# Lecture 7

part of inflammatory response & comes At last (Rs)

# TISSUE REPAIR:

need Mediators (GFs)

- **Inflammation may cause injury and repair is critical after eliminating the enemy** to repair what was damaged depending on degree of damage
- **Repair can be achieved by:**
  - **1. Regeneration** → when mild injury & tissue has regeneration Ability.
  - **2. Scar & fibrosis** → when regeneration Ndt possible or injury is very severe.

  **Both require mediators and cellular proliferation. And interactions with ECM**

growth

# TISSUE REGENERATION:

- Regeneration requires growth factors and interactions between cells and matrix (ECM)
- Tissue types → depending on tissue type → regeneration occur.

Based on their Ability to regenerate.

| | |
|---|---|
| Labile tissue | Continuous regeneration : epithelia of mucosal surfaces → always go proliferation |
| Stable tissue<br>↳ enter $G_0$ But get out to complete cycle when stimulated with growth factors. | Normally in $G_0$, but can be stimulated to regenerate when injured (liver, Kidney, pancreas) → more differentiated |
| Permanent tissue<br>↳ enter $G_0$ & don't leave it. | Terminally differentiated, non proliferative (neurons and cardiac muscle, skeletal muscle) → can't regenerate or proliferate |

iF there is loss of it → there is No regeneration usually replaced by scar tissue when damaged.

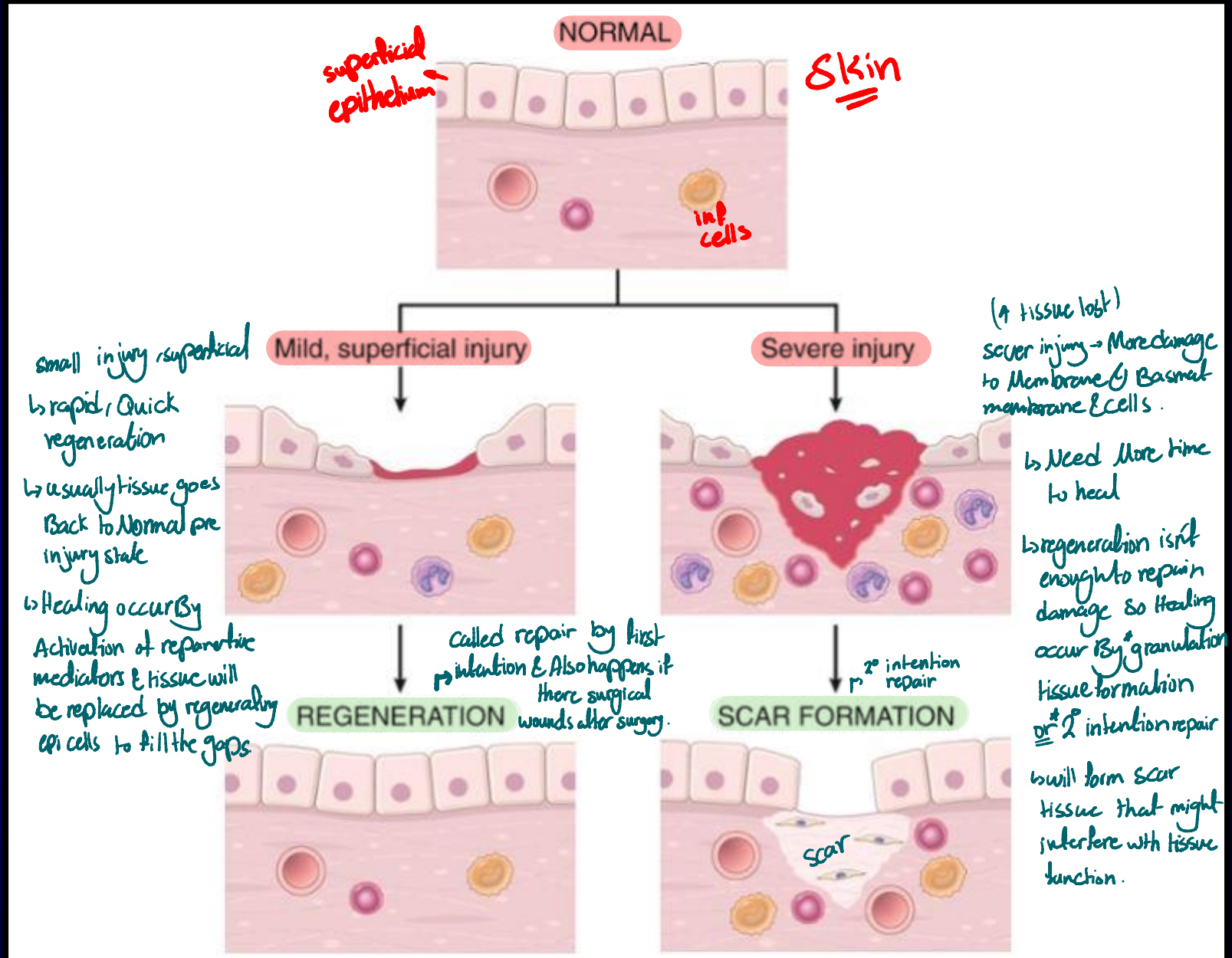



FIG. 3.23 Mechanisms of tissue repair: regeneration and scar formation. Following mil...

