Tissue repair 2.

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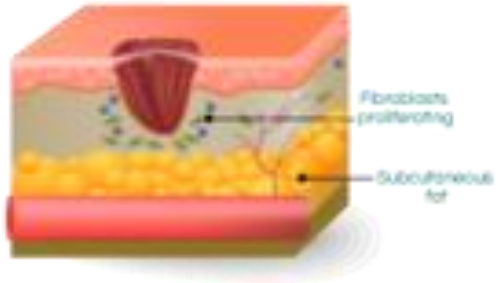
4 STAGES OF WOUND HEALING

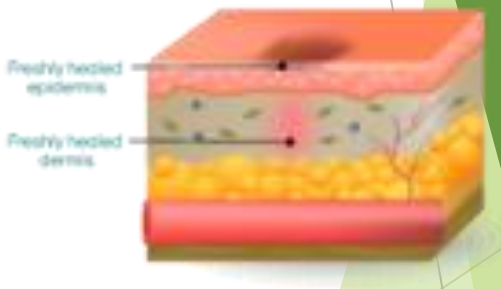
1. Hemostasis

2. Inflammatory

3. Proliferative



4. Remodeling



Steps in Scar formation

Injury

Hemostatic plug → Inflammation → Cell proliferation → Formation of **granulation tissue**

Stops bleeding, provides scaffold for deposition of fibrin

To eliminate offending agent

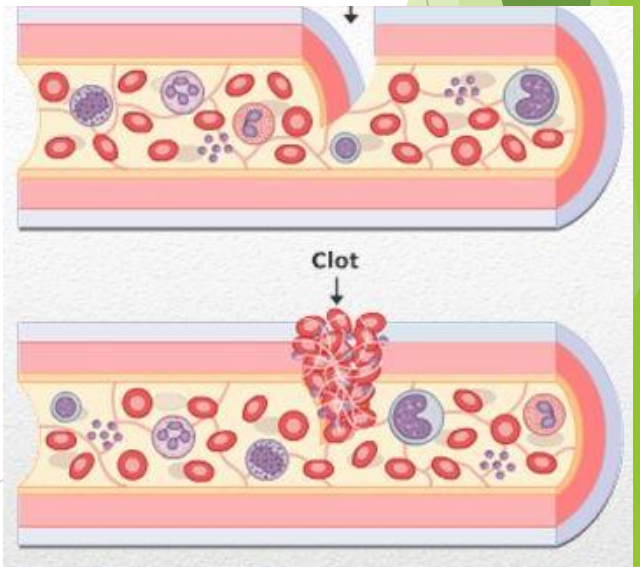
Remnants of injured tissue	Vascular Endothelial cells	Fibroblasts
Attempt to restore normal tissue	Creates blood vessels for nutrition during repair	Forms scar For defects which cannot regenerate

Deposition of **connective tissue (SCAR)**

Steps in Scar Formation

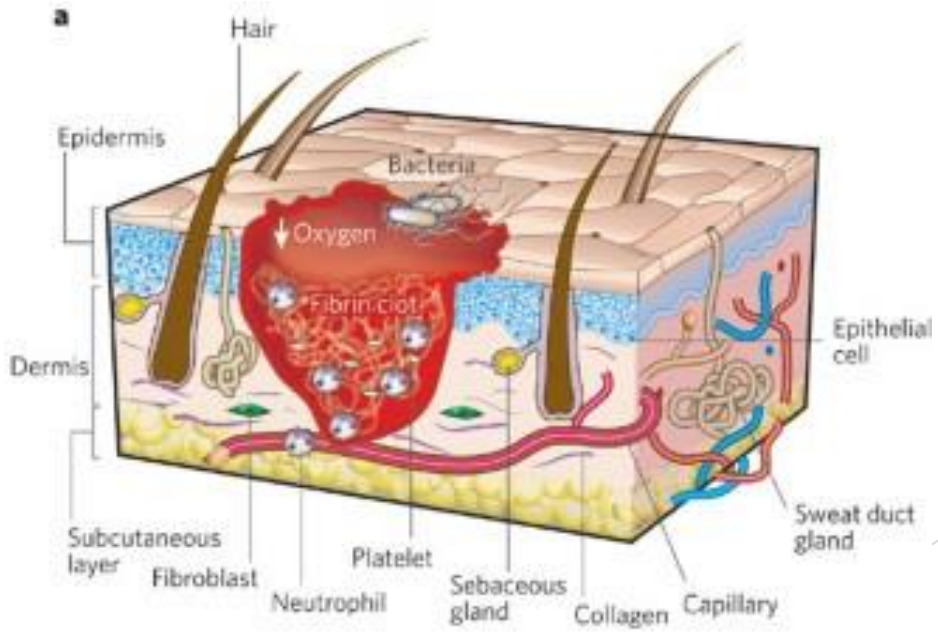
- 1. Within minutes after injury, a hemostatic plug comprised of platelets is formed:

- stops bleeding .
- provides a scaffold for infiltrating inflammatory cells.



- **2.Inflammation:**

- **Include acute and chronic inflammatory responses.**
  - **The inflammatory cells:**
    - **eliminate the offending agents**
    - **clear the debris**



- **Macrophages are the central cellular players in the repair process:**

- **M1 macrophages :**
  - **clear microbes and necrotic tissue and promote inflammation .**

- **M2 macrophages:**
  - **produce growth factors that stimulate the proliferation of many cell types in the next stage of repair.**

- **3.Cell proliferation.**

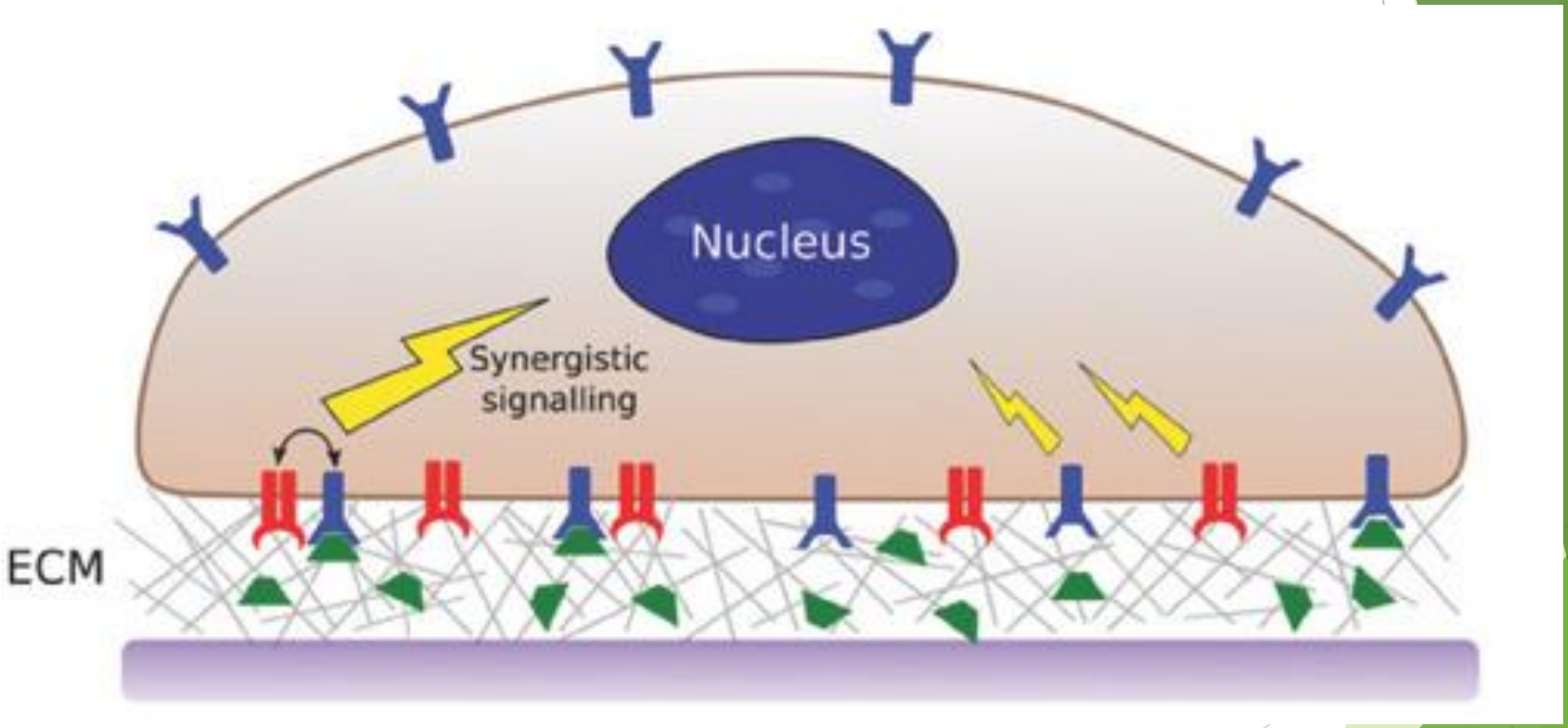
- In the next stage, which takes up to **10 days**, several cell types migrate to close the now-clean wound, including :

  - **Epithelial cells**: migrate over the wound to cover it.

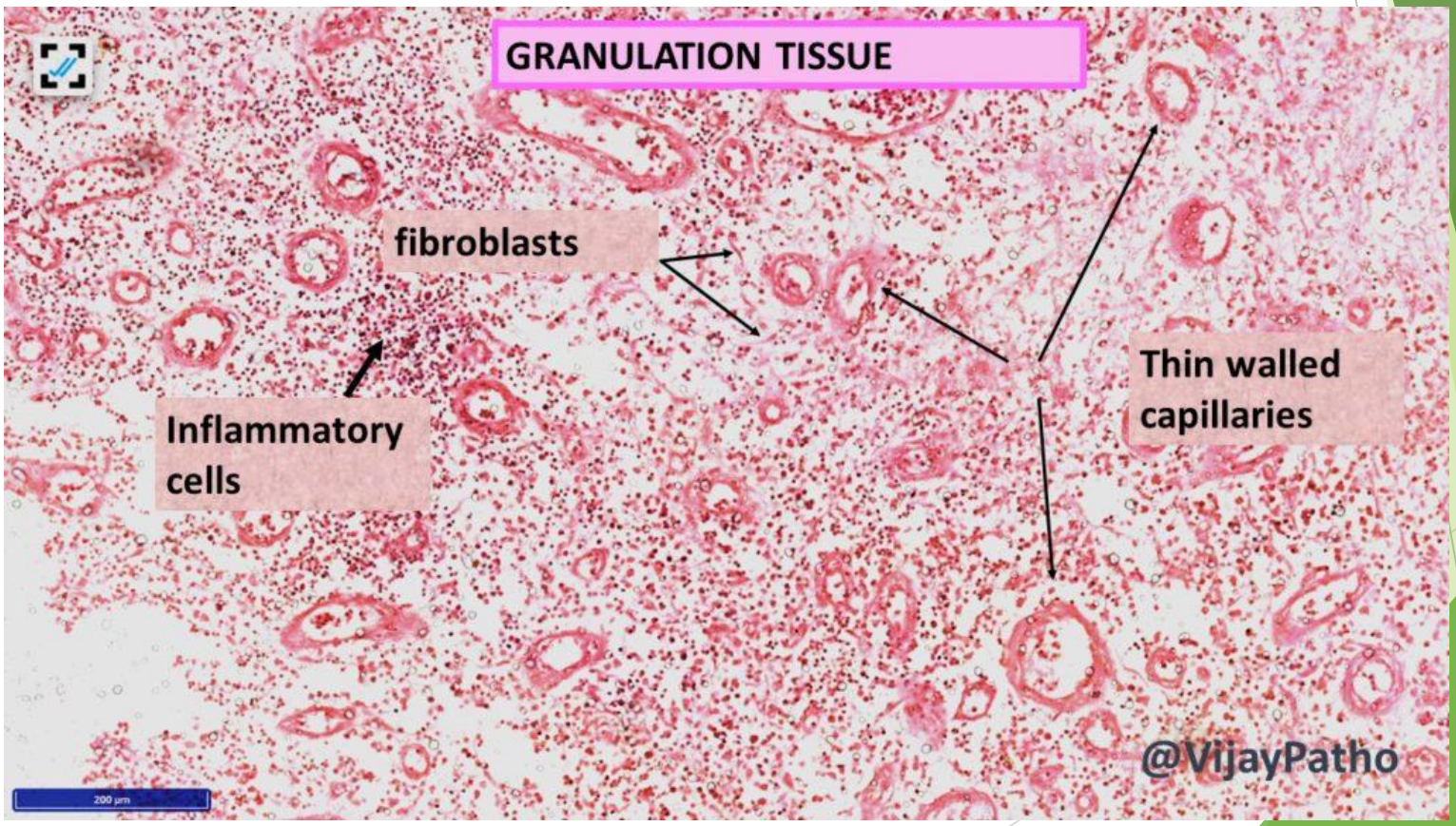
  - **Endothelial** and other vascular cells: proliferate to form new blood vessels, a process known as **angiogenesis**

