Tissue repair 2.

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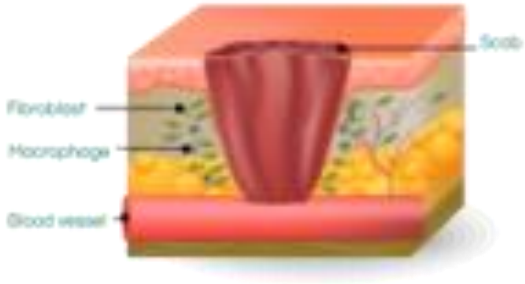
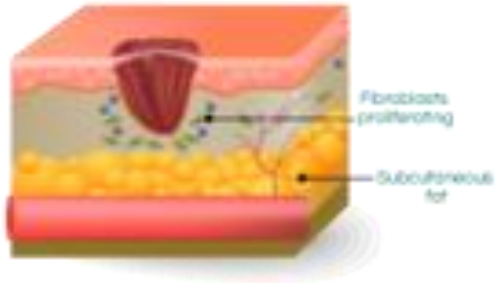
4 STAGES OF WOUND HEALING

1. Hemostasis

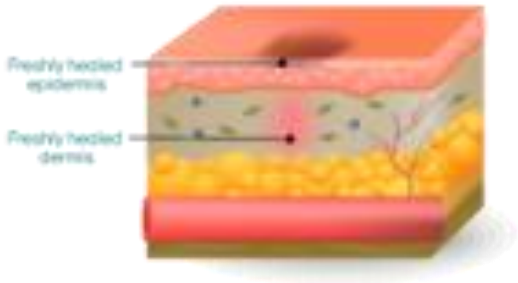
2. Inflammatory



3. Proliferative



4. Remodeling



3.Proliferative phase : proliferation of Fibroblasts

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

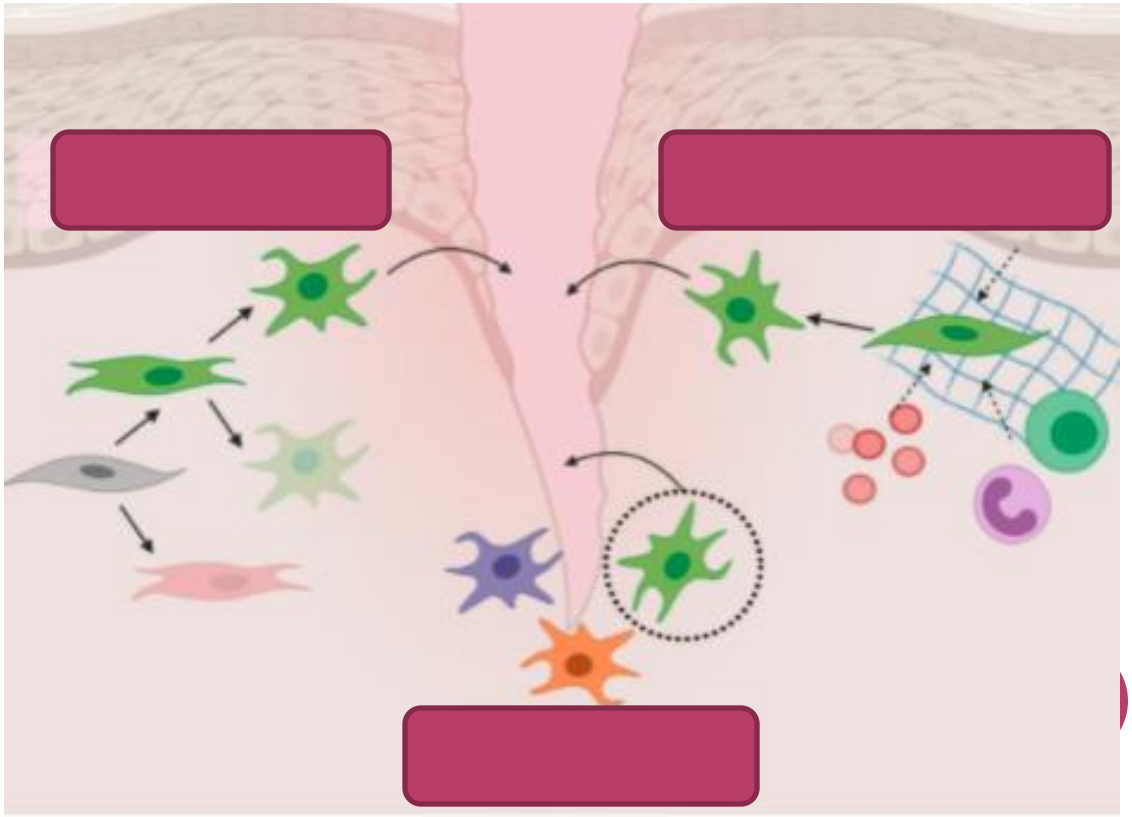
- (1) migration and proliferation of fibroblasts into the site of injury.
- (2) deposition of ECM proteins produced by these cells