# LIVER REGENERATION:

- Liver can regenerate in 2 ways:
  - 1. Hepatocytes proliferation, post partial hepatectomy
  - 2. Progenitor cells gets activated and proliferate and differentiate

Both need growth factors & cytokines and cell matrix interactions

# Summary

## Repair by Regeneration

- Different tissues consist of continuously dividing cells (epithelia, hematopoietic tissues), normally quiescent cells that are capable of proliferation (most parenchymal organs), and nondividing cells (neurons, skeletal and cardiac muscle). The regenerative capacity of a tissue depends on the proliferative potential of its constituent cells.
- Cell proliferation is controlled by the cell cycle, and is stimulated by growth factors and interactions of cells with the extracellular matrix.
- Regeneration of the liver is a classic example of repair by regeneration. It is triggered by cytokines and growth factors produced in response to loss of liver mass and inflammation. In different situations, regeneration may occur by proliferation of surviving hepatocytes or repopulation from progenitor cells.

# ② REPAIR BY SCARRING:

- Large amount of tissue damage
- "Patching", wound healing and Scarring
- Healing by first and second intention.
- Steps:

1. Hemostatic plug (platelets)…minutes
2. Inflammation (Macs, M1 and M2)…6-48 hours
3. Cell proliferation (granulation tissue)…10 days
4. Remodeling…. 2-3 weeks

if during initial phase of injury epith cells or parynchema won't be able to quickly replace damaged cells to repair occurs by scar formation (fibrosis)

this req longer process of repair by

1. to stop bleeding
2. 
3. 

↳ Quick (surgical scars when surgeon cuts like skin & approx tissue & suture it so repair & replacement of lost tissue will be quick)
- repithilization
- small tissue damage & Mild injury
- min scar tissue / won't affect tissue function

↳ more tissue damage
- slower
- need extensive granulation tissue formation & Angiogenesis to prepare ground for scar formation
- more scar tissue formed / Affect function

steps of wound healing by scaring and fibrosis

→ Hemostasis = cf → No Bleeding

1. ↳ close injury to prevent further bleeding. ↳ form

Quick But if patient taking Anti Platlet drug will take longer time.

initial factors Stimulate Platlet aggregation. Quick ↳ platelets + fibrin = Clot

2. starts

3. ↳ this includes Angiogenesis + fibroblast migration & prolif… + New BV formation (Angiogenesis) formation

4. Process starts

& then the extra tissue will be removed & cleared out before strong scar tissue replacing the damaged Parenchyma.

large amount of tissue lost

* Platelet plug → Eschar → collagen scar *

transform to

transform to

↳ initially Blood will leak into the area

* Need to have good Blood supply for proper repair

& platelets will get aggregated on the surface to prevent further Bleeding

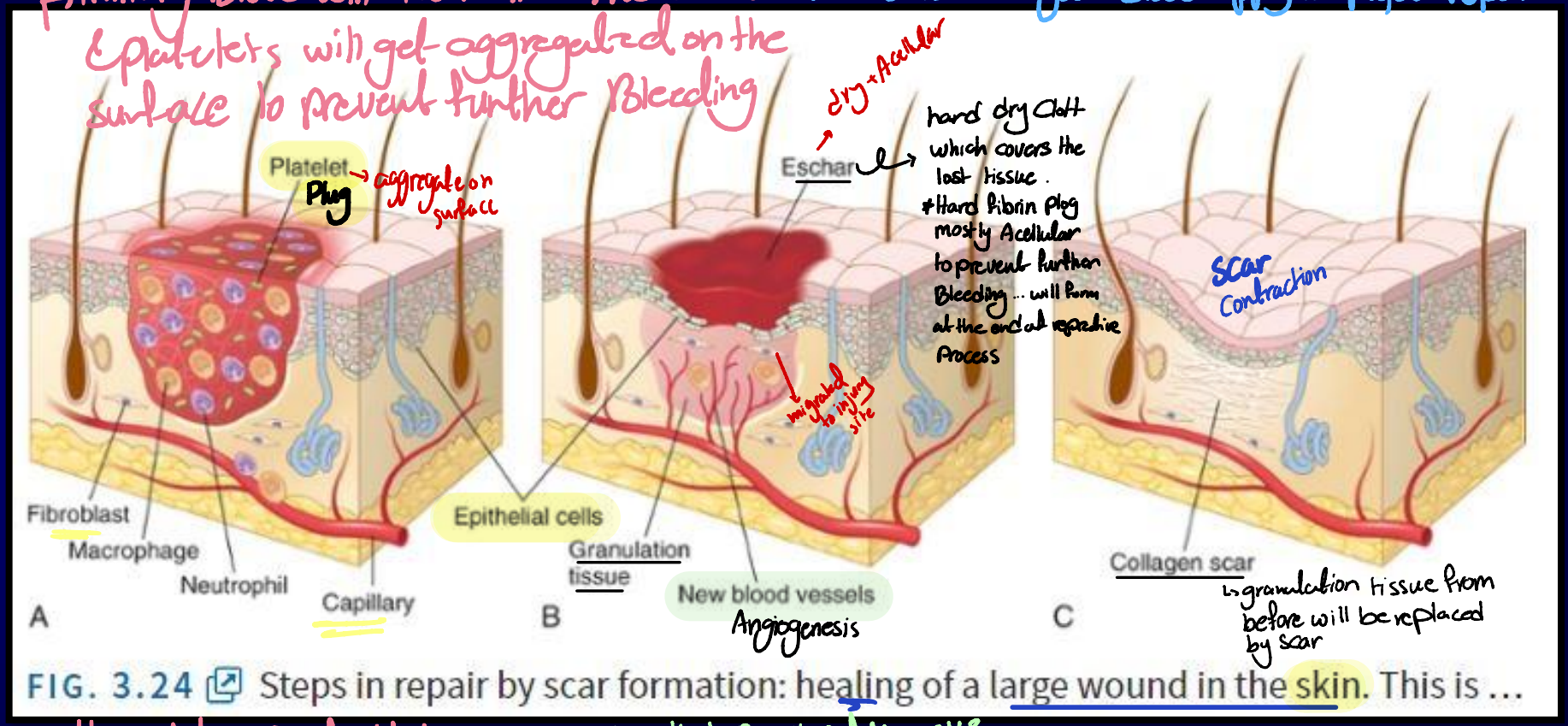



FIG. 3.24 Steps in repair by scar formation: healing of a large wound in the skin. This is ...

the underlying BV, fibroblast of Matrix will Also Be in touch with that injury.