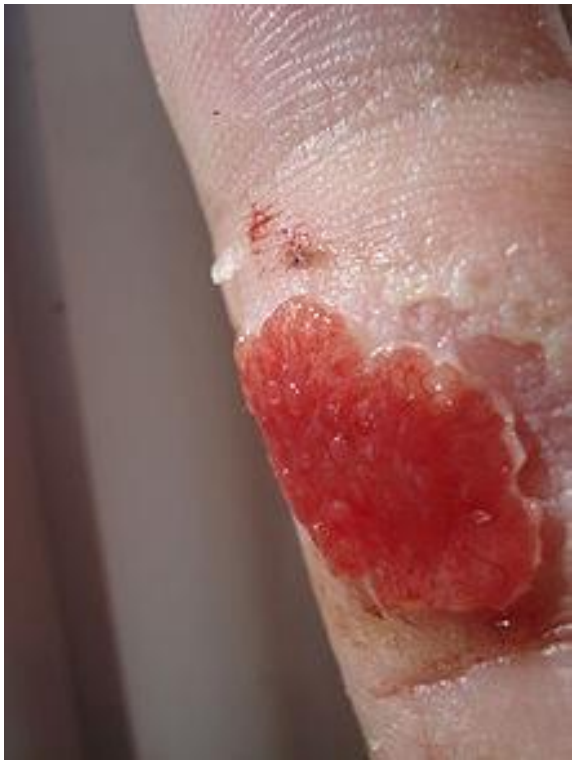
  - **Fibroblasts**: proliferate and migrate into the site of injury and lay down collagen fibers that form the scar.

- **Cell proliferation is driven by signals provided by growth factors and from the extracellular matrix**.



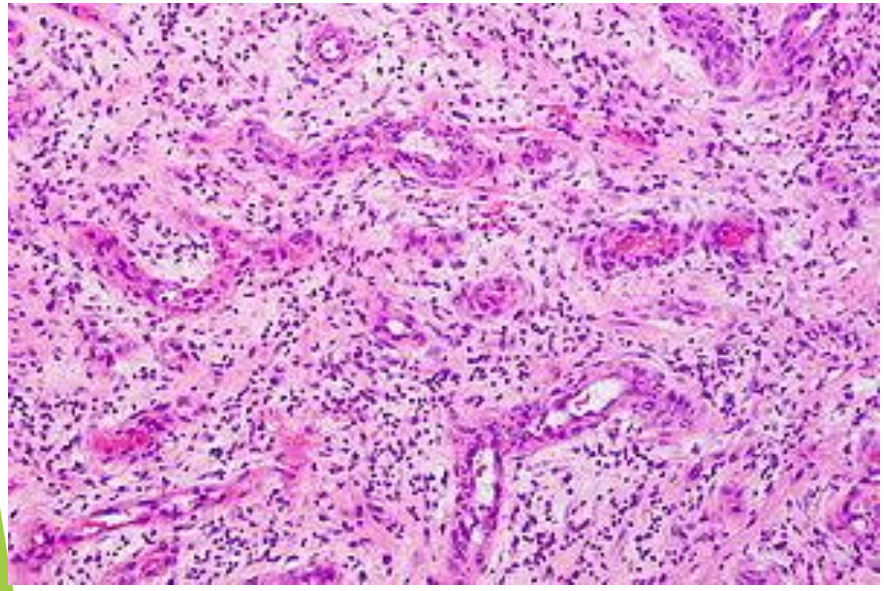
- The combination of proliferating fibroblasts, loose connective tissue, new blood vessels and scattered chronic inflammatory cells, forms a **granulation tissue.**





Granulation tissue.

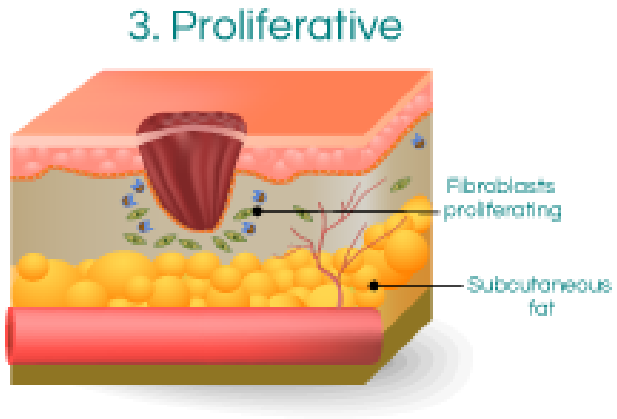
Pink, soft, granular gross appearance, such as that seen beneath the scab of a skin wound.

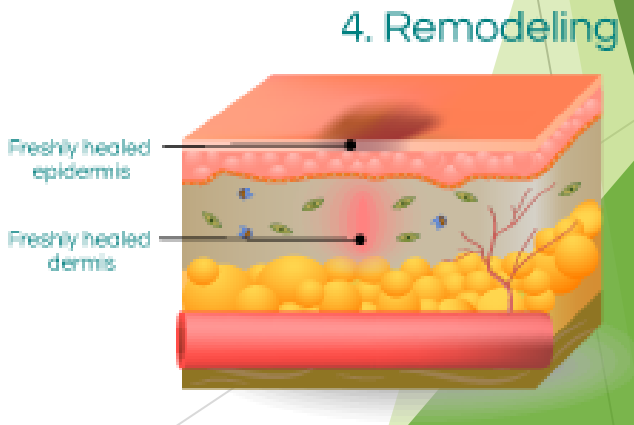


Proliferating fibroblasts, loose connective tissue, new blood vessels and scattered chronic inflammatory cells

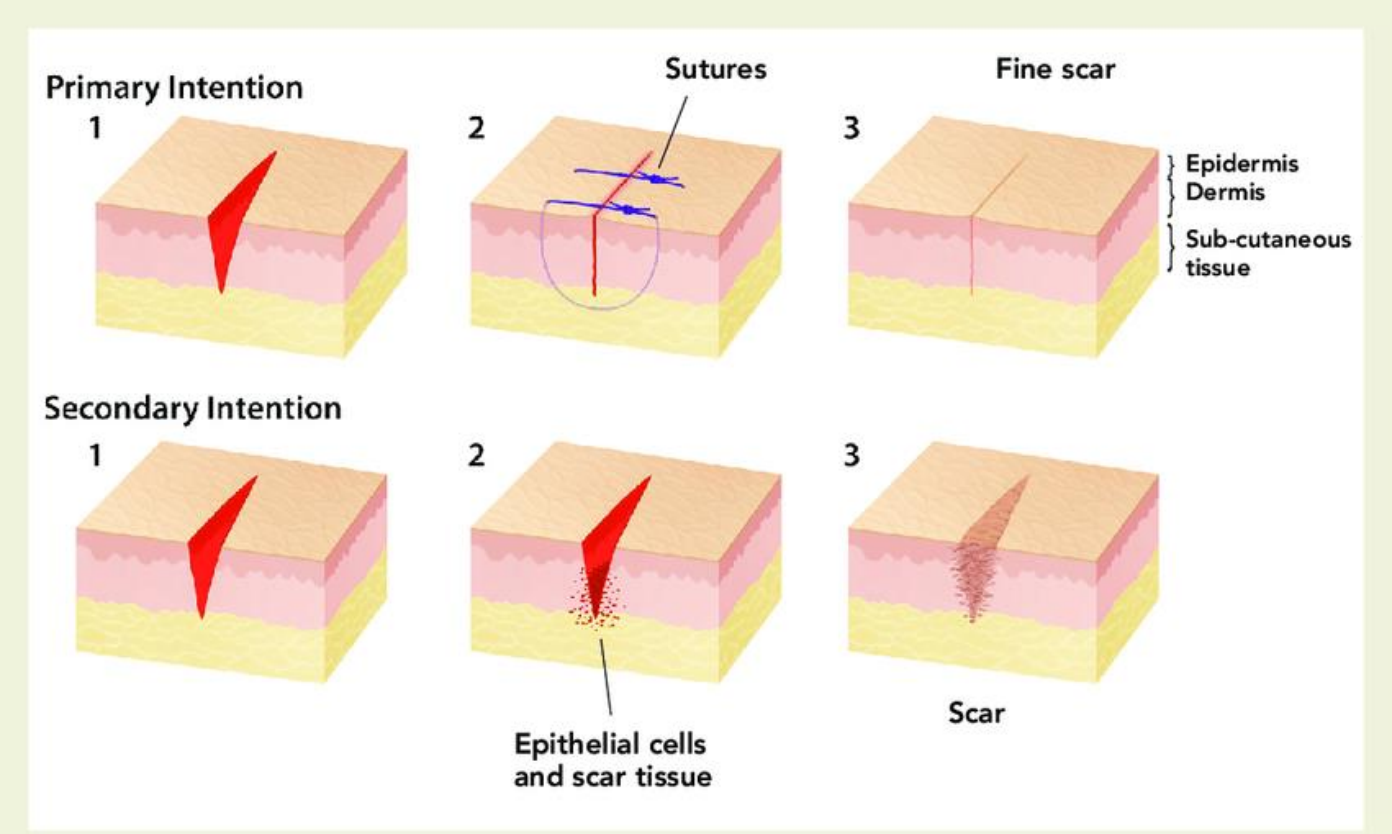
4. Remodeling.

- The connective tissue that has been deposited by fibroblasts is reorganized to produce the stable fibrous scar.
- This process begins **2 to 3 weeks** after injury and may continue **for months or years**





- Healing of skin wounds can be classified into healing by :
- First intention (primary union).
- Second intention (secondary union).