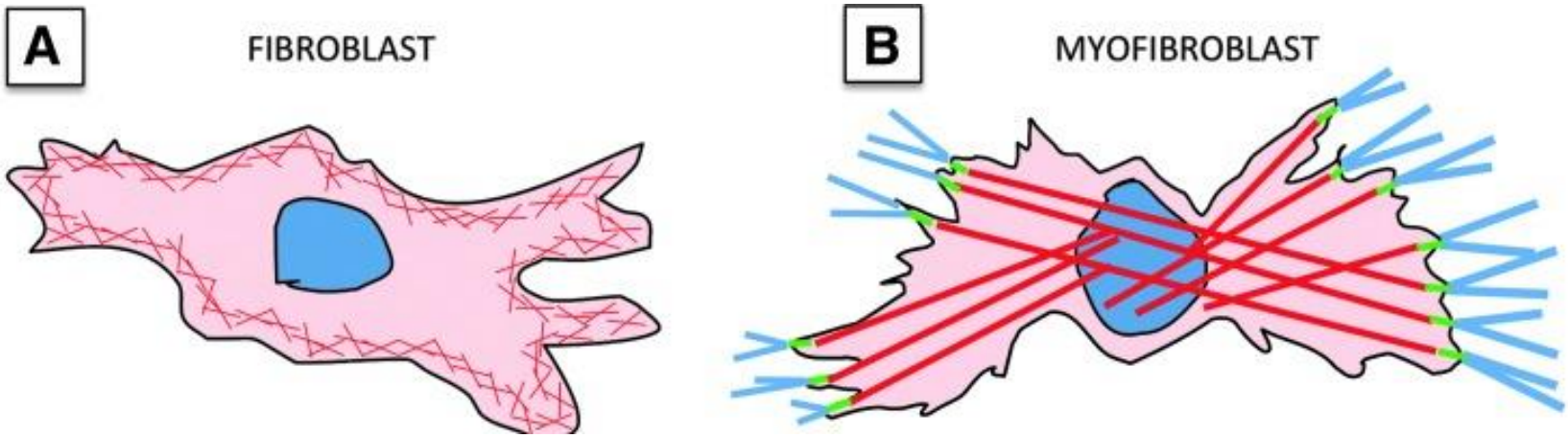
- These processes are under the control of cytokines and growth factors, including:

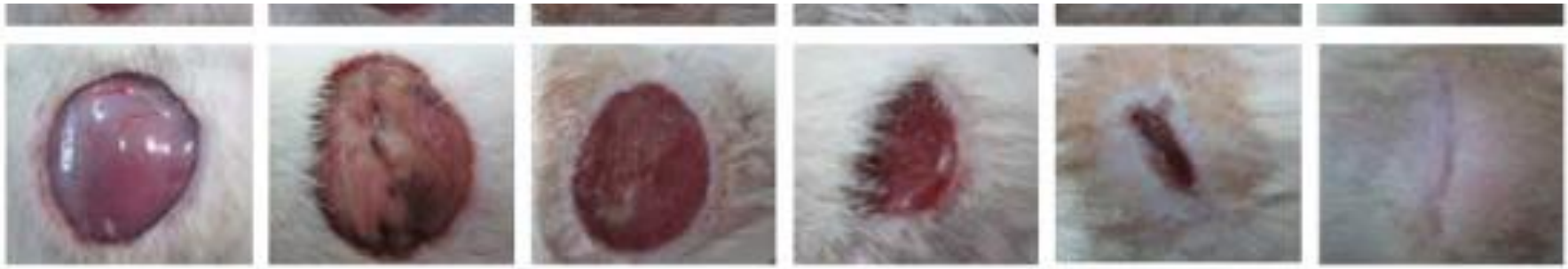
  - PDGF.
  - FGF-2.
  - TGF-β.

- 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



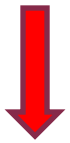
❖TGF-B

- 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

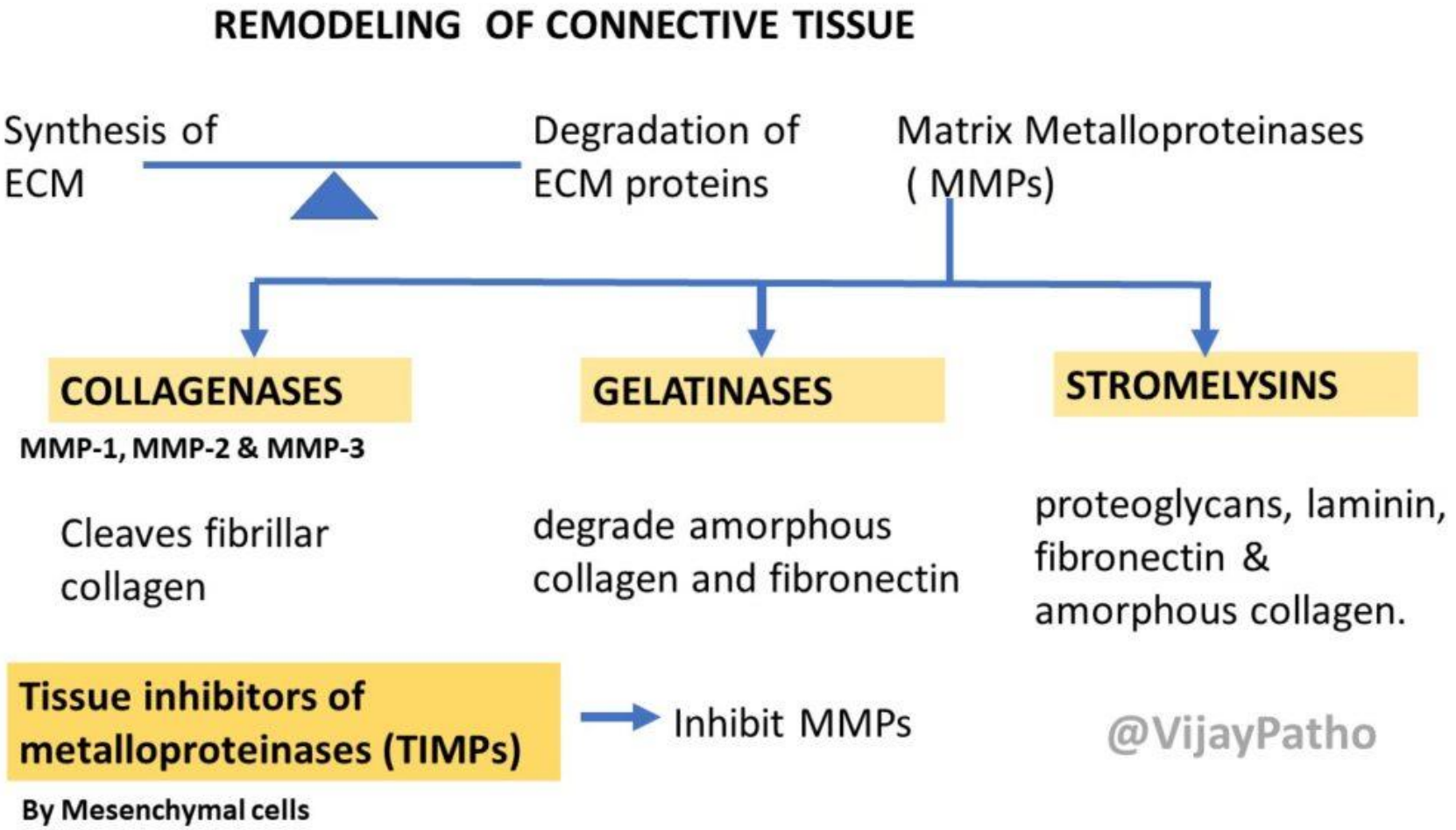
- process of wound matrix breakdown by matrix metalloproteinases and synthesis of new ECM