↳ then cytokines & GF will be released & Angiogenesis starts At the base

↳ multiple Branches of New BV & capillaries will start to crall over

↳ GF stimulating Epith cells Proliferation to cover the lost SA.

↳ the angiogenesis process & the interaction BW the GF released from IV comp & the interaction BW BV, the injured area & ECM will start growing granulation tissue

↳ Then the granulation tissue will be replaced in the final stage of repair (Remodeling) By scar tissue which predomin. ACellular Strong Collagen.

# Lecture 8

# ANGIOGENESIS:

↳ formation of New BVs

- **Central role in healing**
- **Requires multiple steps; signaling pathways, growth factors, cell-matrix interactions and enzymes of remodeling**
  - **GF: VEGF-A, FGFs mainly FGF-2, TGF-ß**
    - **Notch signaling: sprouting**
    - **ECM proteins**
    - **Enzymes for final remodeling**

vascular epithilial GF

Fibroblast GF family

Transforming GF-B

GFs involved in Angiogenesis (major players But Not only)

↳ one of the most Potent Scar forming/fibrogenic mediator.

↳ initial step in Angiogenesis

interact with GFs.

Cut extra Collagen & extra proteins to Clean up area after the reprative process

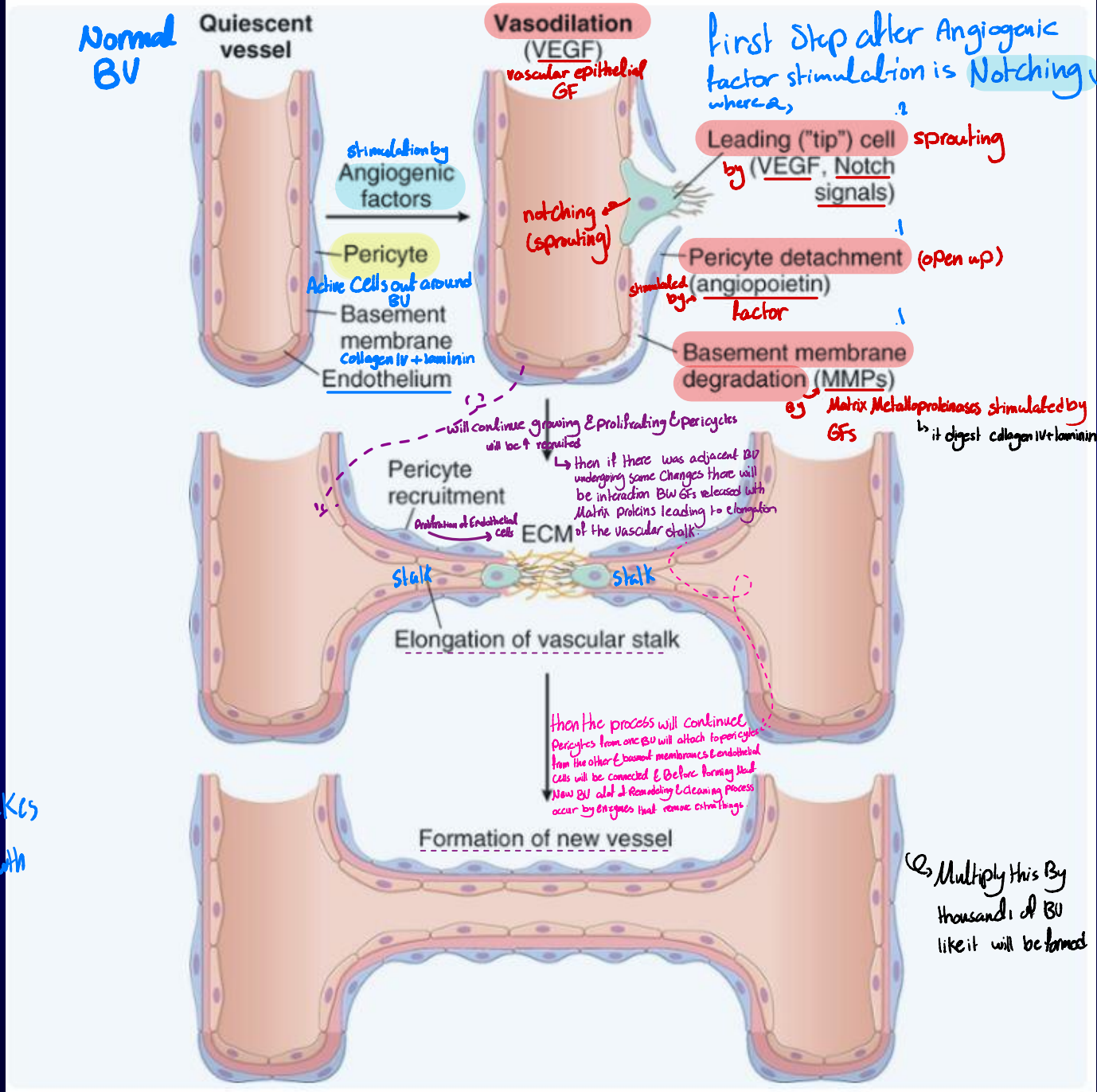



FIG. 3.25 Angiogenesis. In tissue repair, angiogenesis occurs mainly by the sprouting o…

last ★ Step in Repair

# ACTIVATION OF FIBROBLASTS AND DEPOSITION OF MATRIX:

↝ Comes AFter granulation tissue formation & Angio.

