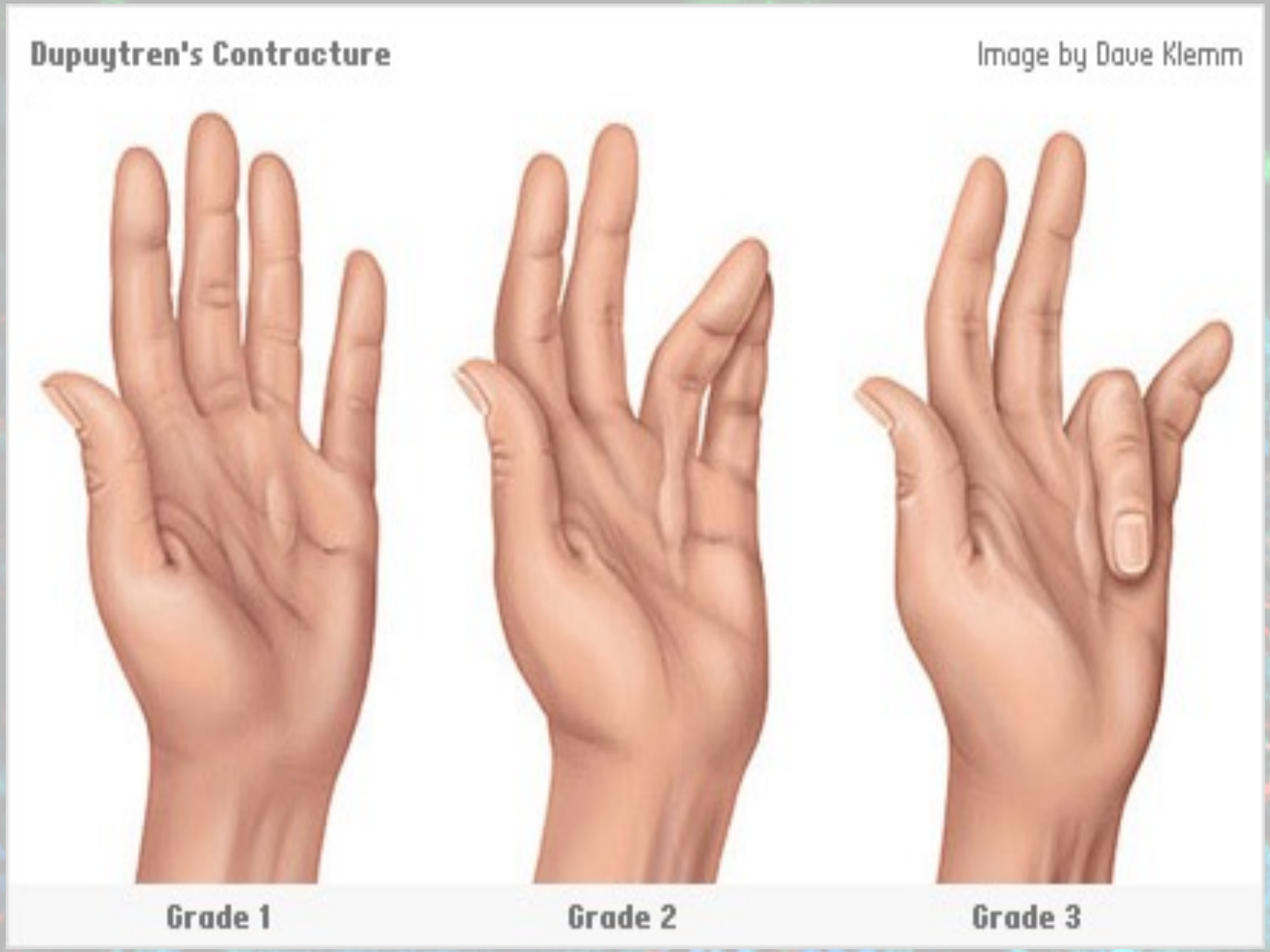
- Cardiac and skeletal can NOT be replaced
- Smooth muscle - some regeneration
- Compensation - cells increase in size and strength
- **Hypertrophy** - Enhanced development of existing cells can “pick up the slack”
-