- 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.**

A balance of MMPs and TIMPs regulates the size and nature of the scar



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

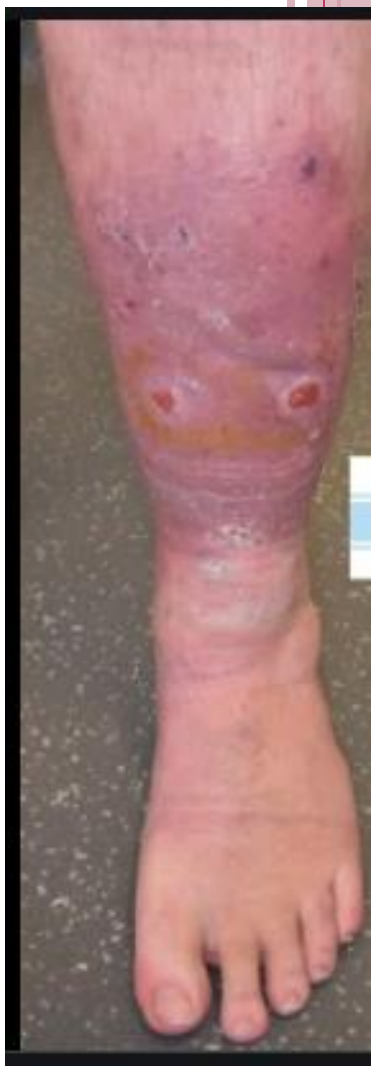
- Deficient scar formation.
- Excessive formation of the repair components.
- Formation of contractures

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.

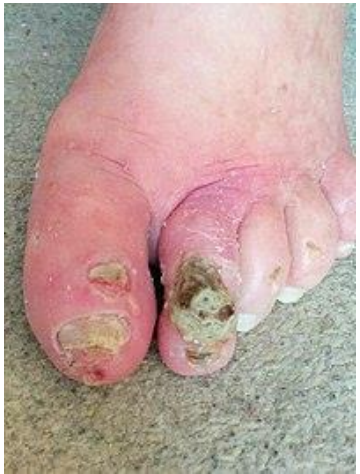


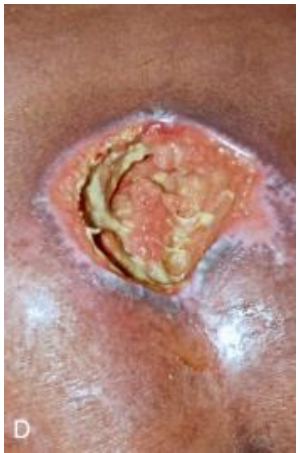
2.Arterial ulcers:

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

3. Pressure sores :

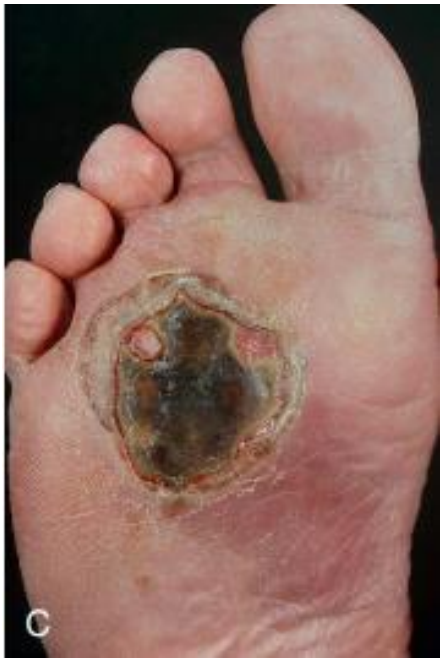
- are areas of skin ulceration and necrosis of underlying tissues.
- caused by prolonged compression of tissues against a bone, for example, in bedridden. The lesions are caused by mechanical pressure and local ischemia.

