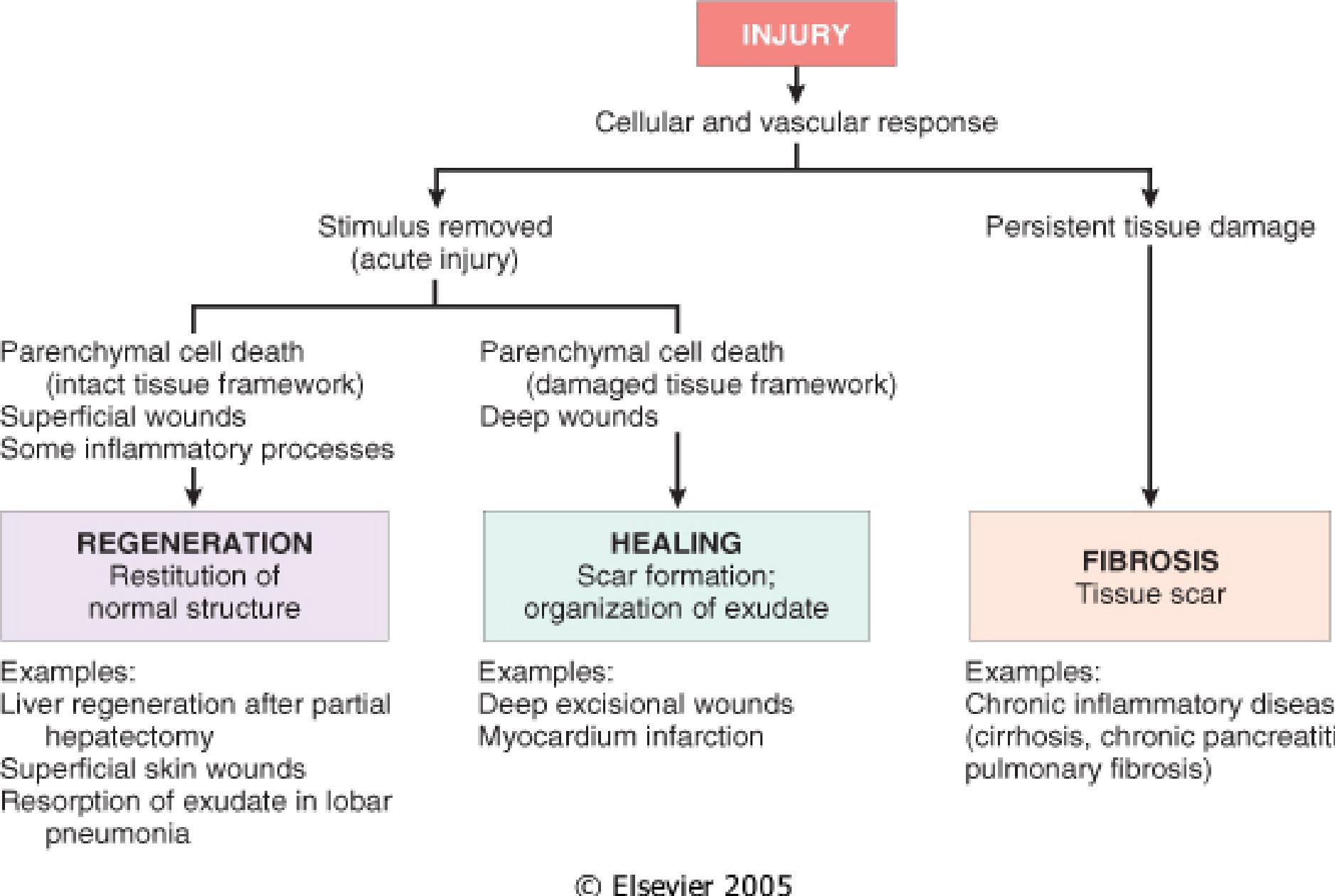


Session Objectives

- 1. Discuss and explain the basic principles of **healing, repair, and regeneration** in regards to different types of tissues (labile, stable, permanent), and differentiate some important growth factors (e.g., PDGF, VEGF, TGF-beta, FGF-2) which mediate the healing/repair process.
- 2. Describe **granulation tissue** and discuss the role of **angiogenesis** and the **importance of connective tissue elements, which include collagen**, in healing and repair.
- 3. Discuss and compare **healing by first and second intention**.
- 4. Discuss/describe **wound contraction and connective tissue remodeling**.
- 5. Give examples of tissue and organs in the process of healing/repair and **describe factors which deter that process**.