Complications in Healing

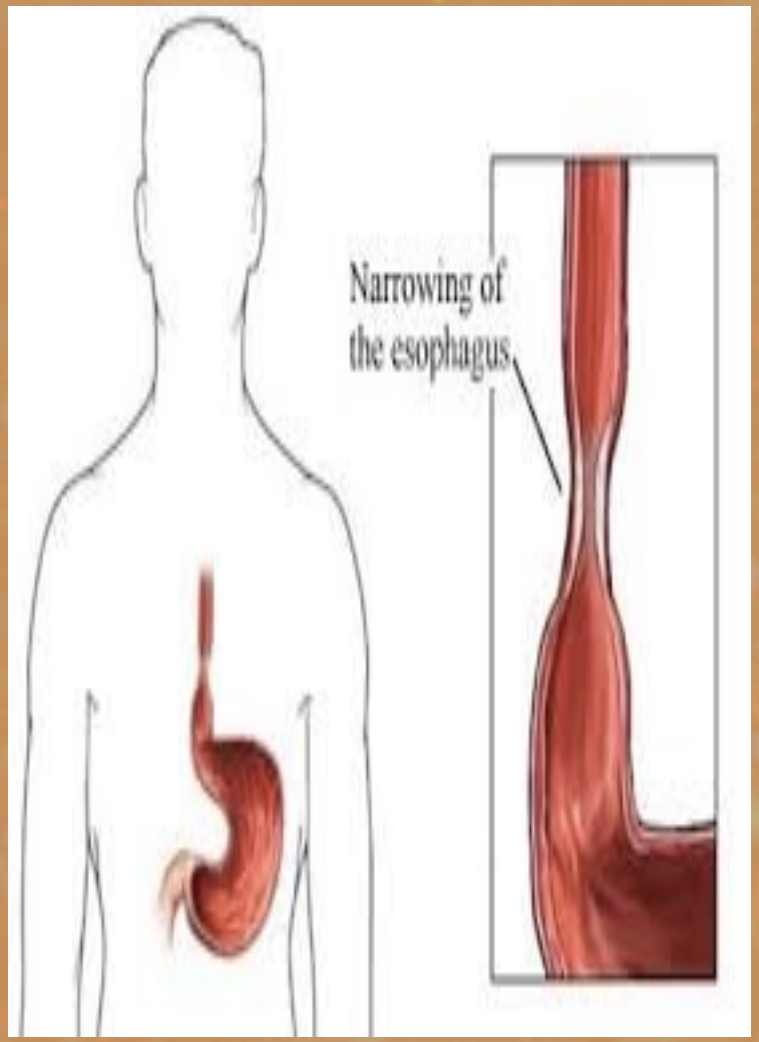
Contracture

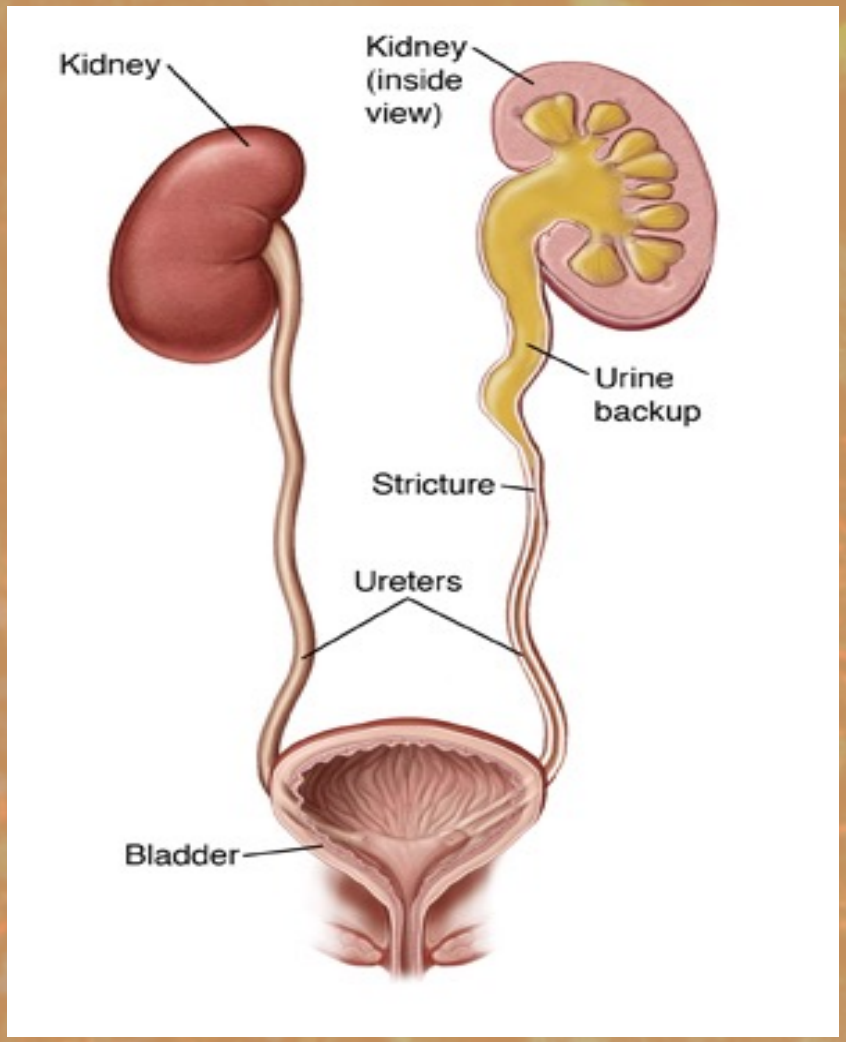
- If damage is extensive newly formed collagen contracts (e.g. skin burn)
- Allows for much less flexibility in tissues; limit mobility
- **Stricture** - Contraction in an important vessel / lumen - lowering interior volume