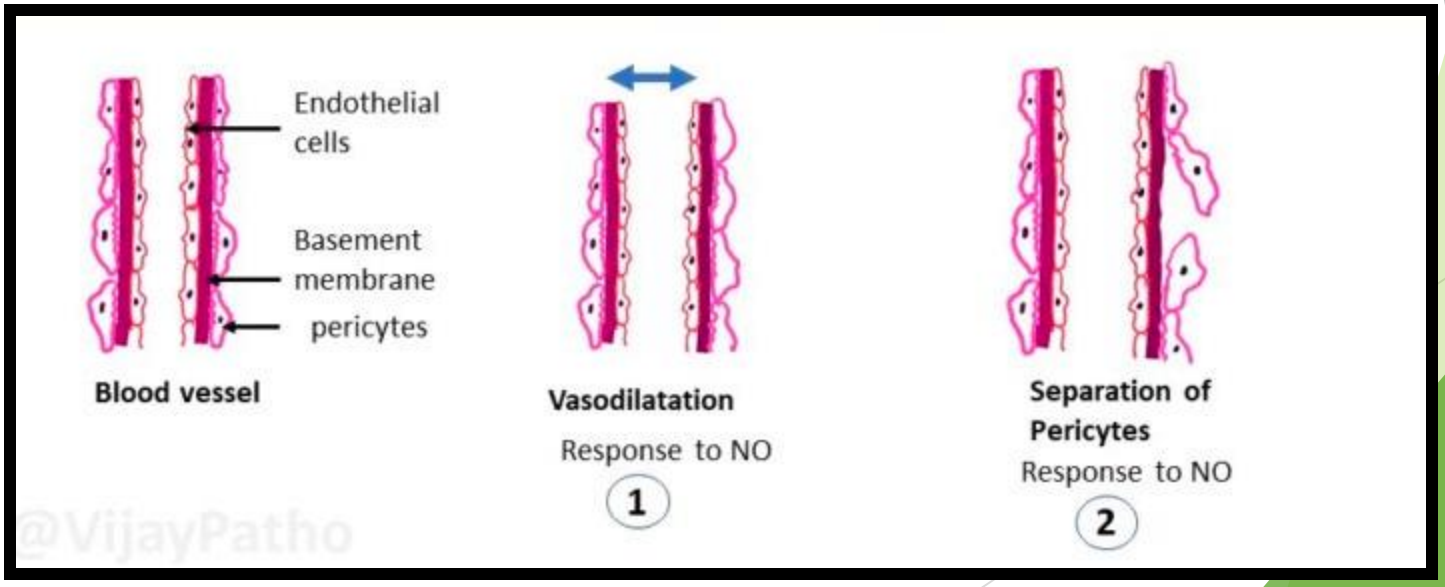
Angiogenesis

- Angiogenesis is the process of new blood vessel development from existing vessels.
- It is critical in:
  - Healing at sites of injury.
  - Development of collateral circulations at sites of ischemia.
  - Allowing tumors to increase in size

- Angiogenesis involves sprouting of new vessels from existing ones, and consists of the following steps:

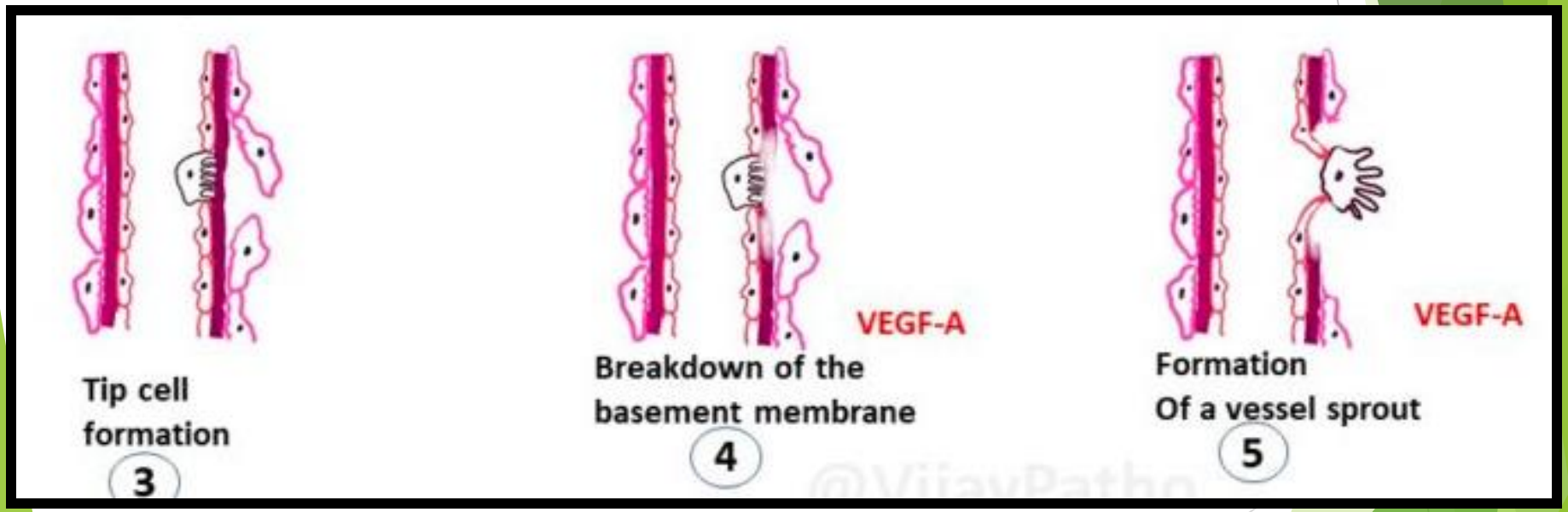
- Vasodilation in response to NO and increased permeability induced by VEGF .

- Separation of pericytes from the abluminal surface and breakdown of the basement membrane to allow formation of a vessel sprout .



- **Migration** of endothelial cells toward the area of tissue injury.

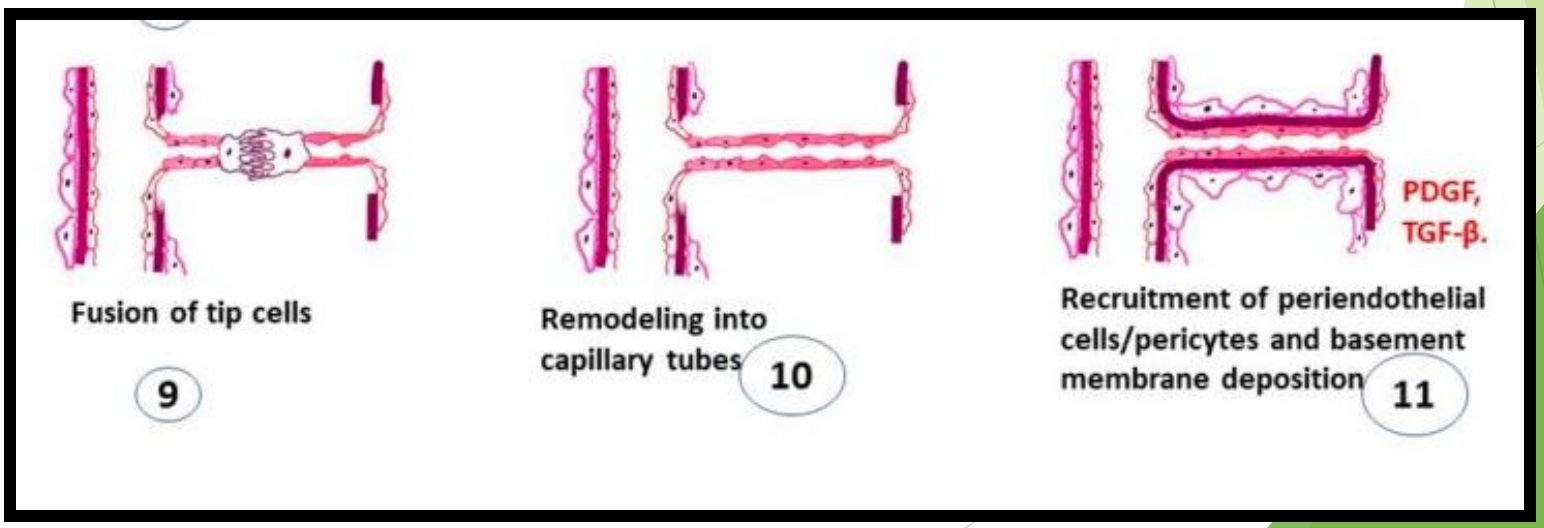
- **Proliferation** of endothelial cells just behind the leading front ("tip") of migrating cells.



- **Remodeling** into capillary tubes.

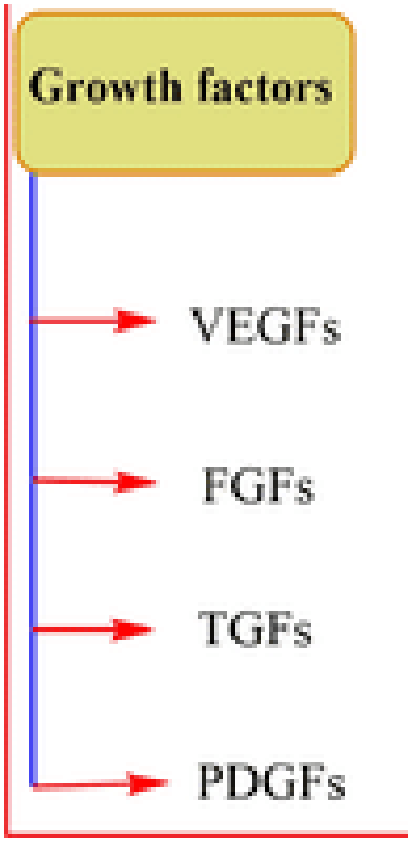
- **Recruitment** of periendothelial cells (pericytes for small capillaries and smooth muscle cells for larger vessels) to form the mature vessel.

- **Suppression** of endothelial proliferation and migration and **deposition** of the basement membrane



The process of angiogenesis involves several signaling pathways, cell–cell interactions, ECM proteins, and tissue enzymes:

1.Growth factors:



- Stimulates both migration and proliferation of endothelial cells
- Proliferation of endothelial cells.
- Suppresses endothelial proliferation and migration.
- Recruits smooth muscle cells

❖So PDGF and TGF-B participate in the stabilization process

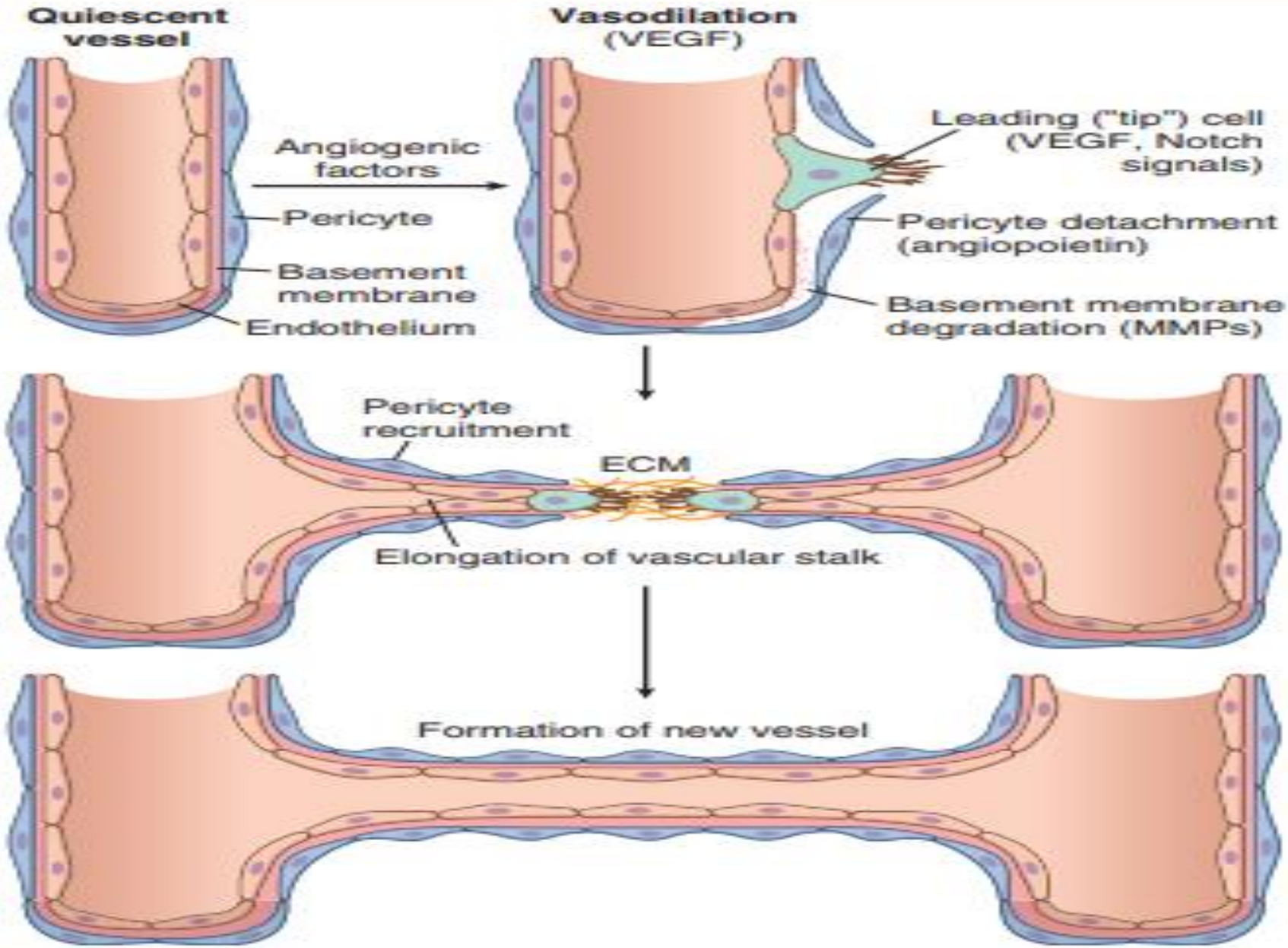


Fig. 3.25 Angiogenesis. In tissue repair, angiogenesis occurs mainly by the sprouting of new vessels. The steps in the process, and the major signals involved, are illustrated. The newly formed vessel joins up with other vessels (not shown) to form the new vascular bed.