- **2 STEPS:**
  - **Migrations** ① **and proliferation** ② **of fibroblasts** — in the area of tissue injury → stimulated by certain GFs.
  - **Deposition of ECM proteins by these cells** — By the Activated Fibroblasts
- **Need cytokines and GFs: PDGF, FGF-2, TGF-ß** ↝ major fibrogenic mediator
  - PDGF: Platelet derived GF
  - FGF-2: Fibroblast GF
  - TGF-ß: Transforming GF.
- **Fibroblasts and myofibroblasts help lay down collagen to close the gap**
  - ↳ fibroblast slightly differentiated toward muscle & has contraction Ability and can lay down collagen in scars.
- **TGF-ß is the most important**
  - ↳ The most potent scar forming/Fibrogenic agent in repair.

* Collagen is the major protein deposited in scar formation At the end of Repare by granulation tissue formation.

After FB migrate & prolif.. → & deposit collagen, this process happens to make scar strong & contract

# * REMODELING OF CONNECTIVE TISSUE: Need GFs.

→ tensile strength of the scar

- It is needed to make the scar strong and contract it cuz the initial scar is composed of young Fb & collagen so it's Not strong enough & additional injury or trauma will destroy healing process.
- Cross linking of collagen by disulfide Bonds
- Switching type III to type I (stronger) collagen
- Degradation of collagen by Matrix Metalloproteinases (MMPs) and balanced by their inhibitors (TIMPs) → enzymes degrade extra collagen & transfer Col 3 to 1

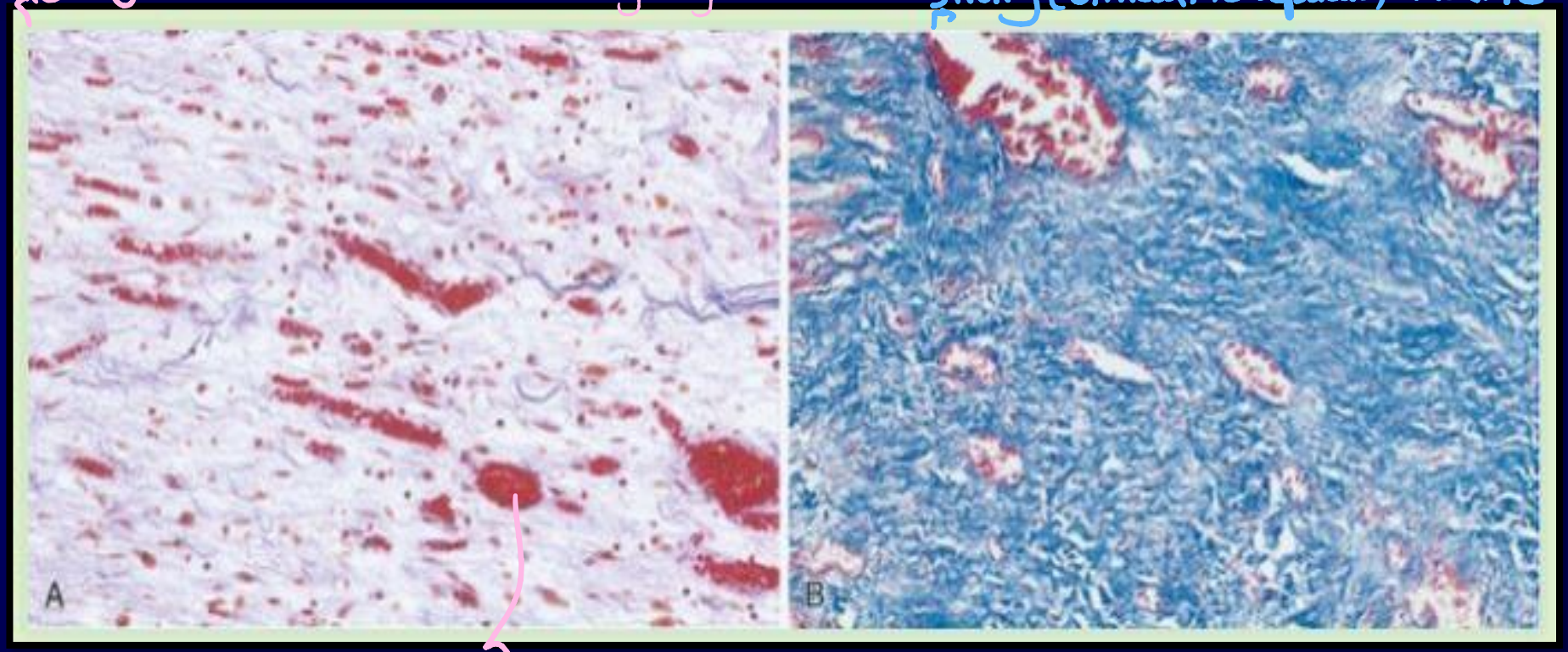
Tissue inhibitors of Metallo proteinases to prevent destroying All collagen structure.

# GRANULATIONS TISSUE VS MATURE SCAR

↳ Not strong enough to withstand further damage so should be transformed in late phases to very strong mature scar.

young

strong (difficult to seperate) mature




H&E stain

Angiogenesis

1. no of BUs more
2. // // mature scar is very Minimal /Col-III

Trichrome stain

to see scar (in blue) of Coll-I

1. less BUs
2. more scar tissue /Col-I

# Summary

## Repair by Scar Formation

- Repair occurs by deposition of connective tissue and scar formation if the injured tissue is not capable of regeneration or if the structural framework is damaged and cannot support regeneration.
- The main steps in repair by scarring are clot formation, inflammation, angiogenesis and formation of granulation tissue, migration and proliferation of fibroblasts, collagen synthesis, and connective tissue remodeling.
- Macrophages are critical for orchestrating the repair process, by eliminating offending agents and producing cytokines and growth factors that stimulate the proliferation of the cell types involved in repair.
- TGF-β is a potent fibrogenic agent; ECM deposition depends on the balance among fibrogenic agents, matrix metalloproteinases (MMPs) that digest ECM, and the tissue inhibitors of MMPs (TIMPs).