Muscular Dystrophy Contractures


Dupuytren's Contracture
Image by Dave Klemm
Grade 1
Grade 2
Grade 3

Strictures

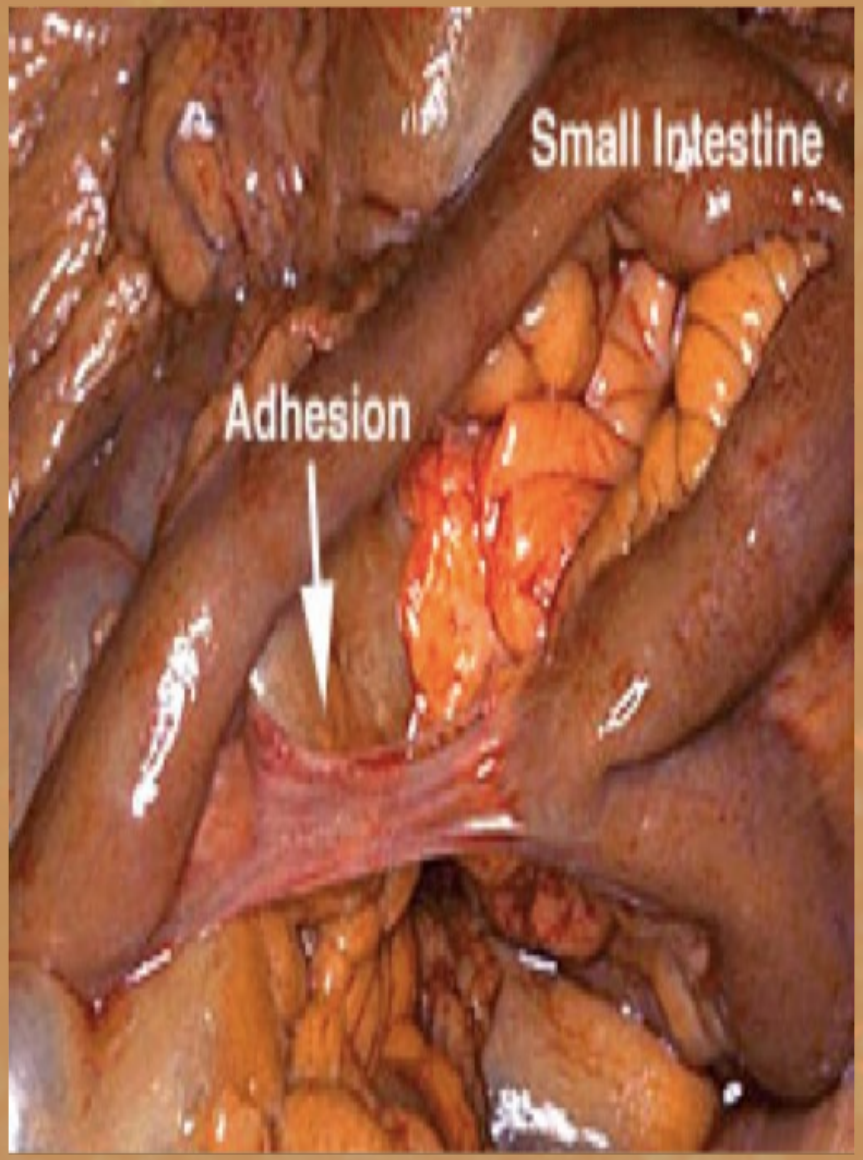

Narrowing of
the esophagus


Kidney
Kidney
(inside
view)