- **2.Notch signaling.**
- Regulates the sprouting and branching of new vessels .

- **3.ECM proteins:**
- Participate in the process of vessel sprouting in angiogenesis, through interactions with integrin receptors .
- Enzymes in the ECM, notably the matrix metalloproteinases (MMPs), degrade the ECM to permit remodeling and extension of the vascular tube.

(3.Proliferative phase : proliferation of Fibroblasts)

- The laying down of connective tissue occurs in two steps:

- (1) Migration and proliferation of fibroblasts into the site of injury.

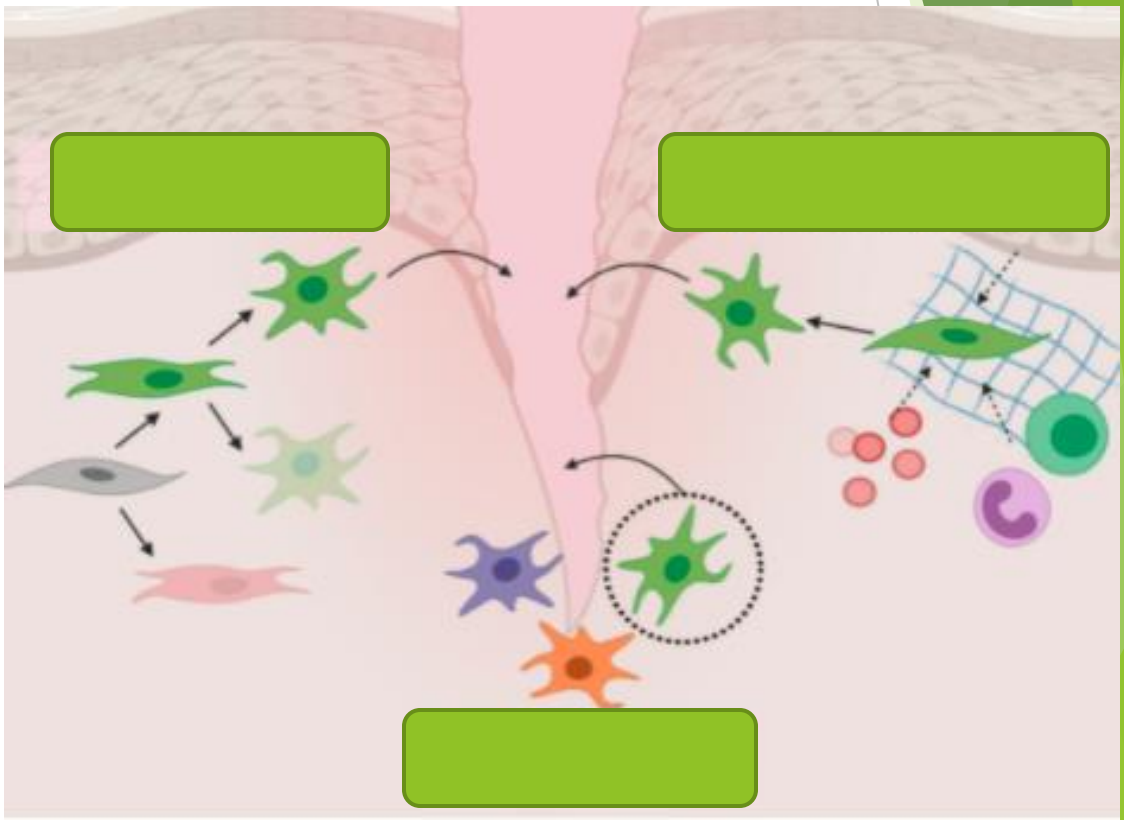
- (2) Deposition of ECM proteins produced by these cells

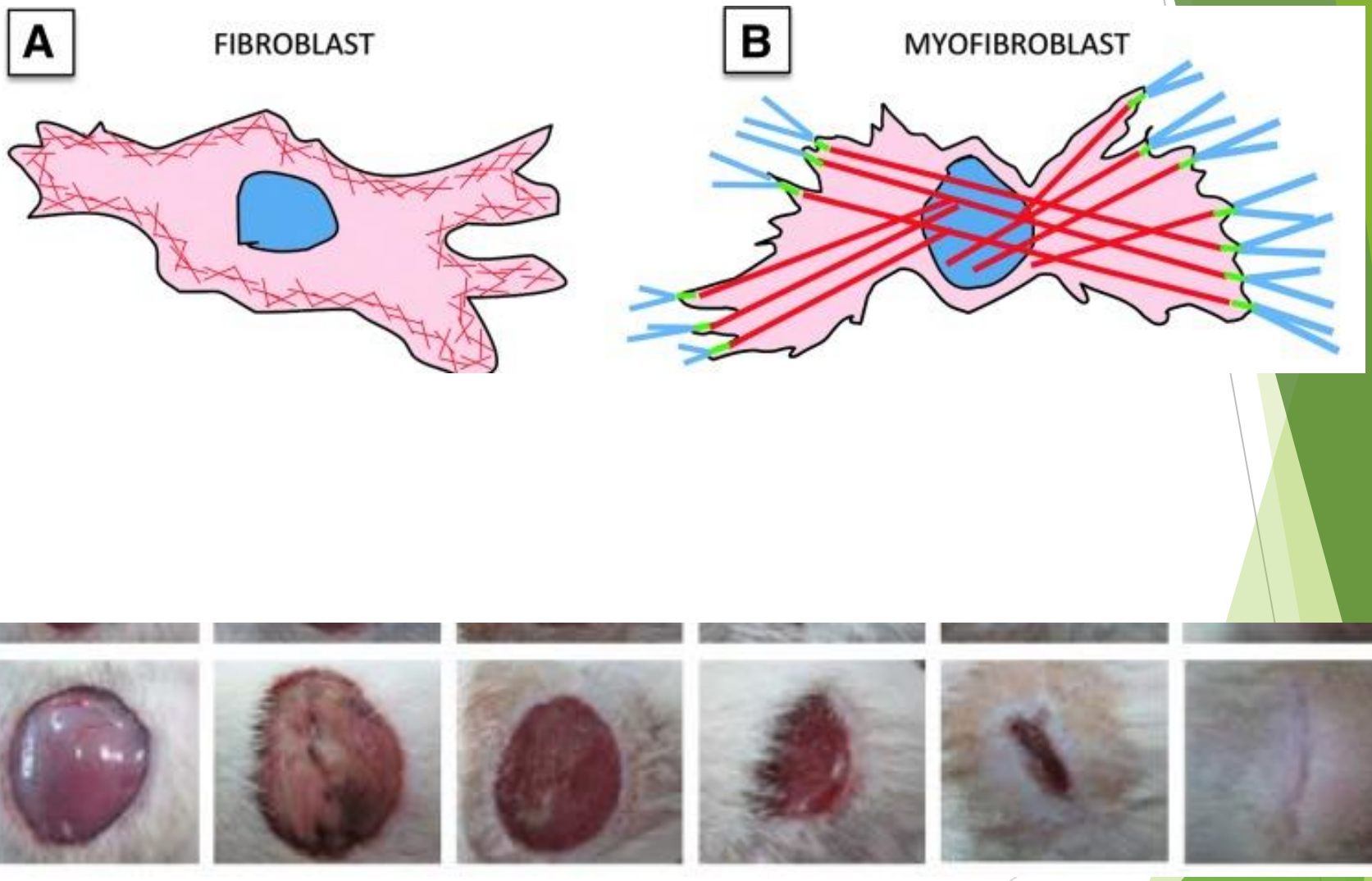
- These processes are under the control of cytokines and growth factors, including:

  - PDGF.
  - FGF-2.
  - TGF-β.

- The major sources of these factors are alternatively activated (M2) macrophages

- In response to cytokines and growth factors.
- fibroblasts enter the wound.
- fibroblasts vs myofibroblasts?
- Activated fibroblasts and myofibroblasts produce **collagen.**




A
FIBROBLAST
B
MYOFIBROBLAST

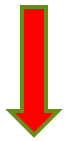
❖TGF-β

- The most important cytokine for the synthesis and deposition of connective tissue proteins.

- It is produced mainly by alternatively activated macrophages.

- TGF-β act to:
  - stimulates fibroblast migration and proliferation.
  - increases the synthesis of collagen and fibronectin.
  - decreases the degradation of ECM by inhibiting metalloproteinases.

- As healing progresses, the number of proliferating fibroblasts and new vessels decreases.



- Fibroblasts progressively assume a more synthetic phenotype and increased collagen synthesis.

- Collagen synthesis by fibroblasts begins early in wound healing (days 3–5) and continues for several weeks, depending on the size of the wound.

scar maturation :

- Transformation of the highly vascularized granulation tissue into a pale, largely avascular scar due to progressive vascular regression.

4. Remodeling of Connective Tissue

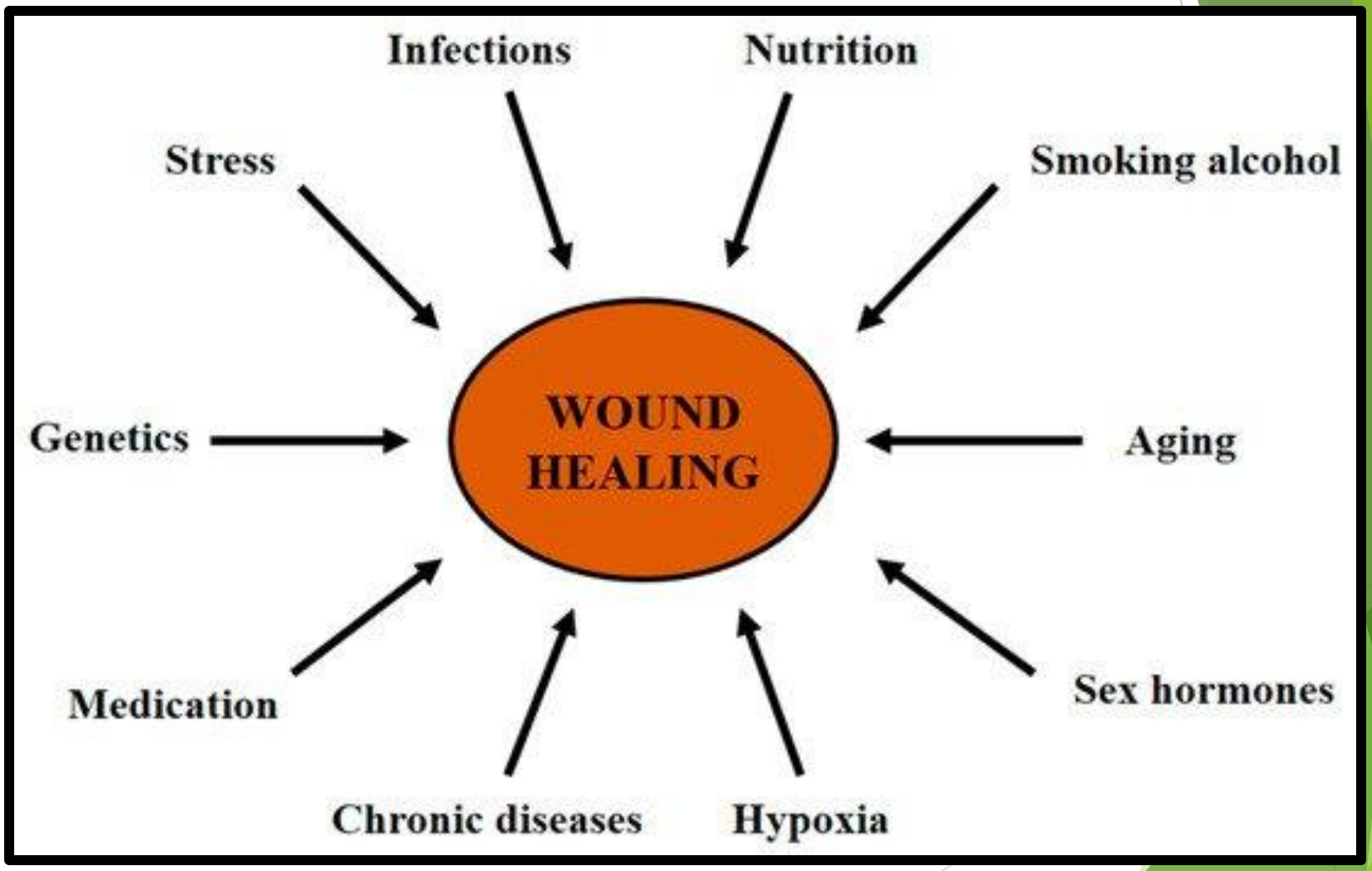
- Process of wound matrix breakdown by matrix metalloproteinases and synthesis of new ECM
- Aimed to increase scar strength.
- Wound strength increases because of:
  - Cross-linking of collagen.
  - Increased size of collagen fibers
  - Shift of the type of collagen deposited, from type III collagen early in repair to more stable type I collagen.