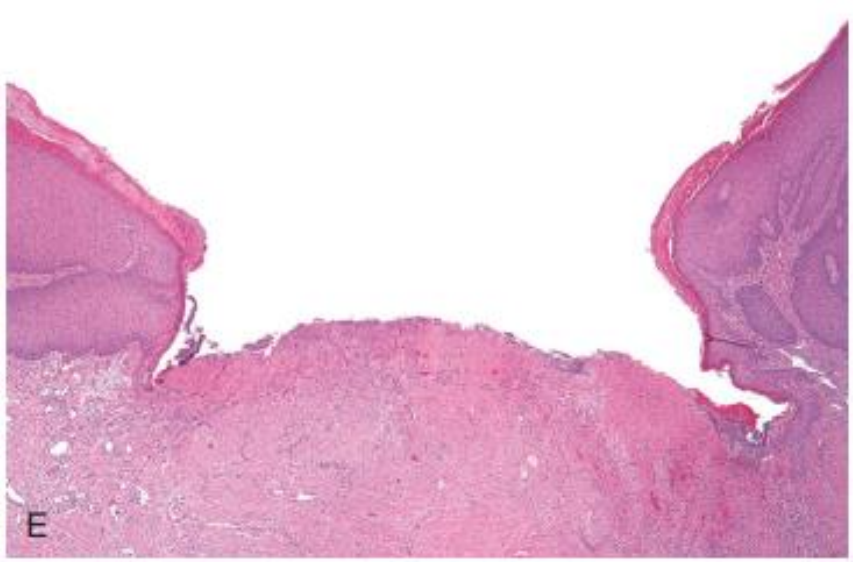


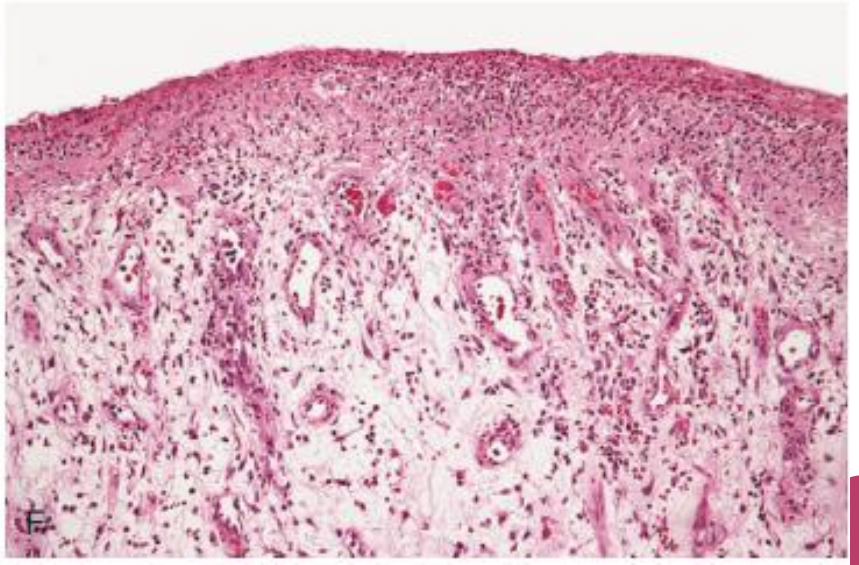


4.Diabetic ulcers;

- 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.



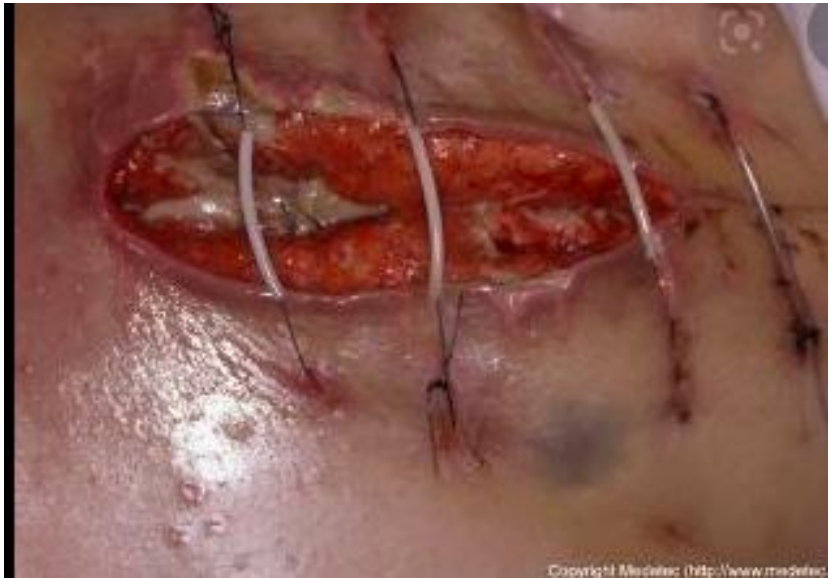




epithelial ulceration and extensive granulation tissue in the underlying dermis

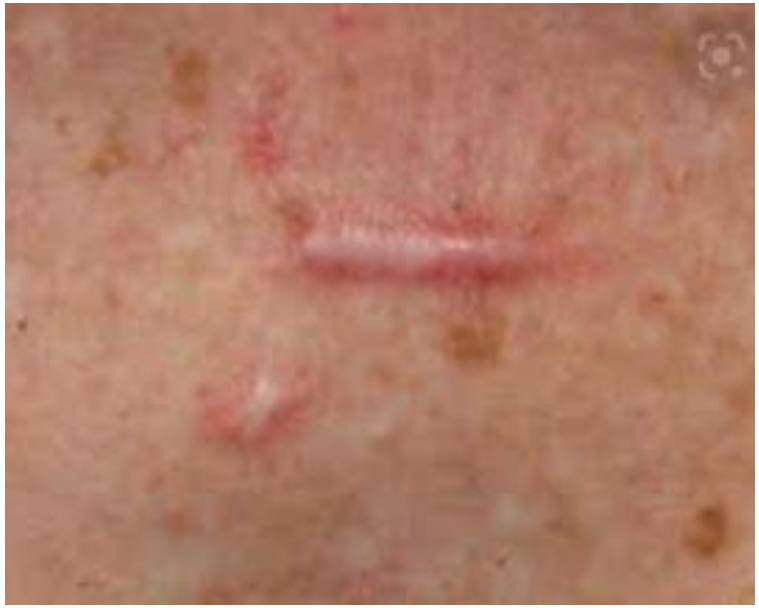
5. wound rupture (dehiscence):