Granulation Tissue: angiogenesis

- Endothelial cells grow extensions (pseudopodia) toward wound site
- The cells divide, and the new cells create a new lumen
- Main control: VEGF-A



Angiogenesis: new blood vessel development from existing vessels

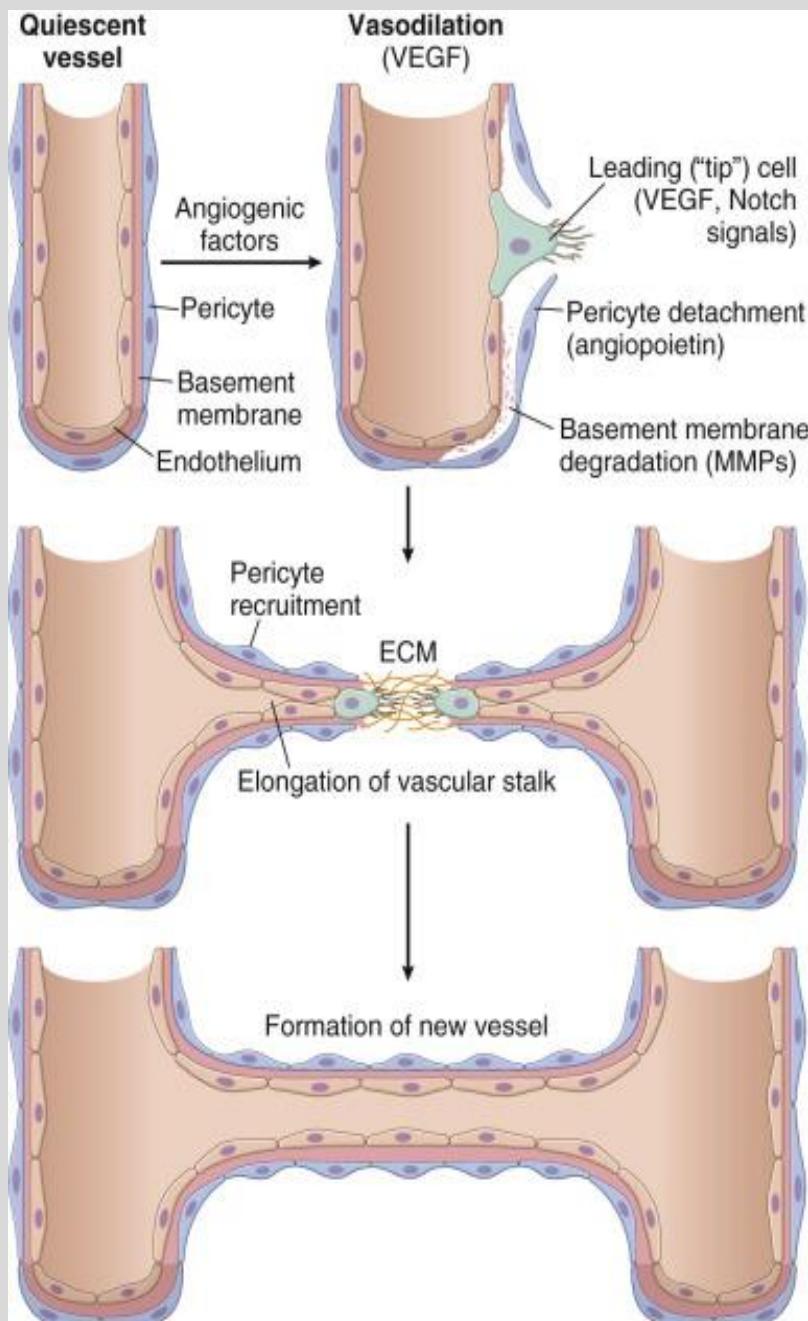
- Pericytes from abluminal surface separate, breakdown basement membrane, form vessel sprout
- Endothelial cells migrate towards angiogenic stimulus (area of tissue injury)
- Endothelial cells proliferate and mature
- Periendothelial cells (pericytes and vascular smooth muscle cells) recruited to form mature vessel