❖In well-sutured skin wounds, strength may recover to 70% to 80% of normal skin by 3 months.

Matrix metalloproteinases (MMPs).

- They are calcium-dependent zinc containing endopeptidases.
- They are capable of degrading all kinds of extracellular matrix proteins.
- Produced by a variety of cell types (fibroblasts, macrophages, neutrophils).

FACTORS THAT IMPAIR TISSUE REPAIR



Clinical Examples of Abnormal Wound Healing and Scarring

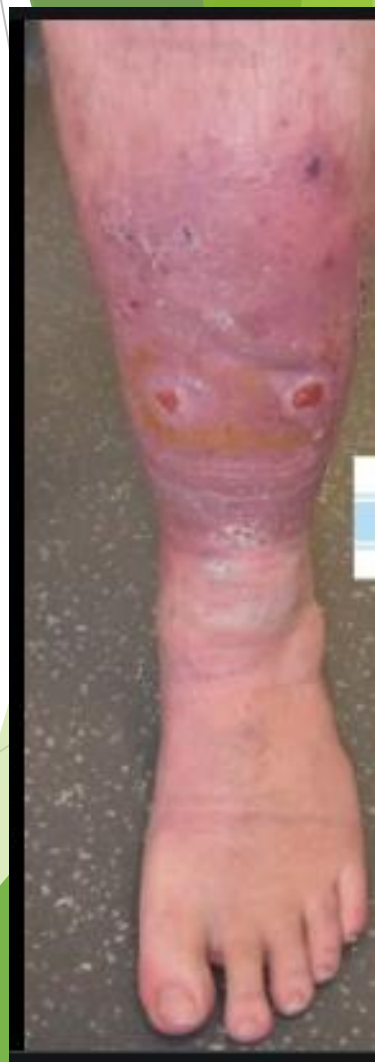
- Deficient scar formation.
- Excessive formation of the repair components.
- Formation of contractures

I. Defects in Healing: Chronic Wounds

- 1.Venous leg ulcers:

- Seen in elderly people as a result of chronic venous hypertension, which may be caused by severe varicose veins or congestive heart failure.

- These ulcers fail to heal because of poor delivery of oxygen to the site of the ulcer.

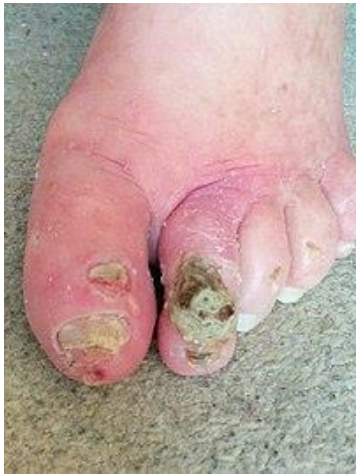


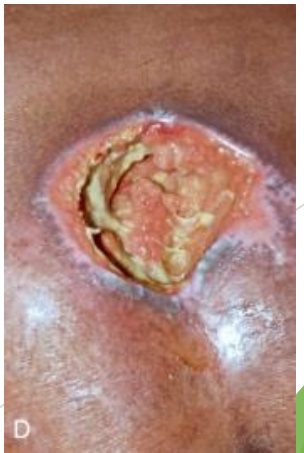
2.Arterial ulcers:

- Develop in individuals with atherosclerosis of peripheral arteries, especially associated with diabetes.

3. Pressure sores :

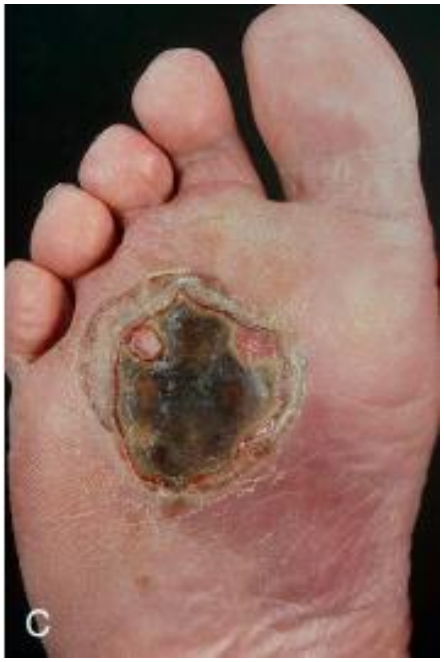
- Are areas of skin ulceration and necrosis of underlying tissues.
- Caused by prolonged compression of tissues against a bone, for example, in bedridden. The lesions are caused by mechanical pressure and local ischemia.

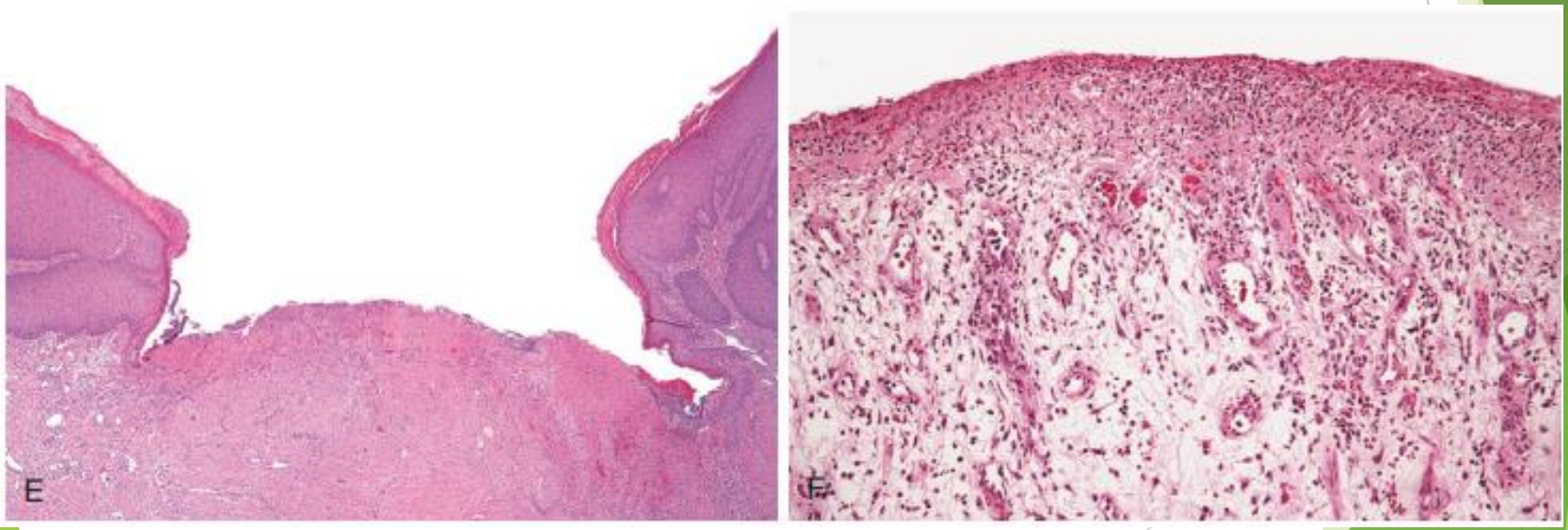




4.Diabetic ulcers;

- affect the lower extremities, particularly the feet. Tissue necrosis and failure to heal are the result of small vessel disease causing ischemia, neuropathy, systemic metabolic abnormalities, and secondary infections.

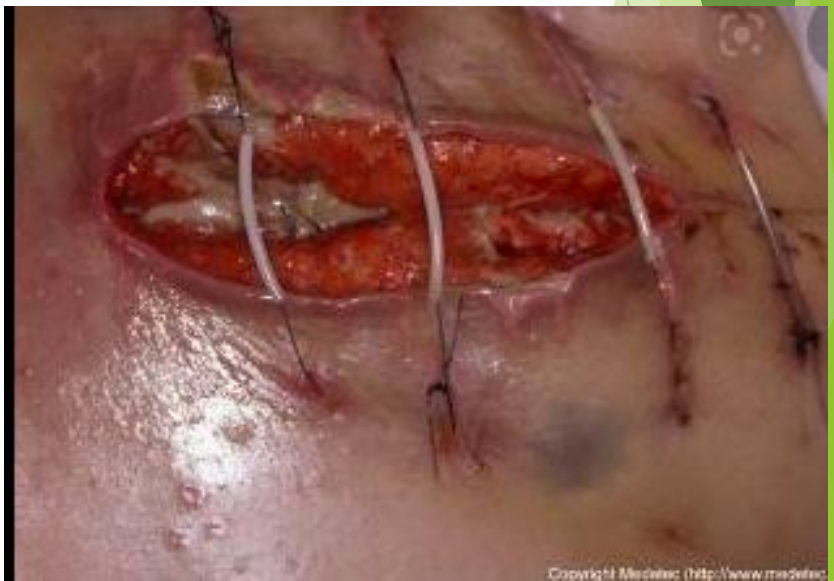




epithelial ulceration and extensive granulation tissue in the underlying dermis

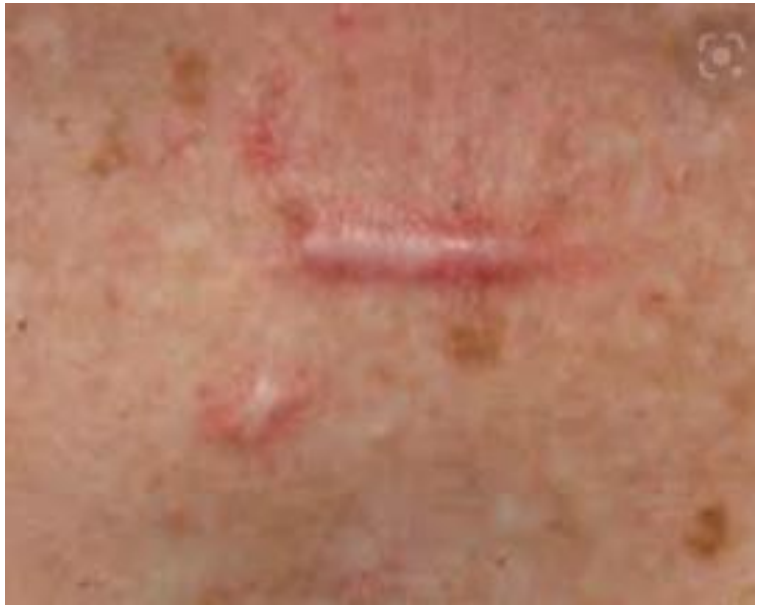
5. wound rupture (dehiscence):