Urine
backup
Stricture
Ureters
Bladder

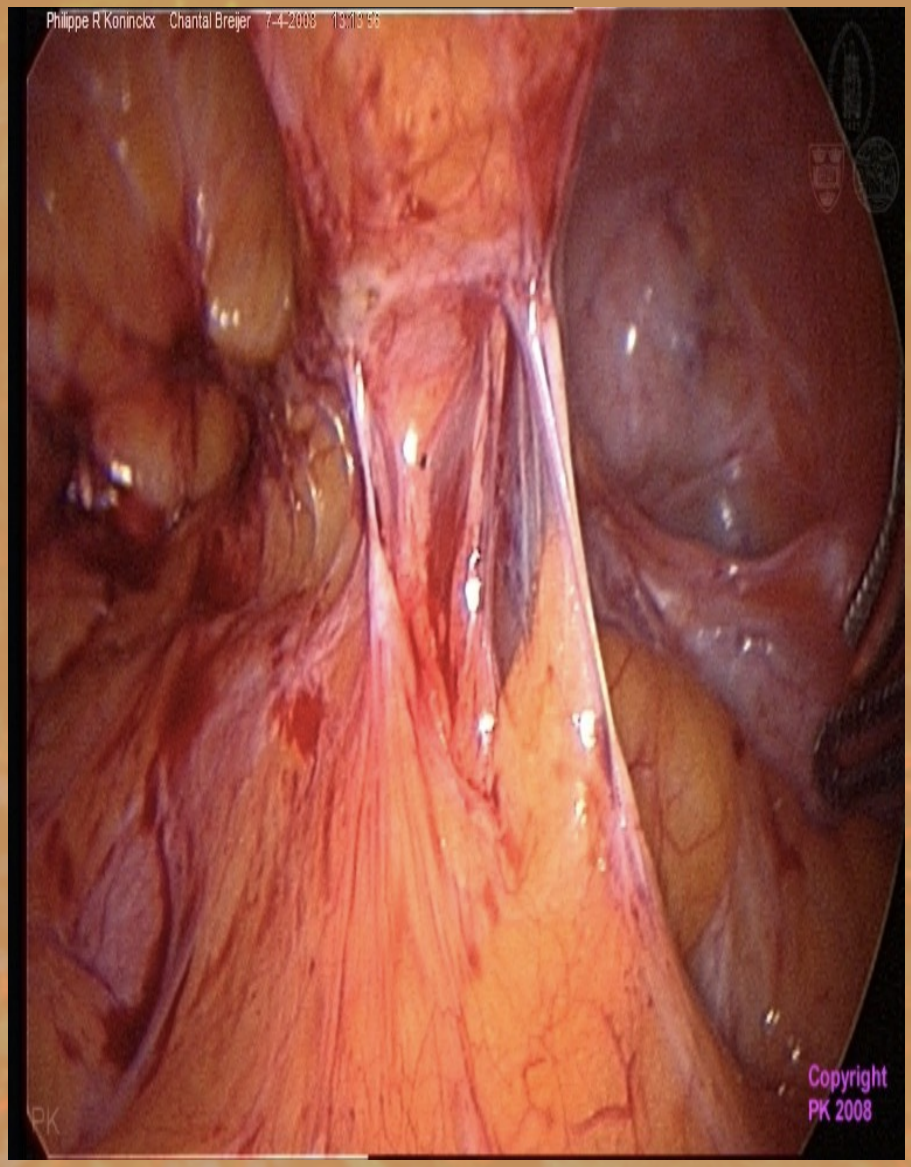
Complications in Healing

Adhesions

- Regions where serous membranes improperly join together
- Often restricts movement in that area