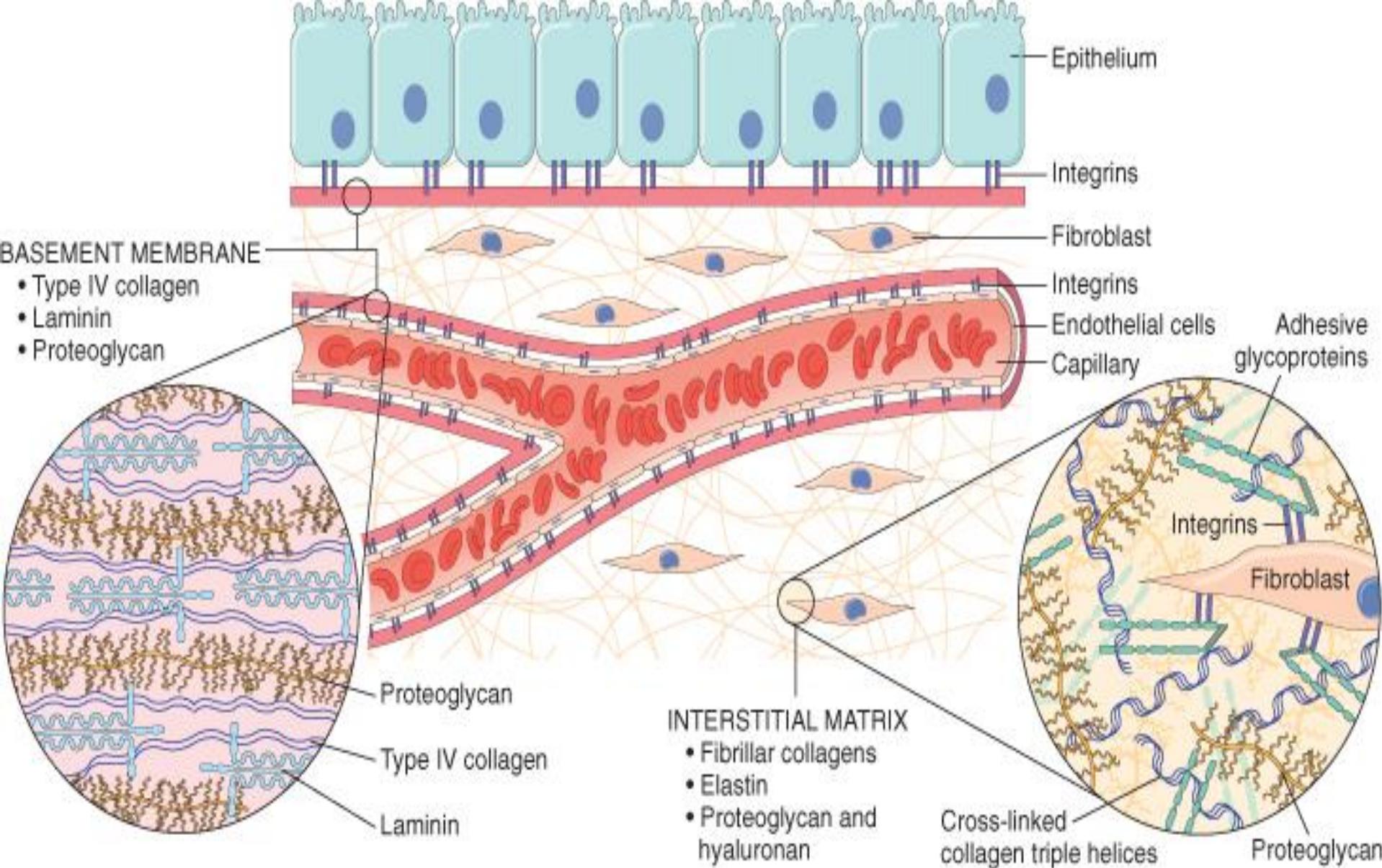
Angiogenesis:

In tissue repair, angiogenesis occurs mainly by sprouting of new vessels.

The newly formed vessel joins up with other vessels (not shown) to form the new vascular bed.

ECM, Extracellular matrix; MMPs, matrix metalloproteinases; VEGF, vascular endothelial growth factor.