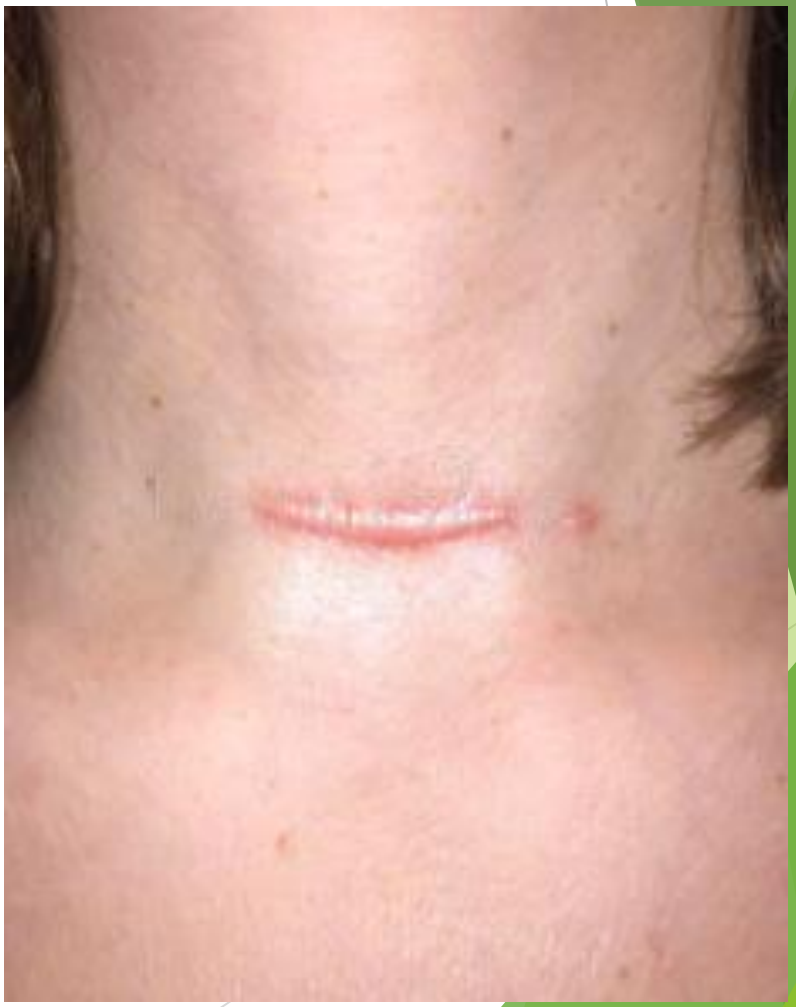
- occurs most frequently after abdominal surgery and is a result of increased abdominal pressure, such as may occur with vomiting, coughing, or ileus.



II Excessive Scarring

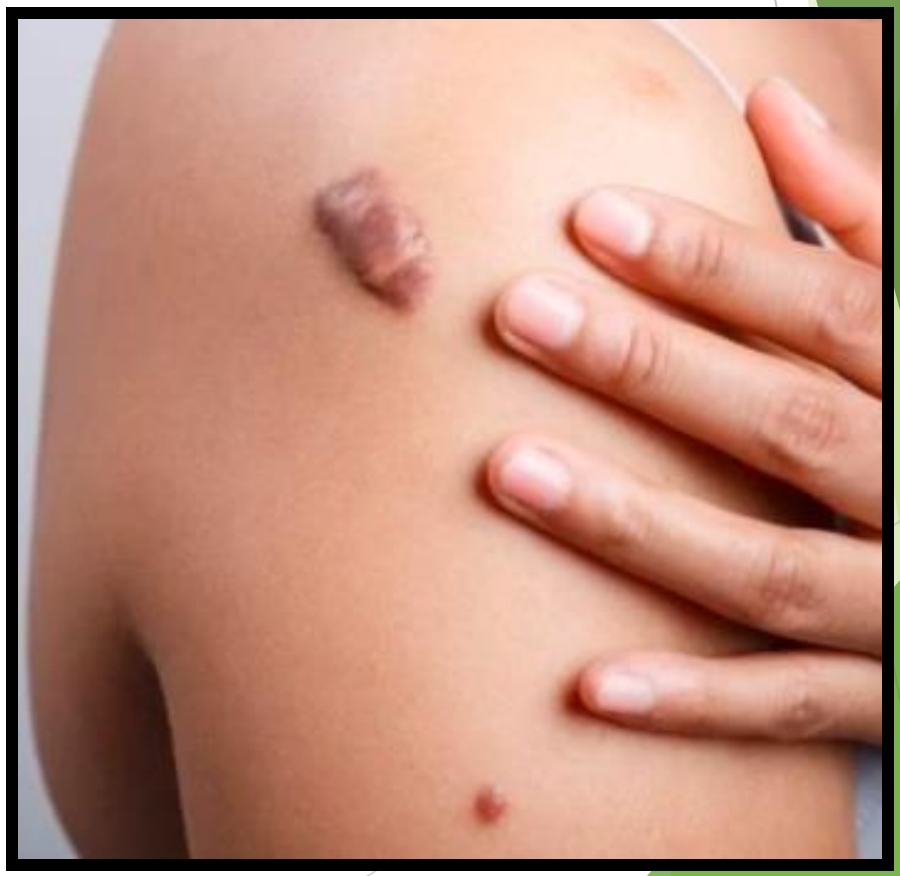
- The accumulation of excessive amounts of collagen may result in a raised scar known as a **hypertrophic scar.**
- These often grow rapidly and contain abundant myofibroblasts.
- develop after thermal or traumatic injury that involves the deep layers of the dermis.
- they tend to regress over several months.

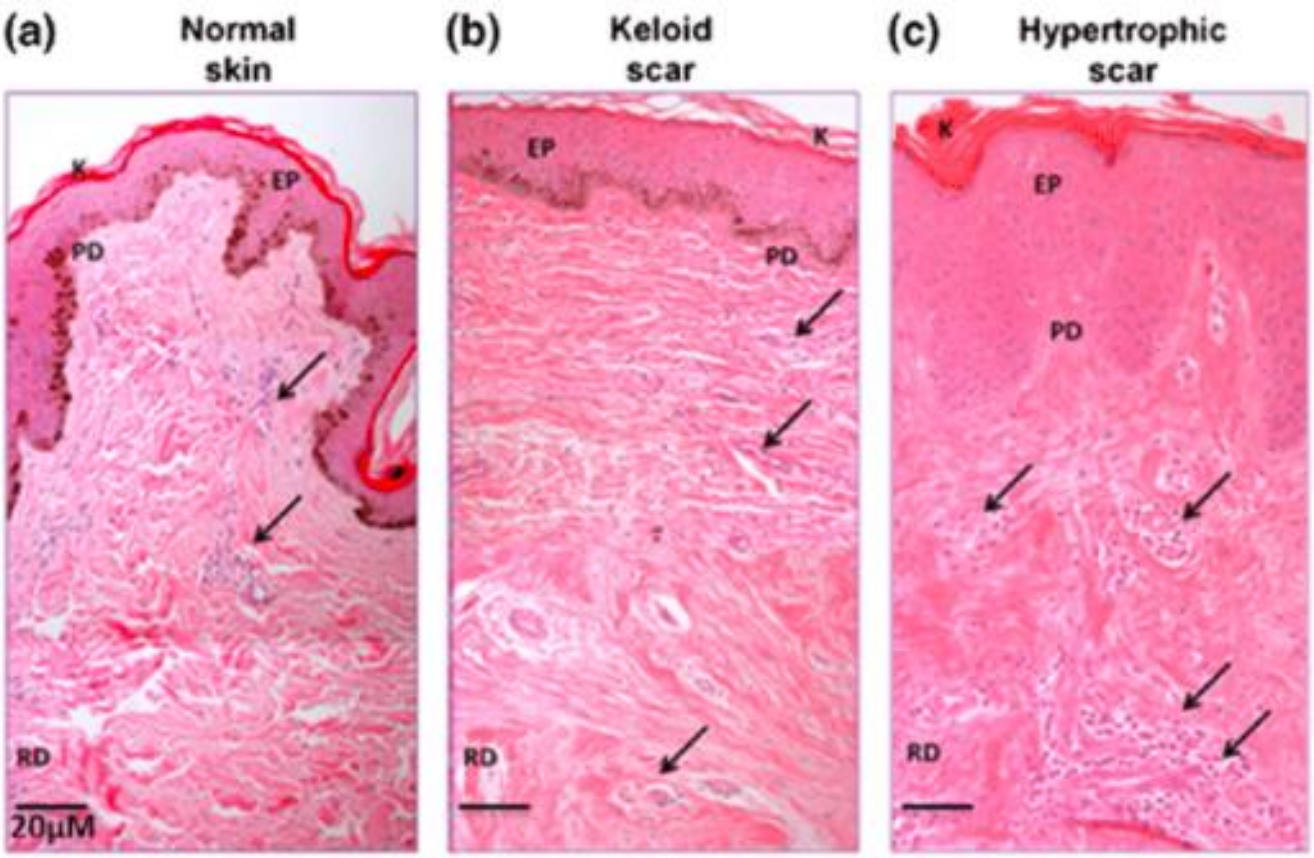




keloid:

- It is a hypertrophic scar that grows beyond the boundaries of the original wound and does not regress.

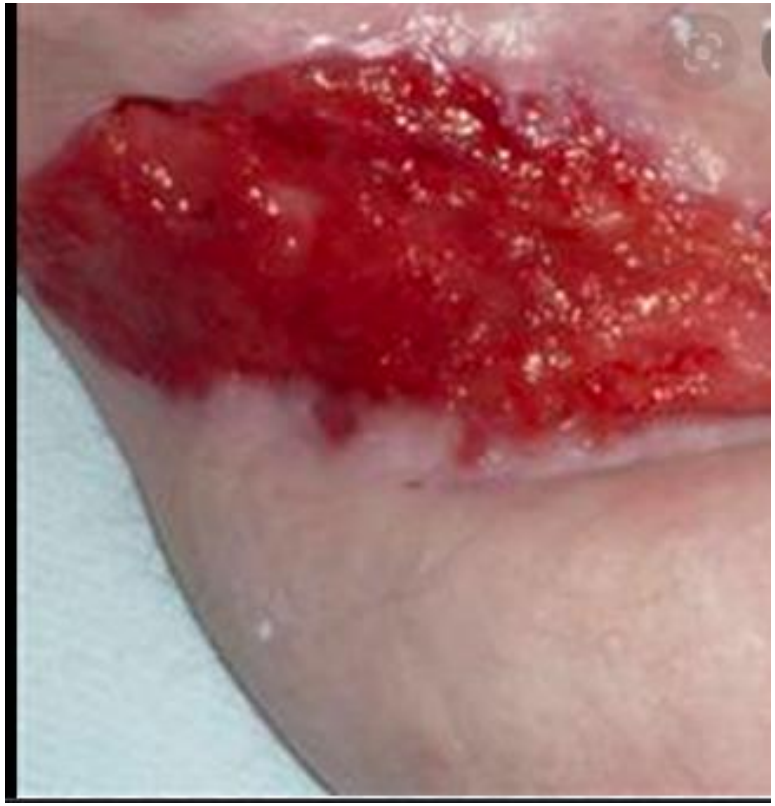


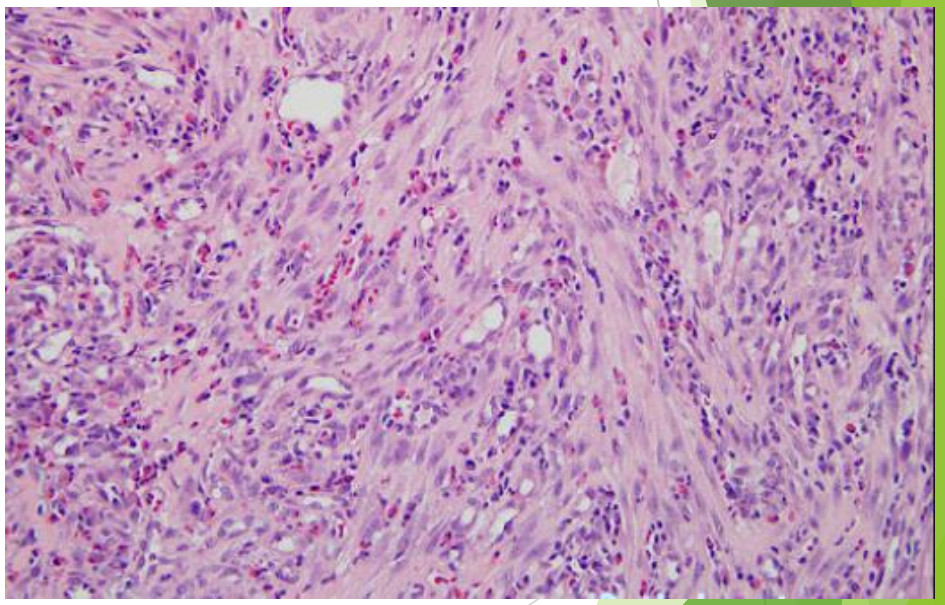


A. In normal skin, the characteristic random orientation and bundle formation of collagen fibres
B. increased number of thick collagen fibres arranged in bundles
C. The collagen fibres were arranged randomly and showed highly cellular zones

Exuberant granulation

- Formation of excessive amounts of granulation tissue, which protrudes above the level of the surrounding skin and blocks reepithelialization .