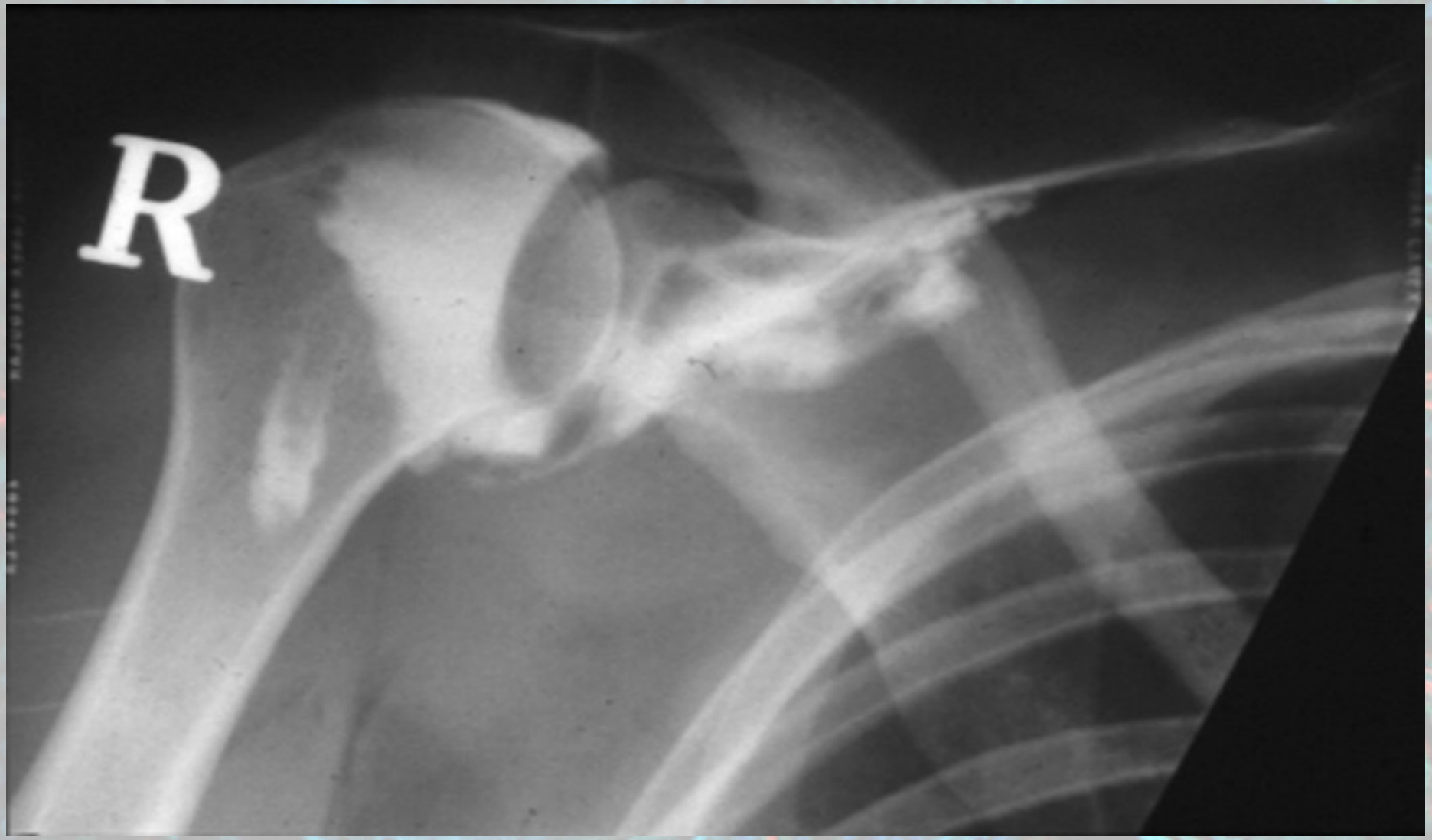


Bowel Adhesions



Uterus Adhesions
are called violin strings

Adhesive Capsulitis of Shoulder
“Frozen Shoulder”



Complications in Healing

Dehiscence

- The breaking open of a healing wound
- Commonly seen in abdominal wounds (much internal pressure)
- A dreaded surgical complication
  - #1 Risk: May also expose healing area to infectious microbes
  - #2 Risk: May cause **herniation** of the intestine through the wound - loss of blood supply

- **Risk factors of dehiscence**
  - Include age, collagen disorders, diabetes, obesity, poor knotting or grabbing of stitches, and trauma to the wound after surgery.

Dehiscence

Complications in Healing

Keloid Formation

- Irregular masses of scar tissue form at site of injury (usually on skin)
- Result from overproduction of collagen or overproduction of a growth factor (TGF-β)

Complications in Healing

Proud Flesh

- Overproduction of granulation tissue
- Can protrude from wound and interfere with surface restoration
- Often referred to as overgranulation tissue
-

Overgranulation Scars

Complications in Healing

Suture Complications

- Small puncture wounds stimulate epithelial tissue mitosis - may cover suture
- Carried off when sutures removed - leaves scars

Requirements for Healing

- Clearance of debris from area
- Wound should be immobilized to allow tissues to repair/regenerate properly
- Adequate vasculature must form to deliver blood eventually
- Proper nutrients (vitamins, minerals) must be provided