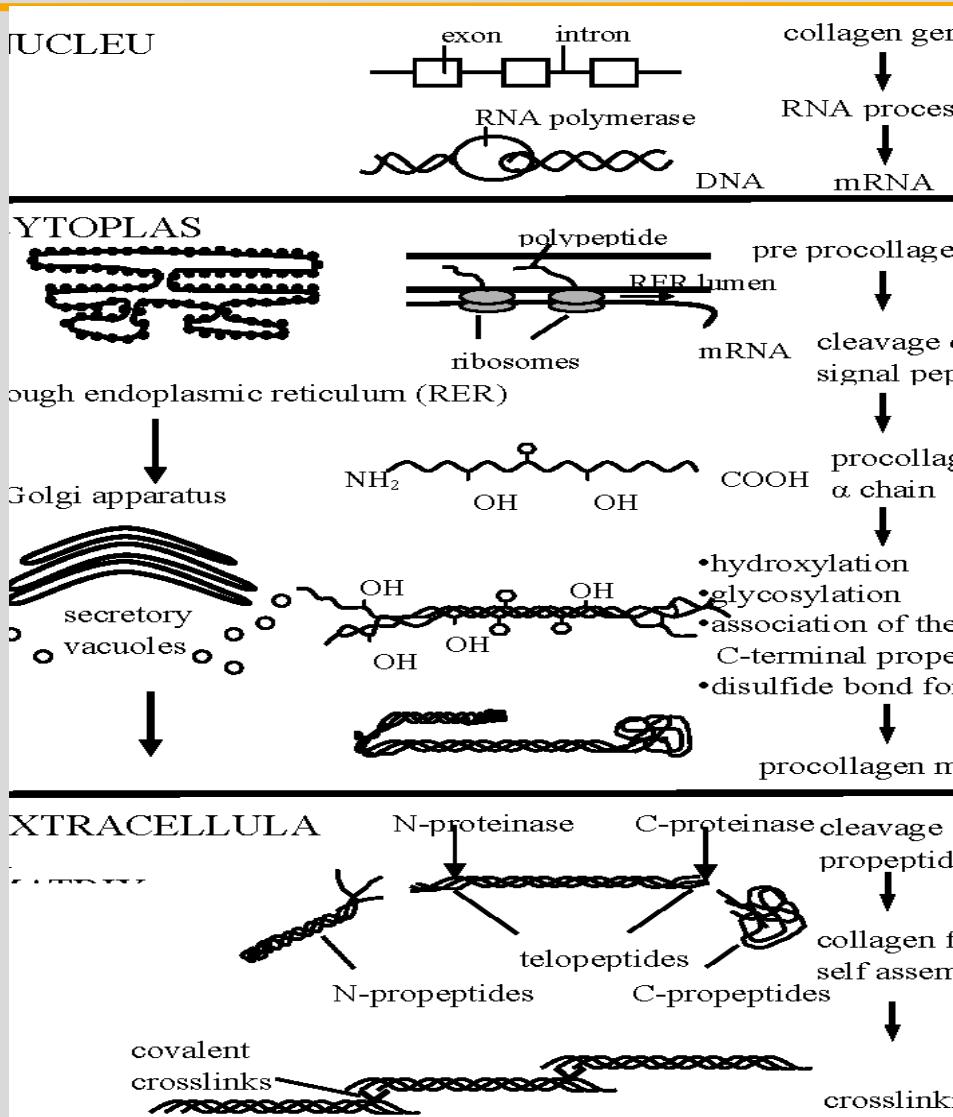




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COLLAGEN

- Laid down by fibroblasts in proliferative phase, modified in maturation phase
- Made up of 3 polypeptide chains (alpha chains) forming triple helix
- Preprocollagen to procollagen to collagen
- Extensive posttranslational modification
- Requires Vitamin C (Scurvy)