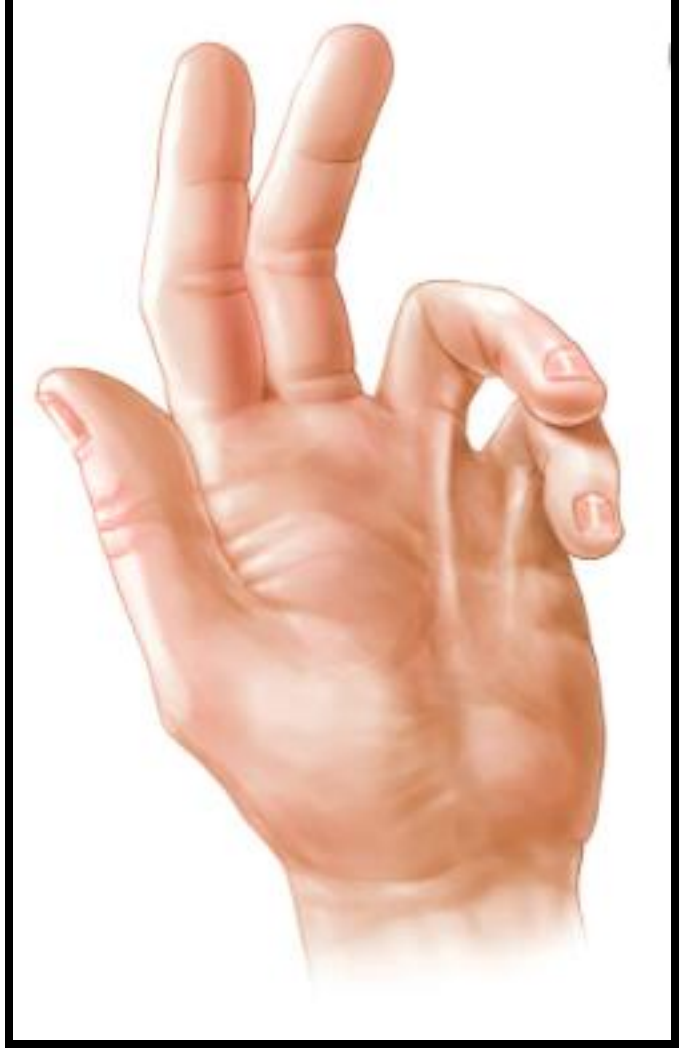


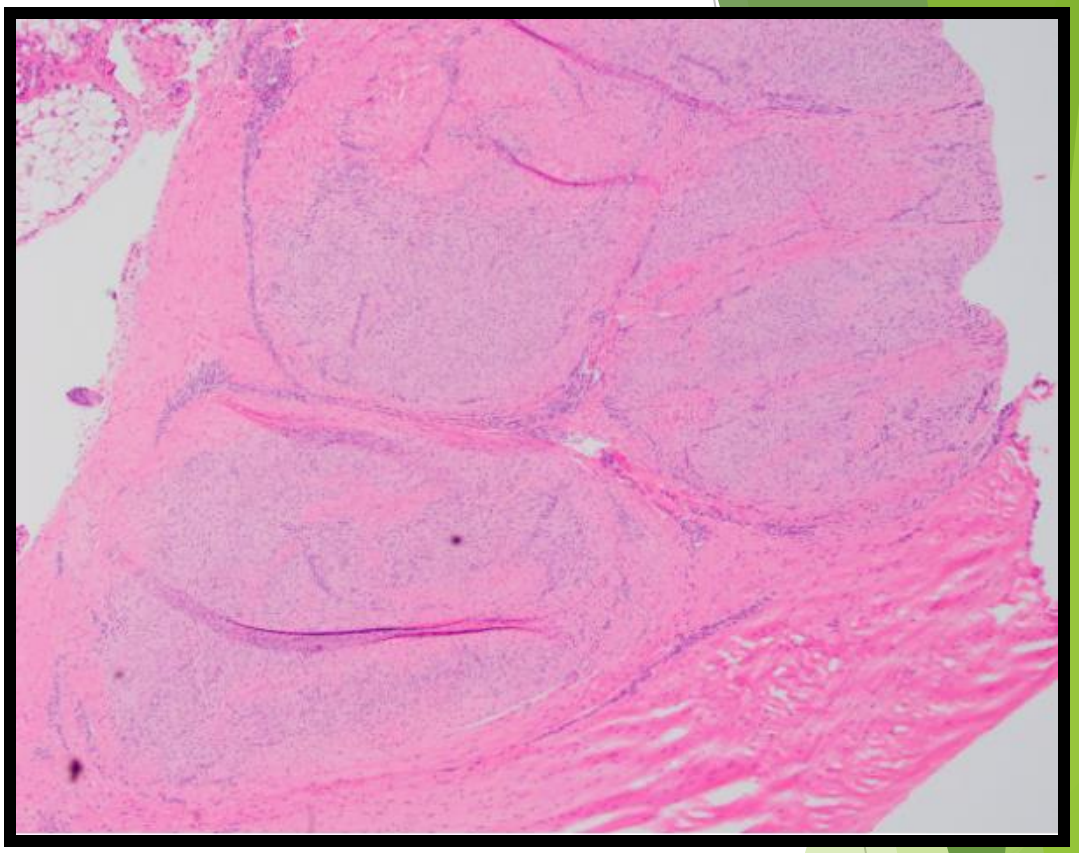
Ill contracture

- Permanent shortening of a muscle or joint develop when normally elastic tissues such as muscles or tendons are replaced by inelastic tissues (fibrosis).

- Prone to develop on the palms, the soles, and the anterior aspect of the thorax.

- Contractures are commonly seen after serious burns and can compromise the movement of joints.

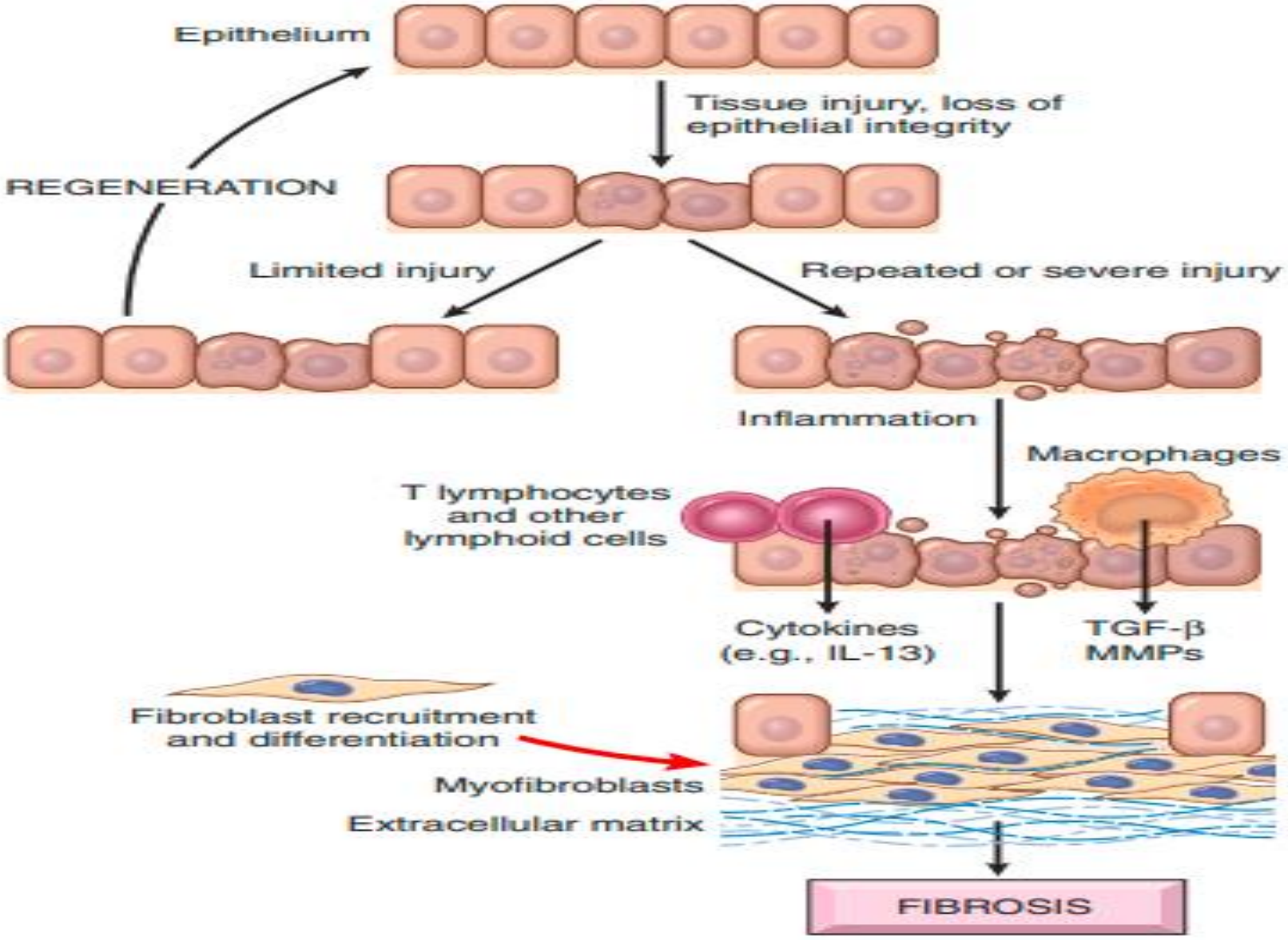




Nodule formation:
Composed of spindle cells (myofibroblasts and fibroblasts) with dense collagen.

Fibrosis in Parenchymal Organs

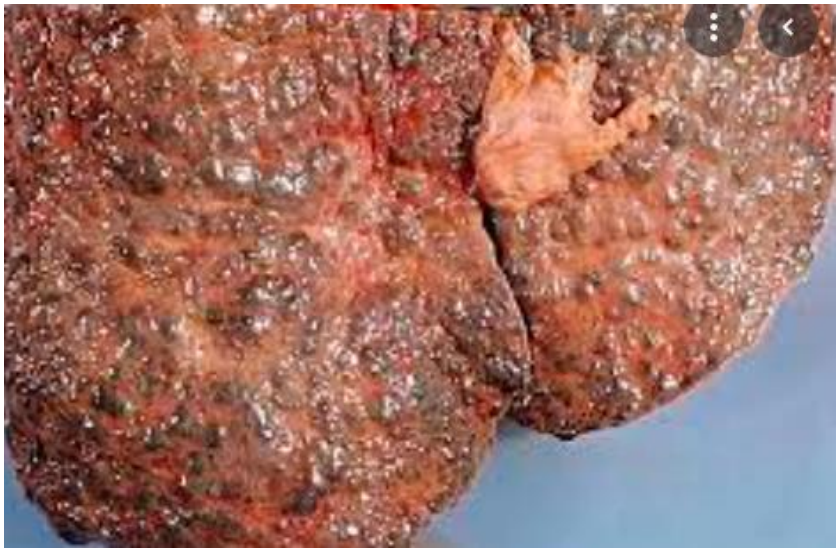
- Excessive deposition of collagen and other ECM components in a tissue.
- Scar vs fibrosis????
- Fibrosis is a pathologic process induced by persistent injurious stimuli such as chronic infections and immunologic reactions, and is typically associated with loss of tissue.
- It may be responsible for substantial organ dysfunction and even organ failure.