  - **Vitamin C**- Required to convert amino acids into procollagen
  - **Copper**- Cofactor for enzyme that cross-links collagen molecules

Control and Regulation of Healing

Growth should be orderly and limited to replace lost tissue

1. **Growth Factors** - Promote growth
2. **Growth Inhibitors** - Stop the growth when appropriate
3. **Contact Inhibition**- When dividing cells contact other dividing cells, mitosis stops

Growth Factors	Effects
Platelet derived growth factor	Stimulates collagenase, fibronectin and hyaluronic acid synthesis
Transforming growth factor	Promotes angiogenesis and collagen production
Vascular endothelial growth factor	Promotes angiogenesis during tissue hypoxia
Epidermal growth factor	Stimulates keratinocytes and fibroblast proliferation
Fibroblast growth factor	Promotes angiogenesis, granulation and epithelialisation
Interleukins	Chemotactic for neutrophils and fibroblasts
Colony stimulating factor	Stimulates granulocyte and macrophage proliferation
Keratinocyte growth factor	Stimulates keratinocyte migration, differentiation and proliferation

Orthopedic Healing Times

Exercise Muscle Soreness	0 to 3 Days	
Muscle Strain	Grade 1	1 Day to 2 Weeks
	Grade 2	4 Days to 3 Months
	Grade 3	3 Weeks to 6 Months
Ligament Strain	Grade 1	1 Day to 3 Weeks
	Grade 2	3 Weeks to 6 Months
	Grade 3	5 Weeks to 1 Year
Tendon	Tendinitis	3 Weeks to 7 Weeks
	Tendinosis	3 Weeks to 6 Months
Bone		5 Weeks to 3 Months
Articular Cartilage Repair or Ligament Graft		2 Months to 2 Years