Robbins and Cotran, Pathologic Basis of Disease, 10th ed. , 2020, Ch. 3



Day 0



Day 2



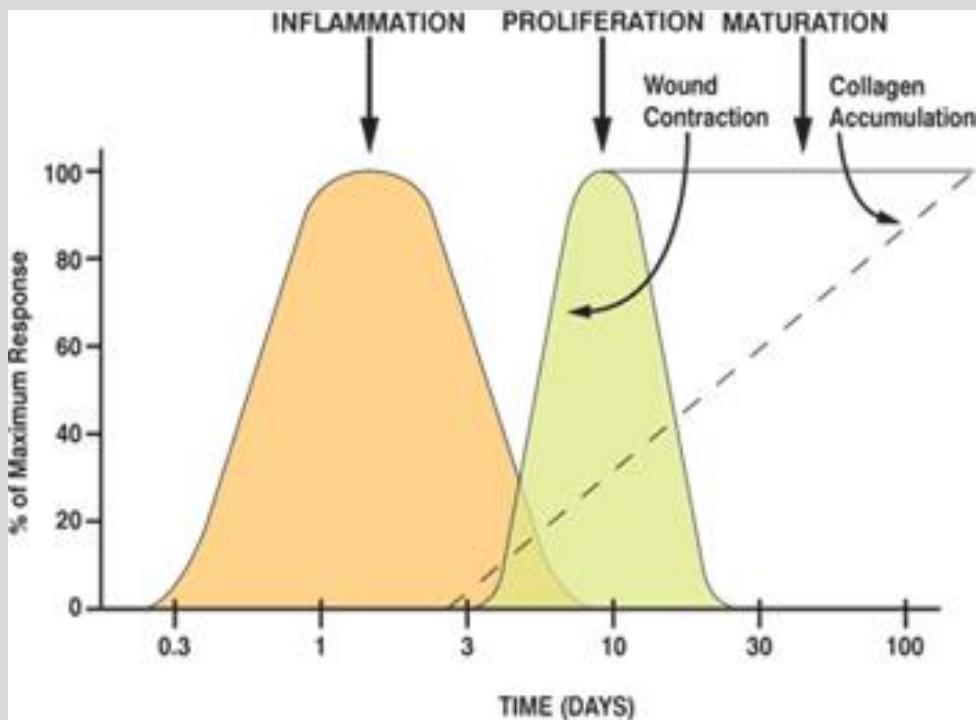
Day 17



Day 30

A cutaneous injury

- Three phases of cutaneous wound healing:
 - Phase 1- Inflammation
 - Phase 2- Proliferation
 - Phase 3- Maturation



These phases are artificial constructs to help understand what is a dynamic, overlapping process



Day 0



Day 2



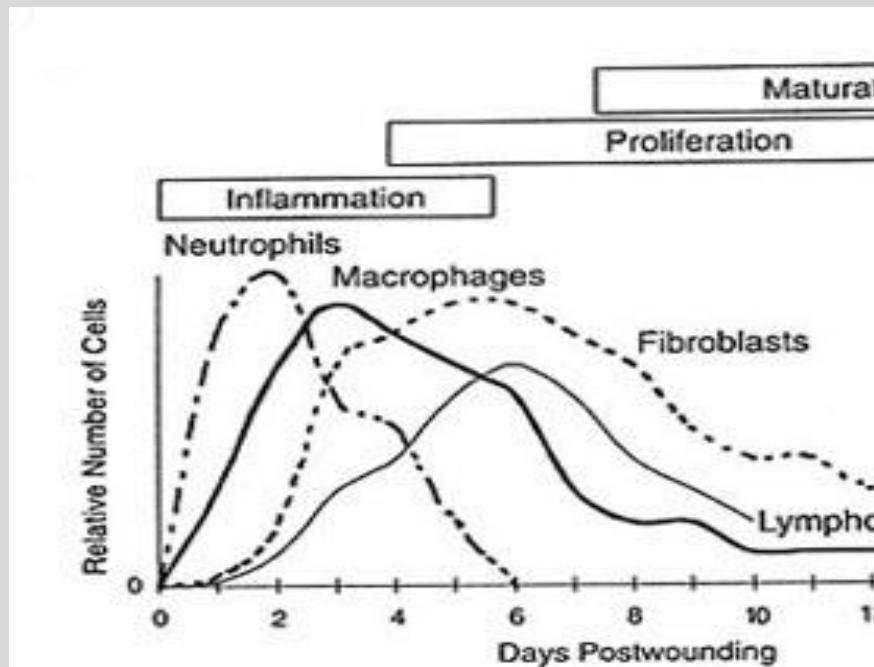
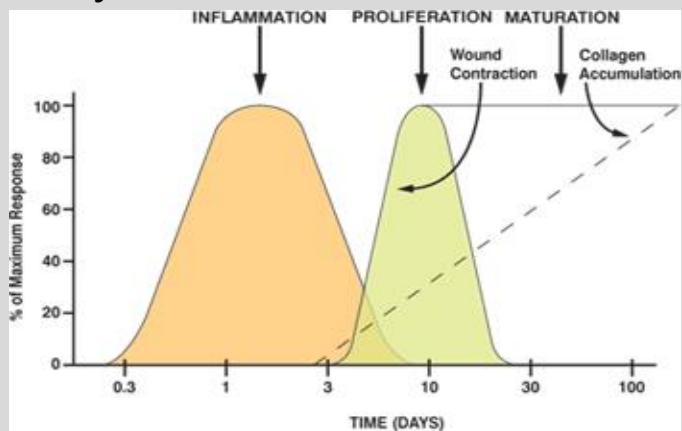
Day 17



Day 30

PHASE 1 - INFLAMMATION

- Immediate → 2-5 days
- Bleeding stops- constriction of vessels, **formation of clot**
- Triggers for acute inflammation:
 - Cell damage, bacteria, and **clotting cascade**
- Acute inflammation- vasodilation, phagocytosis
- Cells- neutrophils then macrophages