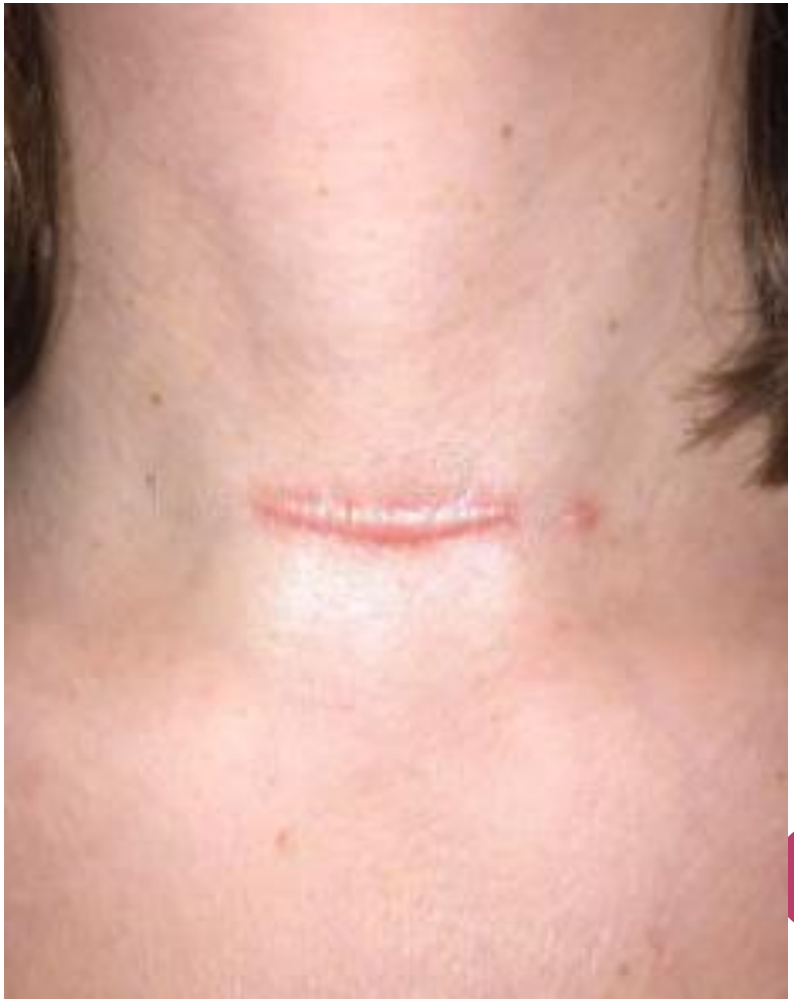
- occurs most frequently after abdominal surgery and is a result of increased abdominal pressure, such as may occur with vomiting, coughing, or ileus.



II Excessive Scarring

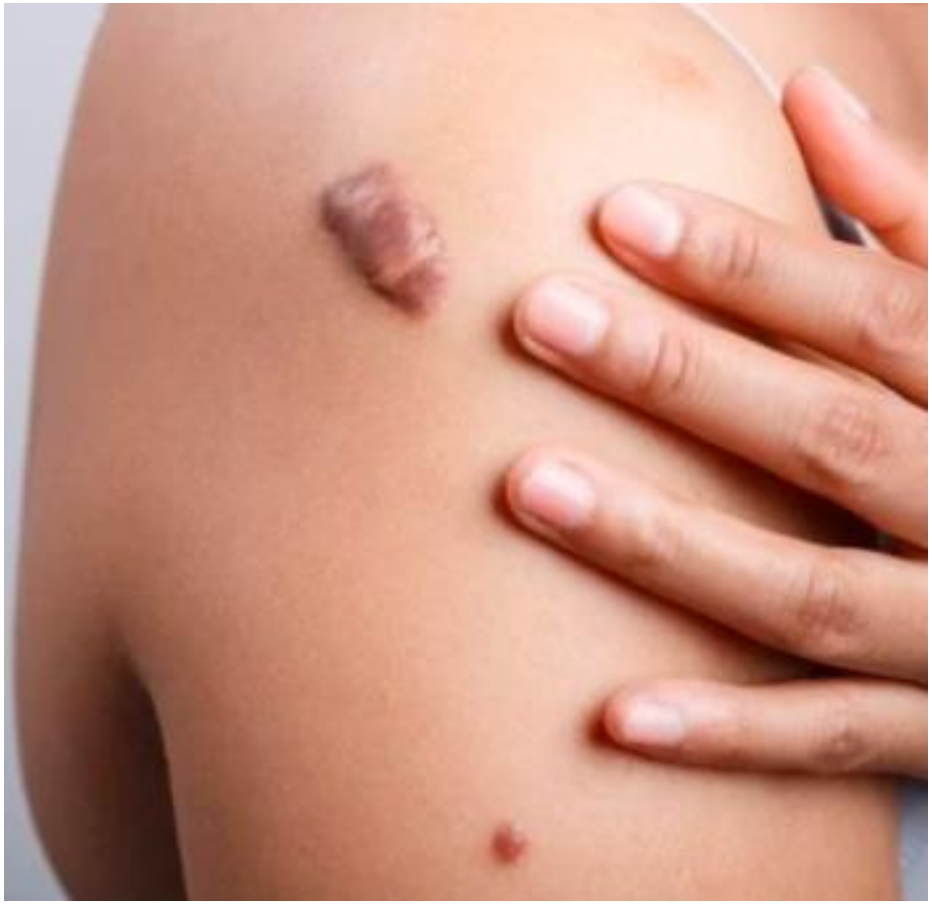
- The accumulation of excessive amounts of collagen may result in a raised scar known as a hypertrophic scar.
- These often grow rapidly and contain abundant myofibroblasts.
- develop after thermal or traumatic injury that involves the deep layers of the dermis.
- they tend to regress over several months.