# Lecture 9

imP

↗ more than one can be present in one case

# ✦ FACTORS THAT IMPAIR TISSUE REPAIR *(IMPORTANT):*

1. **Infections** — enemy of the surgins or some one undergo surgery ⇒ if one get infected All reporative process will be interrupted & proper healing process will be delayed & proper healing would occur → there will be more complications, improper scar formation · that's why in severe Acute injury sometimes patient is Covered with Antibiotics specially in high risk intra Abdominal surgery where risk of infn & postoperative infn is high so patient is covered with Ab Before surgery to prevent infections
2. **Diabetes mellitus** — Patients with DM will have delayed reparative process & More time for healing → why? cuz DM affect liver, BV & every single cell → the glycosylation in Blood stream into tissues is toxic & very impact degree of Activation of GFs & Mediators .... specially in patients who aren't compliant & have bad control → the more control patient has, the more proper healing.
3. **Nutritional status** — if patient has Malnutrition .. won't have proper healing → u need to have prope Nu to have proper healing → so sometimes if u have depleted, Malnutried patient & u have to do surgery for him for certain reason → first you give him Parenteral nutrition giving him ↑ Calorie, ↑ protein in BV to Build up his immunity Before surgery.
4. **Steroids** — Strong Anti-infl drugs → ↓ immunity (immunocompromized) ⇝ Patients who take them will have delayed repair
   ↳ that's why they have ↑ chance for infections
5. **Mechanical factors** — ⇝ presence of Foreign body will delay healing & make it improper so you have to remove them
   • or u have patient who is very obese & he is Chronic smoker with COPD, continuously coughing & want to do to him Abdominal surgery → u have to take care of his Abdominal wound cuz of the increased intra Abdominal pressure when coughing, this'll - ugly impact healing & sometimes wound will seperate making what's called wound dihiscence.
6. **Poor perfusion** (Blood supply) — ⇝ Poor BS due to severe ischemia, hypertension, hyperlipidemia, Atherosclerosis ⇒ they need ↑ time for healing, need to take care of their nut & cover them with Ab.
7. **Foreign body** → u have to remove them, But sometimes removing them is more damaging so u can keep them for a while or keep it forever if it's for ex small needle in Soft tissue of the foot cuz removing it cause more damage so body will heal it by scar it self.
8. **Type and extent of tissue injury**
9. **Site of injury**
   ↳ facial injury heal quickly for child 15yo
   • if 75yo with ASE smoker & vascular Disease will take ↑ time to heal cuz his injury will be ↑ severe.
   ↳ Abdominal wounds heal slower than facial
   • peripheral lower limb injury take ↑ time than Abdomen.

# * ABNORMAL HEALING

1. • Deficient scar formation
2. • Excessive repair — more scar formation
3. • Contractures — Fibromatosis syndroms (superficial & Deep Fibromatosis)
   - has 3 types
     1. dupuytren contracture in the palm of the hand
     2. peyronic disease in penis
     3. solar fibromatosis
   - occurs in Abdomen & thigh called (Dismoid tumors)

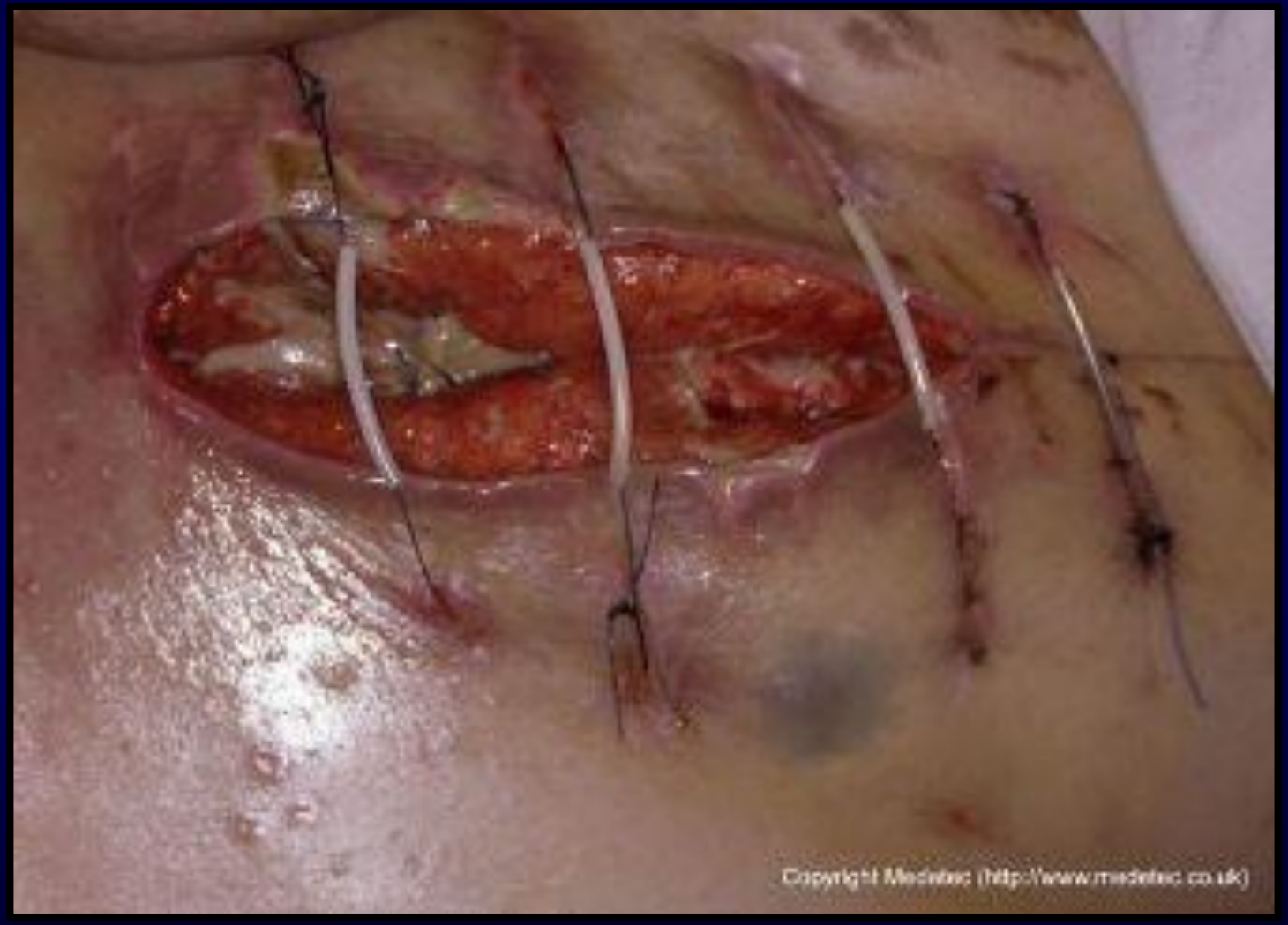
# DEFICIENT HEALING:

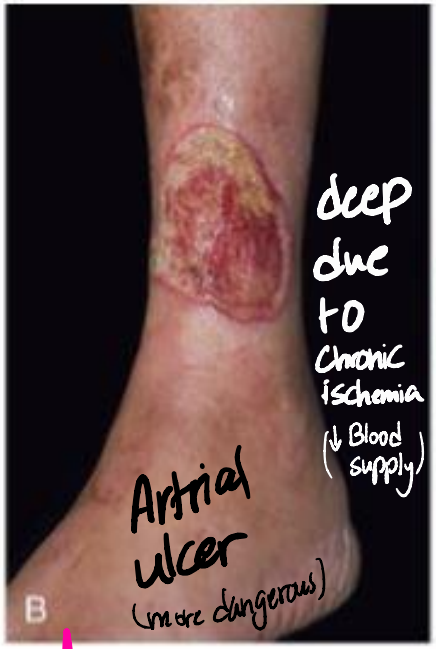
↳ Most of the time Produce ulcers

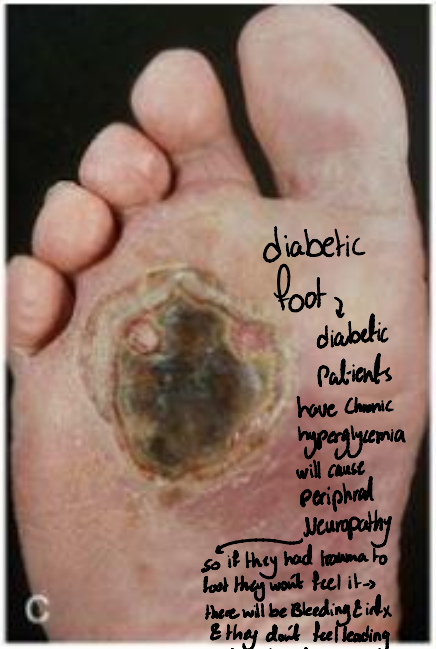
1. • Venous leg ulcers due to ↑ venous pressure
2. • Arterial ulcers when there is difficiency in artrial BS/perfusion (No Angiogenesis)
3. • Pressure sores (Decubitus ulcers) ulcers
4. • Diabetic ulcers Diabetic foot
5. • *** Wound dehiscence due to Mechanical factors mainly Abdominal surgery

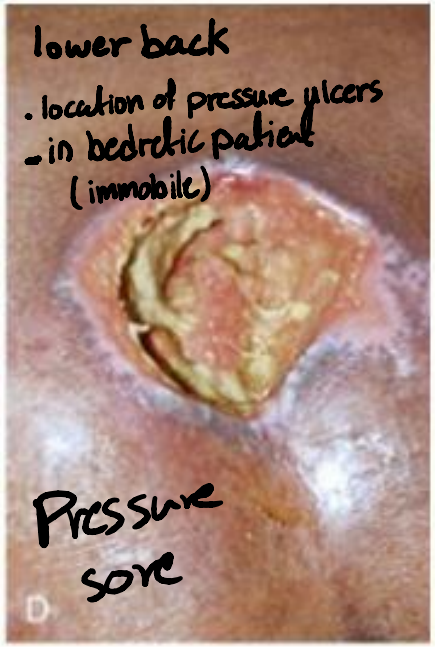
# Wound dehiscence:

due to ↑ intra Abdominal pressure

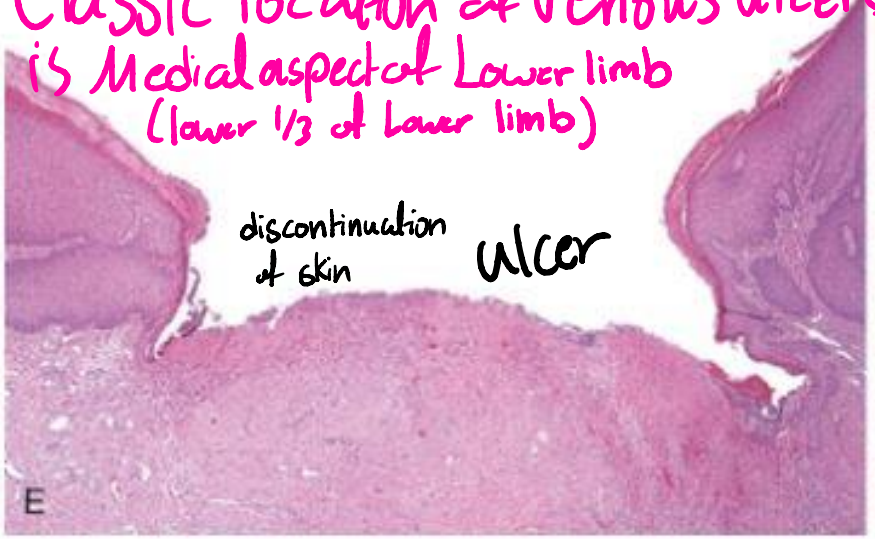


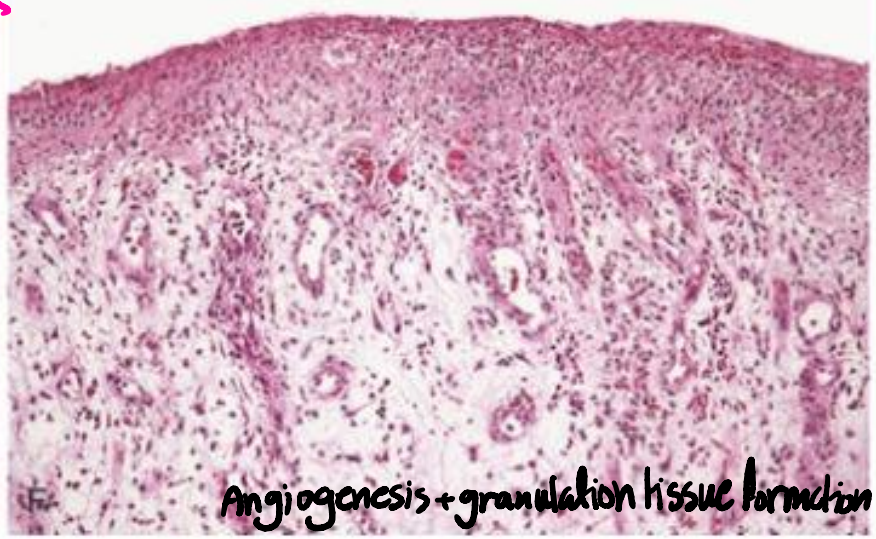




Classic location of venous ulcers is Medial aspect of Lower limb (lower 1/3 of Lower limb)



# * EXCESSIVE SCARRING:

Abnormal healing

- 1. Hypertrophic scar
- 2. Keloid
- 3. Exuberant granulation tissue (proud flesh)
- 4. Aggressive fibromatosis (desmoid tumor)
- 5. Contractures