<http://emergencty.com/2013/06/10/suturing-knots-and-wound-care/>



Day 0

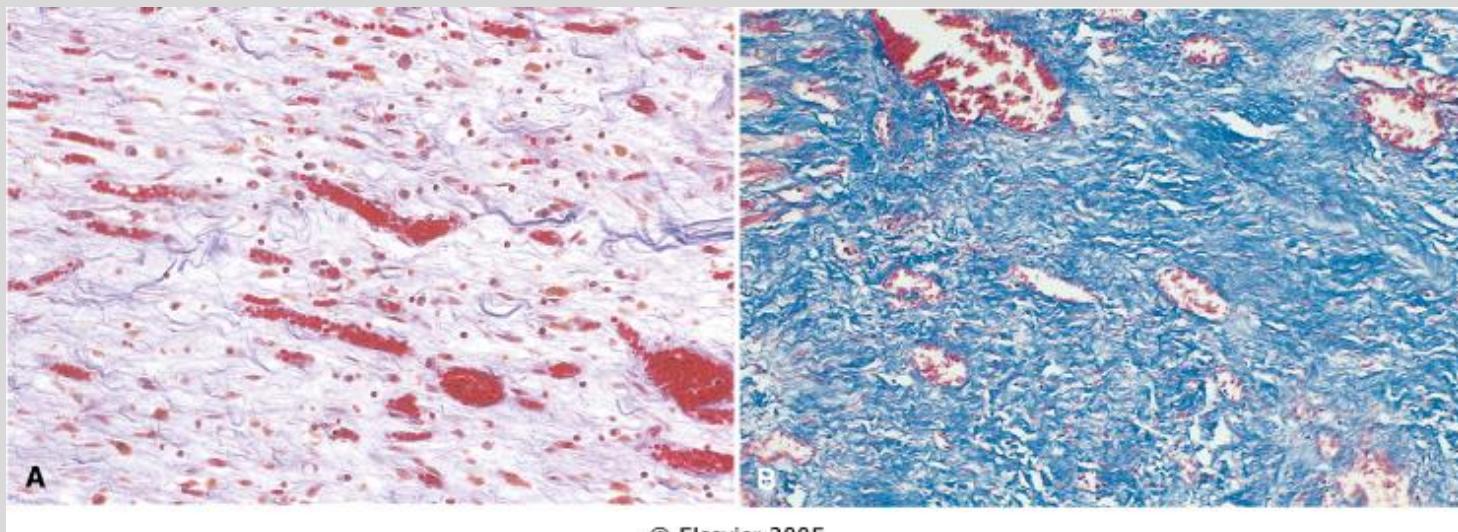
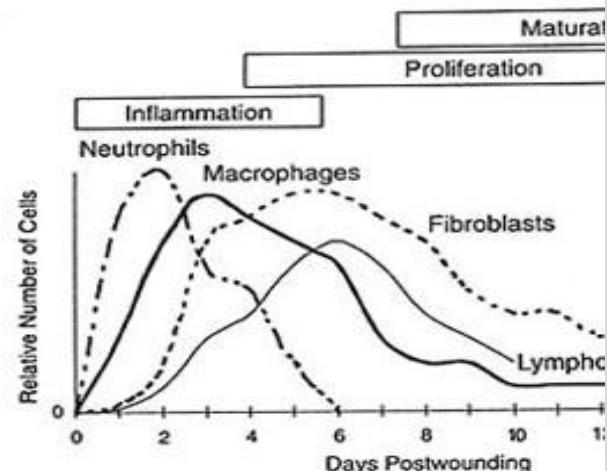
Day 2

Day 17

Day 30

Phase 2- proliferation

- 2 days to 3 weeks
- Granulation tissue-
 - 1- fibroblasts: to lay down collagen
 - 2- angiogenesis : to supply the repair/regeneration process



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Phase III: Maturation

- **Type III collagen is replaced by type I**
 - Acquires final tensile strength
- **Remodeling: scar tissue becomes avascular and acellular**
- Wound contraction- wound edges pull together to close the defect
 - **Myofibroblasts**- fibroblasts with muscle filaments
 - Display features of fibroblasts and smooth muscle cells



Healing by combinations of regeneration and repair

- Best example - skin wound
- Healing by **first intention or primary union** (epithelial regeneration):
 - When injury **only involves epithelial layer**
 - Clean skin wounds (e.g., **surgical excision**) – death of limited number of epithelial and connective tissue cells
- Healing by **second intention**
 - Edges of skin cannot be brought together
 - **tissue loss greater**
 - epidermal cells need longer time to cover surface
 - **more intense inflammatory reaction**
 - **abundant granulation tissue, extensive collagen deposition forming substantial scar**