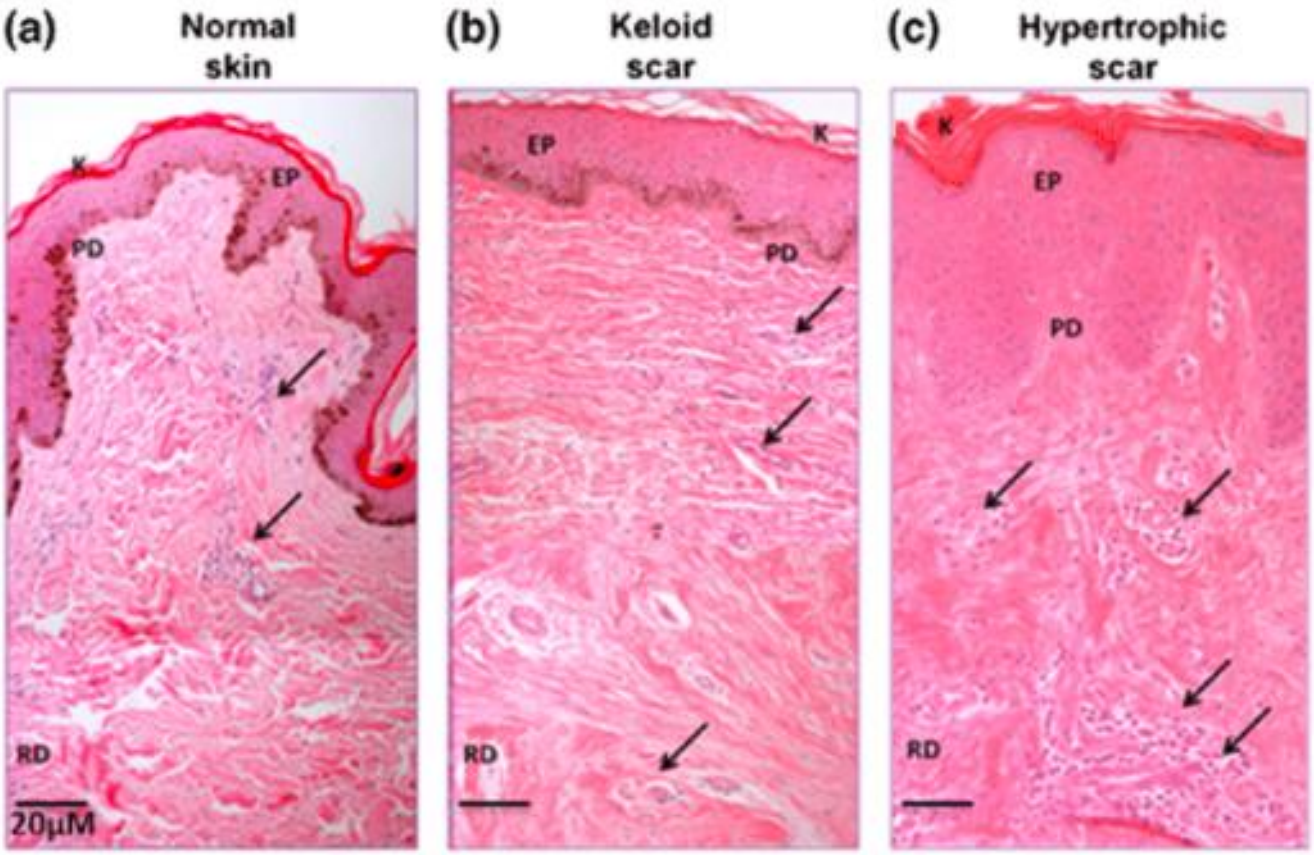




- **keloid:**

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

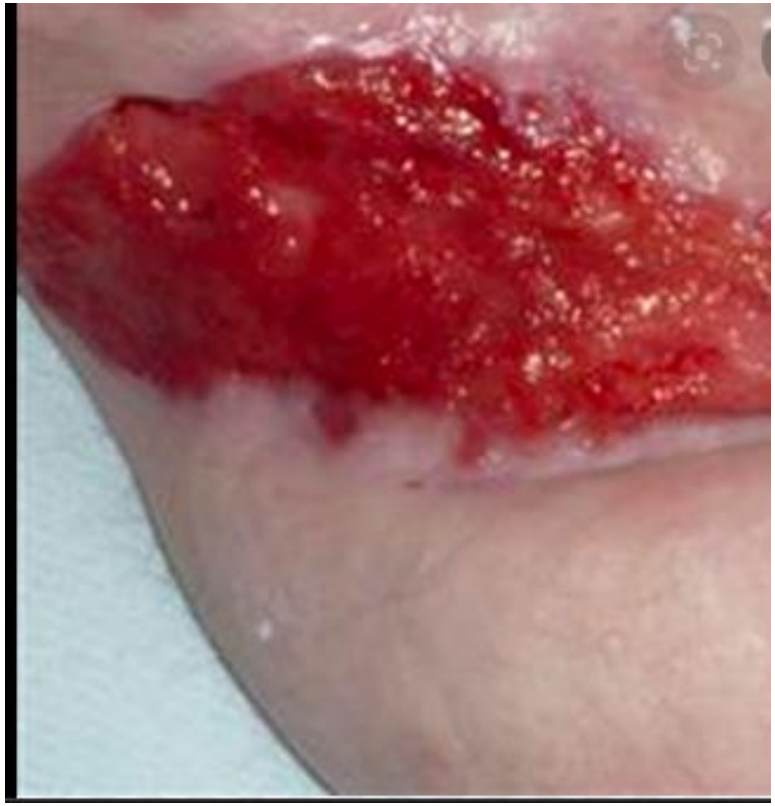


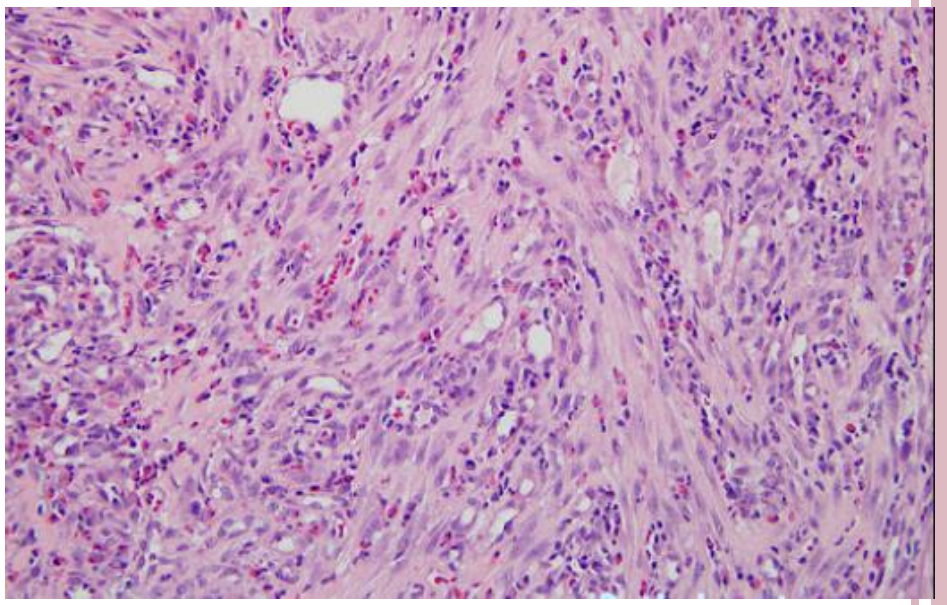


A. In normal skin, the characteristic random orientation and bundle formation of collagen fibres