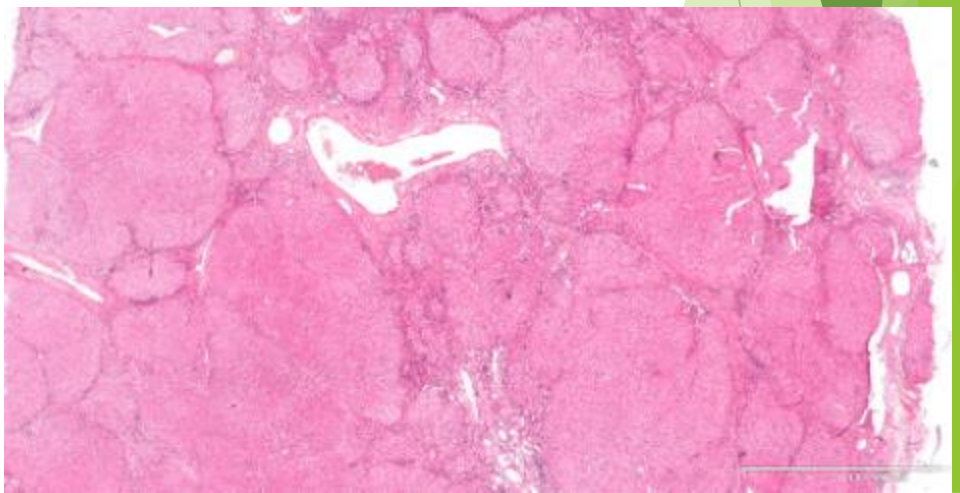


- Cell death by necrosis or apoptosis and the production of ROS seem to be important triggers for increased TGF-β activity.

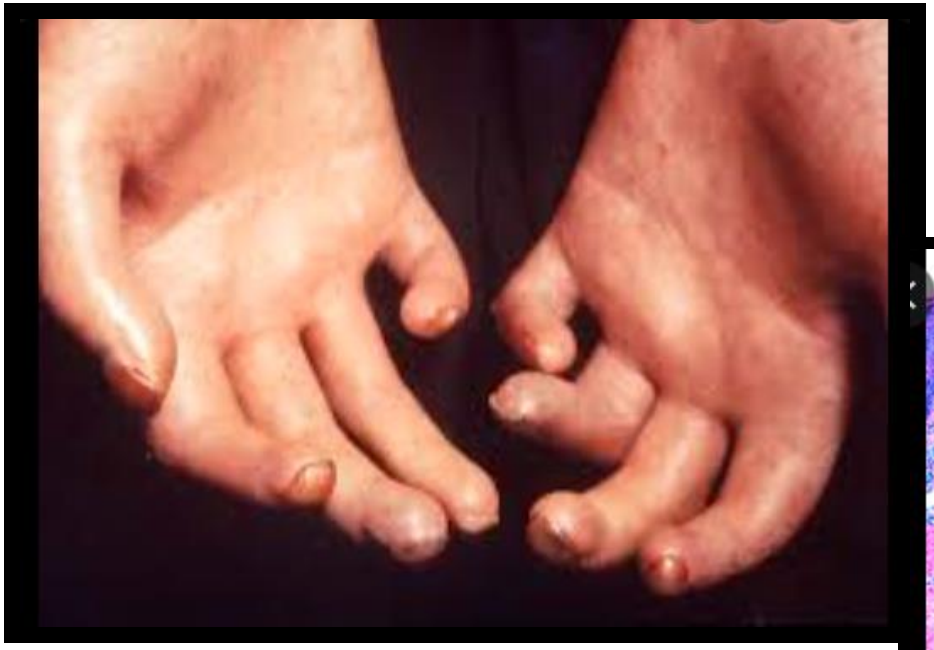
Examples of Fibrotic disorders

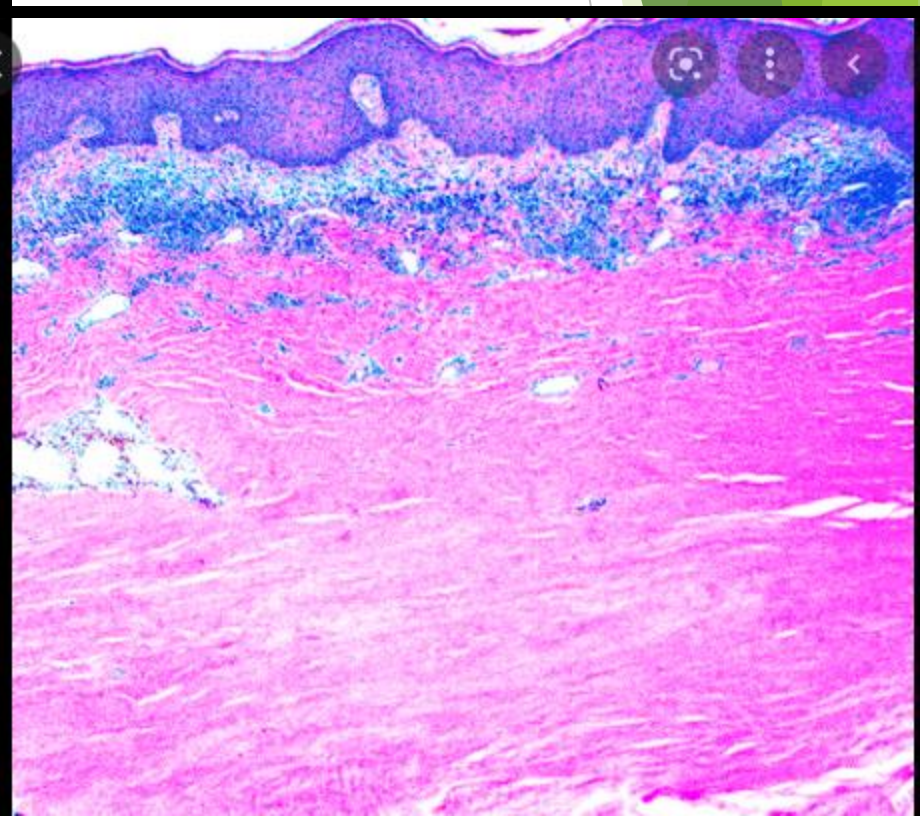
- **1. Liver cirrhosis.**



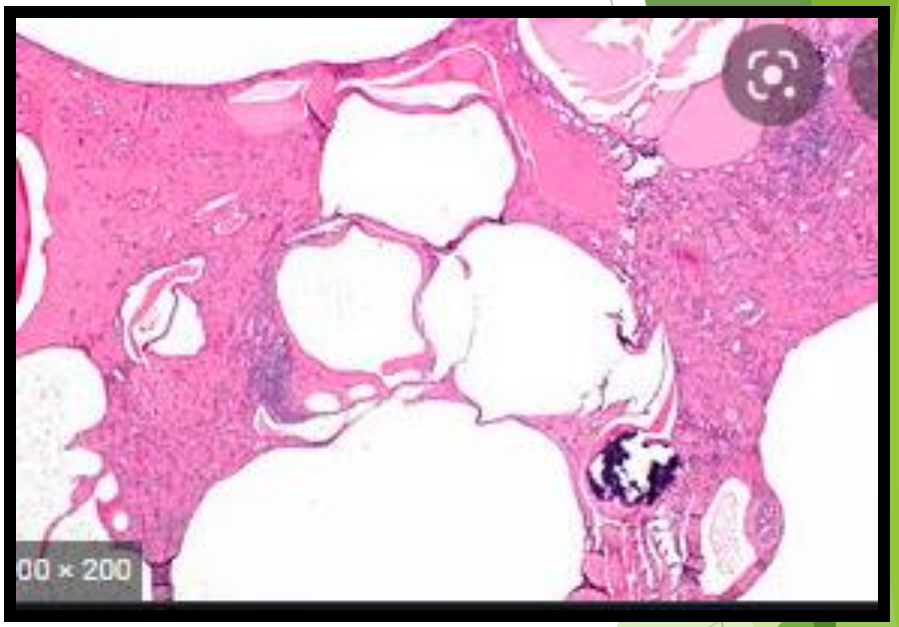


2.systemic sclerosis (scleroderma).



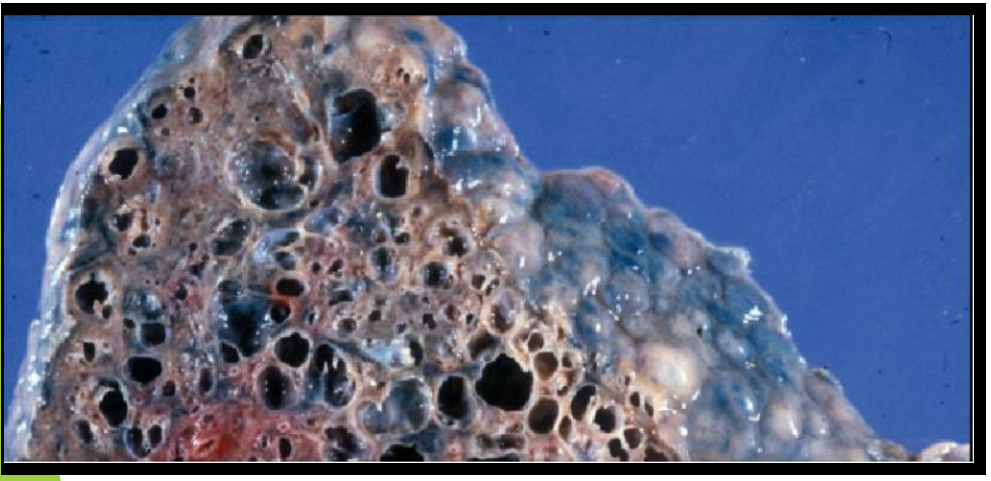


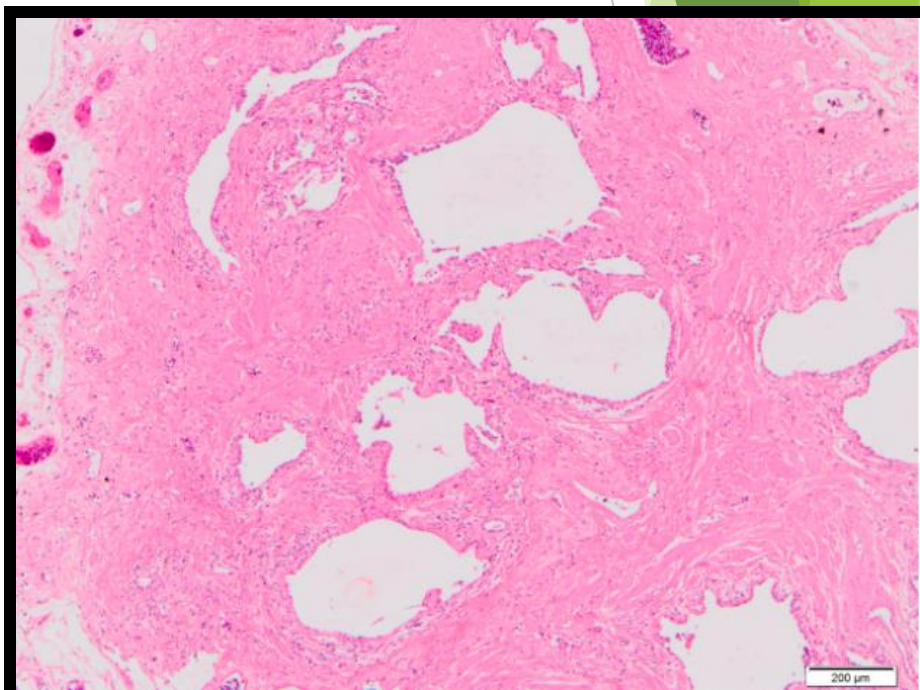
3. End-stage kidney disease.



❖fibrosing diseases of the lung.

Grossly: Honeycomb, Cystic spaces with fibrotic wall
Histology: cystic spaces lined by bronchiolar epithelium and fibrotic wall





The End

Questions