Healing by Primary (First) Intention – Epithelial Regeneration

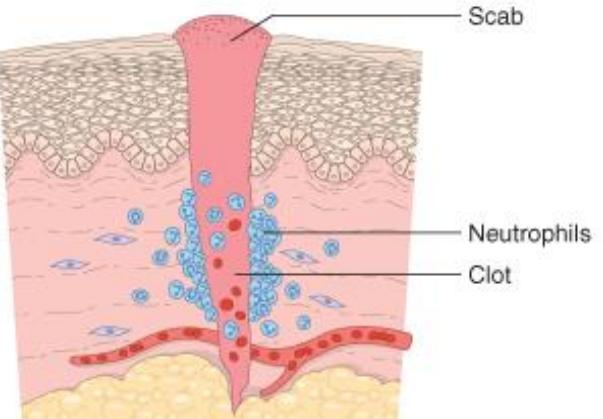
- Inflammation, proliferation of cells, maturation of connective tissue
- Wounds with opposed edges; involves only epithelial layer
- Ex; healing of a clean, uninfected surgical incision approximated by surgical sutures



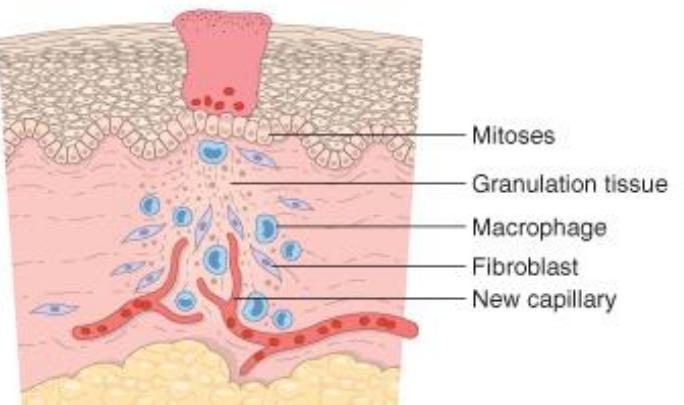
HEALING BY FIRST INTENTION

HEALING BY SECOND INTENTION

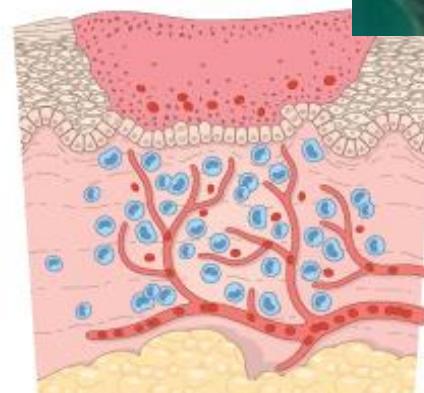
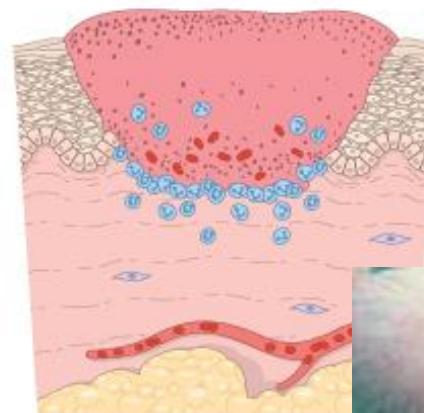
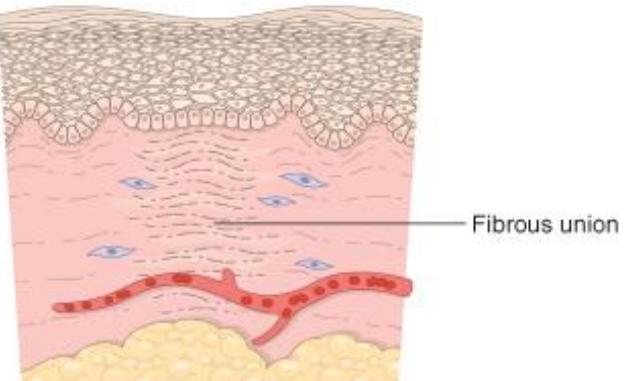
24 hours