B. increased number of thick collagen fibres arranged in bundles
C. The collagen fibres were arranged randomly and showed highly cellular zones

EXUBERANT GRANULATION

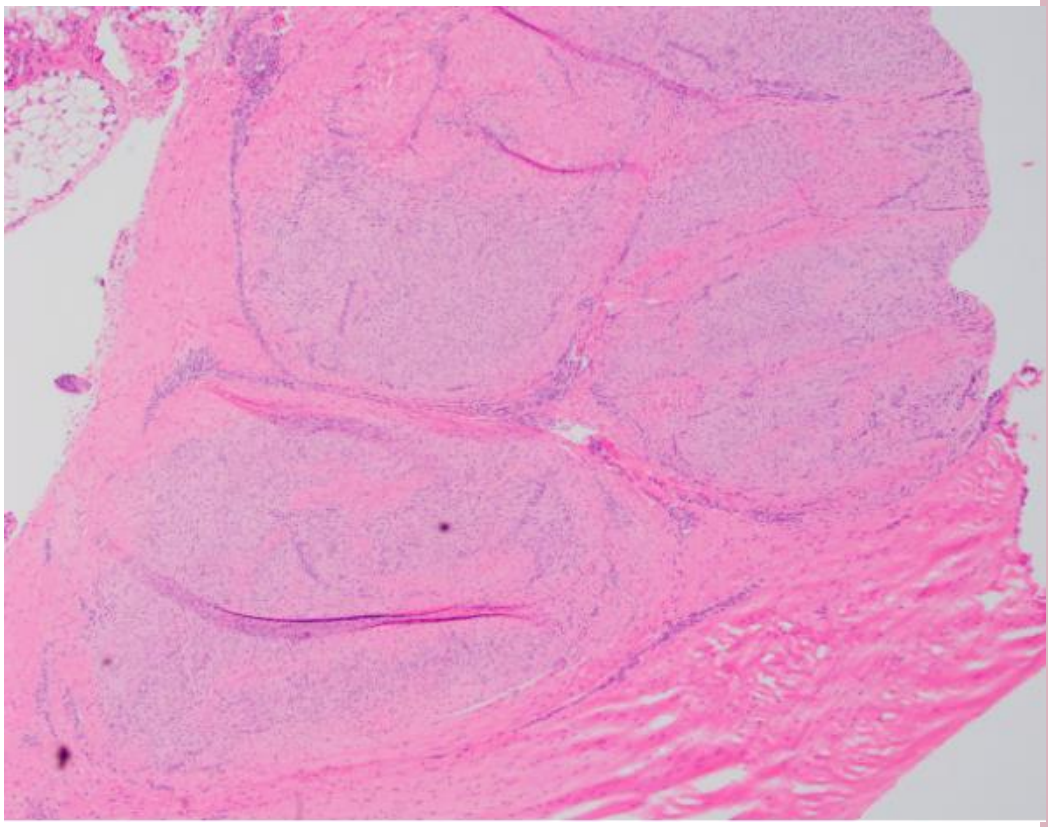
- formation of excessive amounts of granulation tissue, which protrudes above the level of the surrounding skin and blocks reepithelialization .