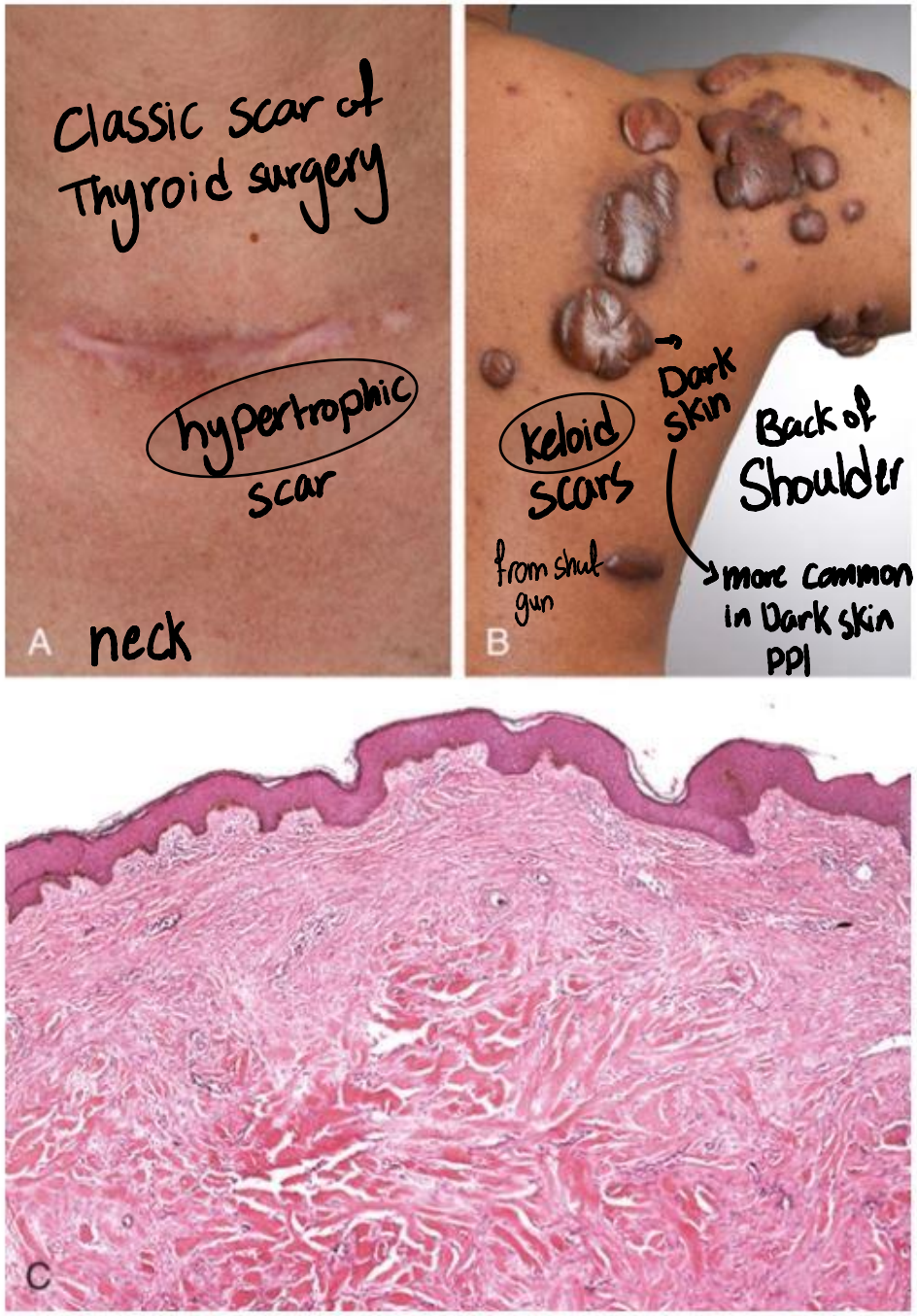



FIG. 3.28 Clinical examples of excessive scarring and collagen deposition. (A) Hypertro…

# FIBROSIS OF ORGANS:

- Scar and fibrosis: excessive deposition of collagen and ECM.
- Continuous infections and immunologic injuries cause organ fibrosis and loss of function
- TGF-ß is the most common cytokine of fibrosis
- Examples: liver cirrhosis, Idiopathic lung fibrosis, ESKD

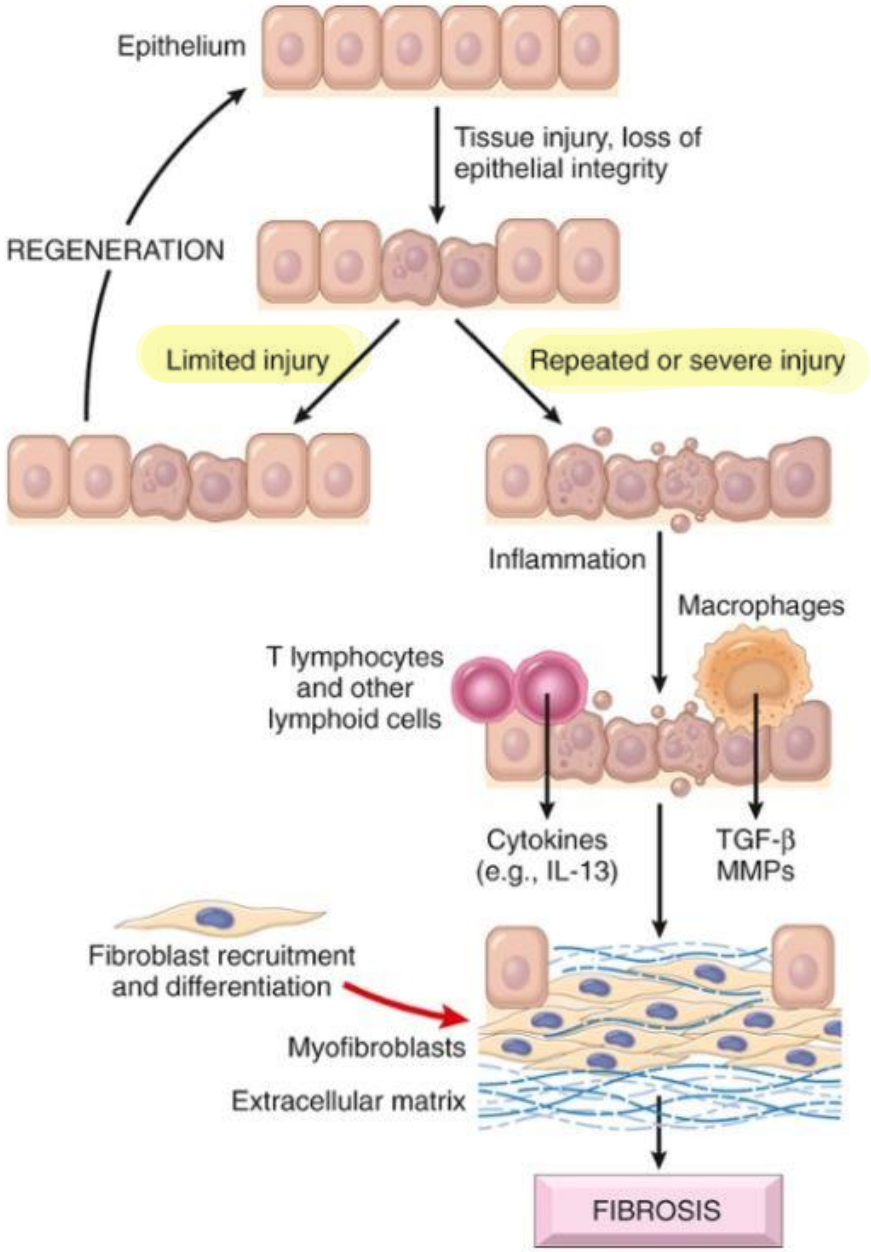



FIG. 3.29 Mechanisms of fibrosis. Persistent tissue injury leads to chronic inflammatio…

# Summary

## Cutaneous Wound Healing and Pathologic Aspects of Repair

- The main phases of cutaneous wound healing are inflammation, formation of granulation tissue, and ECM remodeling.
- Cutaneous wounds can heal by primary union (first intention) or secondary union (secondary intention); secondary healing involves more extensive scarring and wound contraction.
- Wound healing can be altered by many conditions, particularly infection and diabetes; the type, volume, and location of the injury are important factors that influence the healing process.
- Excessive production of ECM can cause keloids in the skin.
- Persistent stimulation of collagen synthesis in chronic inflammatory diseases leads to tissue fibrosis, often with extensive loss of the tissue and functional impairment.

# Lecture 10
# REVIEW

# GOOD LUCK