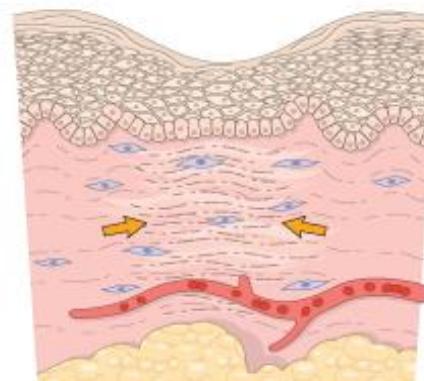
3 to 7 days



Weeks



Wound contraction



**PERSISTENT STIMULUS
(chronic inflammation)**

Activation of macrophages and lymphocytes

Growth factors
(PDGF, FGF, TGF β)

Cytokines
(TNF, IL-1, IL-4, IL-13)

Decreased metalloproteinase
activity

Proliferation of fibroblasts,
endothelial cells, and
specialized fibrogenic cells

Increased collagen
synthesis

Decreased collagen
degradation

FIBROSIS

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REGENERATION OF THE LIVER

Partial hepatectomy of 60% of the liver → doubling of the size of the liver remnant within 1 month

- Mechanism= proliferation of remaining hepatocytes and repopulation from progenitor cells
- Situation where proliferative capacity of hepatocytes is impaired (e.g chronic liver injury)
- NOT regrowth of the lobes that were resected
- **Primary phase** – hepatocytes primed by cytokines made by Kupffer cells (macrophages) to receive and respond to GF signals
- **Growth factor phase** – hepatocytes are stimulated into metabolism
- **Termination phase** – hepatocytes return to quiescence

Robbins and Cotran, Pathologic Basis of Disease, 10th ed., 2020, Ch. 3

Deterrents to wound healing

- **Local infection**....pro-inflammatory cytokines and tissue proteases degrade granulation tissue; persistent tissue injury and inflammation
 - **Hypoxia**....deters collagen fibril crosslinking (hydroxylation of proline and lysine), e.g, arteriosclerosis, inadequate circulation
 - **Trauma**
 - **Foreign bodies**
 - **Diabetes**....glycosylation (bonding of glucose to RBC and protein) impairs neutrophil and macrophage phagocytosis
 - **Malnutrition**....decrease in proliferation phase, Vit C needed for hydroxylation
 - **Immunodeficiency**
 - **Medications**..corticosteroids blunt inflammatory process; NSAIDS inhibit platelet function
- Hormones** – glucocorticoids (anti-inflammatory and inhibit collagen synthesis)
- Mechanics** – early motion of wound can separate edges
- Size, location, type of wound** – e.g. face (more vascular) heals faster than foot



Dehiscence:
Most commonly after
abdominal surgery
secondary to
increased abdominal
pressure:
obesity, vomiting,
coughing, etc.

<http://usmlepathslides.tumblr.com/post/34870481649/wound-dehiscence-with-evisceration-abdomen-wound>



Ulceration –
e.g., lower extremity,
poor circulation in
diabetes, PVD

<http://missinglink.ucsf.edu/lm/DermatologyGlossary/ulceration.html>



Keloid following ear piercing

Keloid v. Hypertrophic scar

Disorganized
collagen
formation

Extends beyond
borders of
original wound
wound

Frequently recur
after resection

Parallel
collagen
formation

Confined to
borders of
original

Infrequently
recur after
resection

<http://medicalpictures.net/keloid-pictures/>

Case Question

- An experiment is being conducted on the effects of certain drugs on wound healing. After the administration of drug A, a cut is made in the thigh of a laboratory rat and **one week later**, a biopsy is taken of the area. At high magnification, the tissue has capillaries, fibroblasts, and a variable amount of inflammatory cells (mostly mononuclear such as macrophages, but with occasional neutrophils still present). What type of tissue does this best represent?
 - A. scar tissue
 - B. granulation tissue
 - C. purulent tissue
 - D. permanent tissue

Summary Slide

- Definitions of healing, repair, regeneration
- Labile, stable, permanent cells – see slide 6
- Three phases of wound healing
- Repair by scar – granulation tissue, angiogenesis, connective tissue deposition (collagen and ECM)
- Example of skin injury – healing by primary and secondary intention
- Wound contraction, connective tissue remodeling, tensile strength
- Liver regeneration, examples of repair and healing
- Deterrents to wound healing – see slide 38
- Complications of wound healing – slides 39 - 42

Lecture Feedback Form:

<https://comresearchdata.nyit.edu/redcap/surveys/?s=HRCY448FWYXREL4R>