III CONTRACTURE

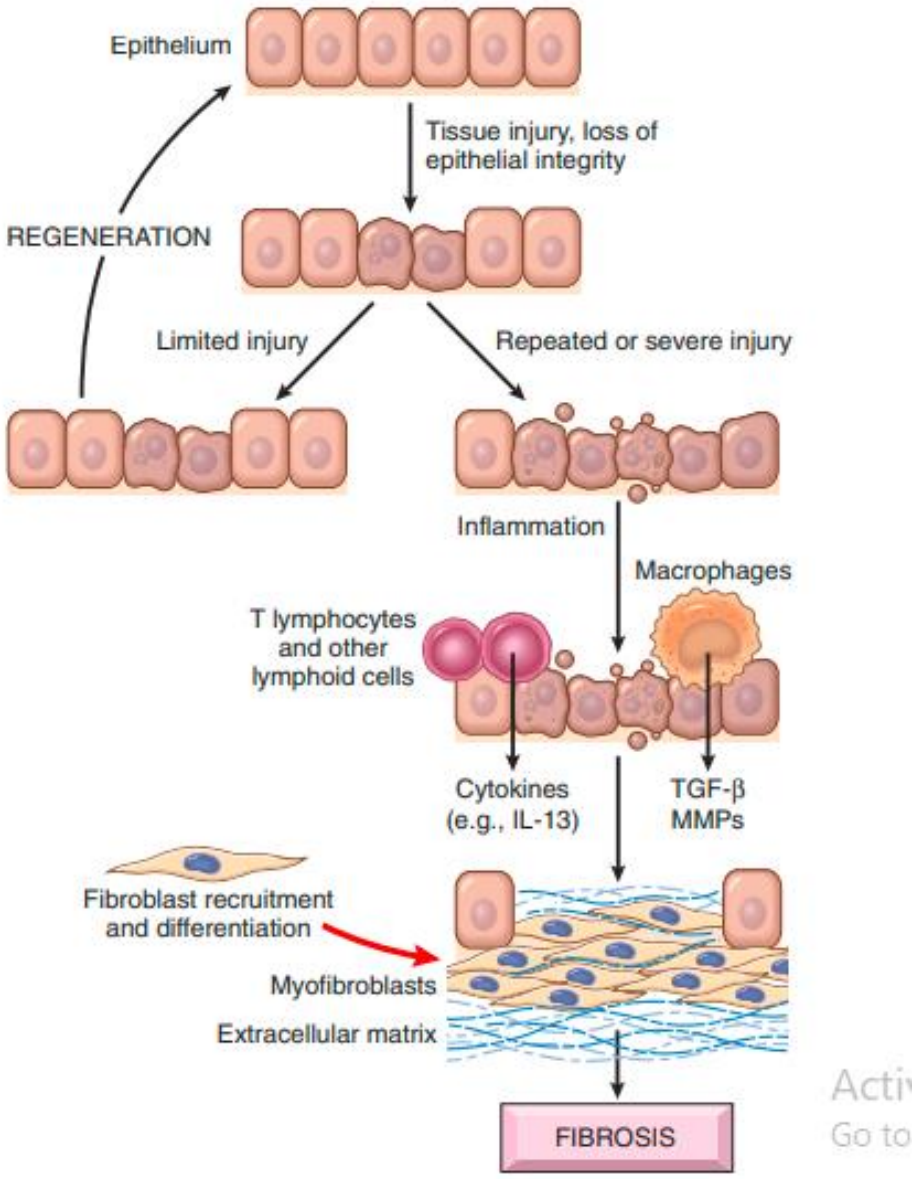
- permanent shortening of a muscle or joint develop when normally elastic tissues such as muscles or tendons are replaced by inelastic tissues (fibrosis).
- prone to develop on the palms, the soles, and the anterior aspect of the thorax.
- Contractures are commonly seen after serious burns and can compromise the movement of joints.



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

Fibrosis in Parenchymal Organs

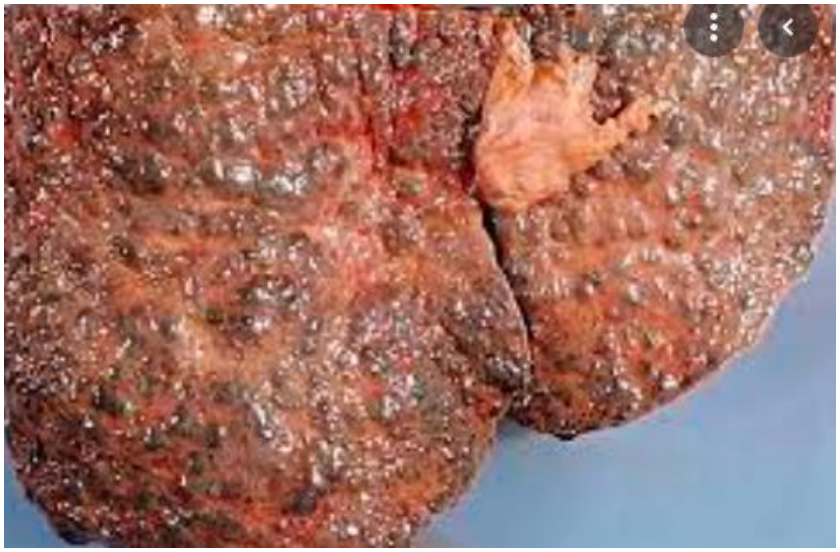
- excessive deposition of collagen and other ECM components in a tissue.
- scar vs fibrosis????
- Fibrosis is a pathologic process induced by persistent injurious stimuli such as chronic infections and immunologic reactions, and is typically associated with loss of tissue.
- It may be responsible for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

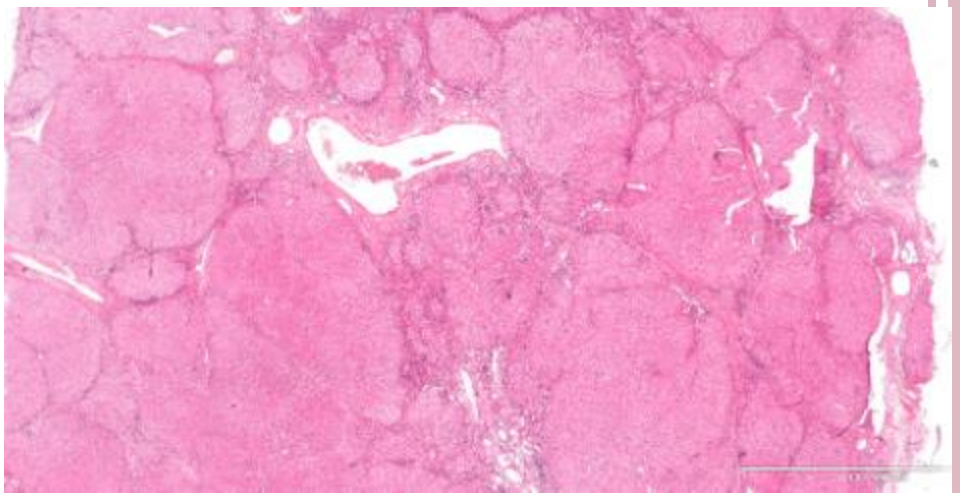


- Cell death by necrosis or apoptosis and the production of ROS seem to be important triggers for increased TGF-ß activity.

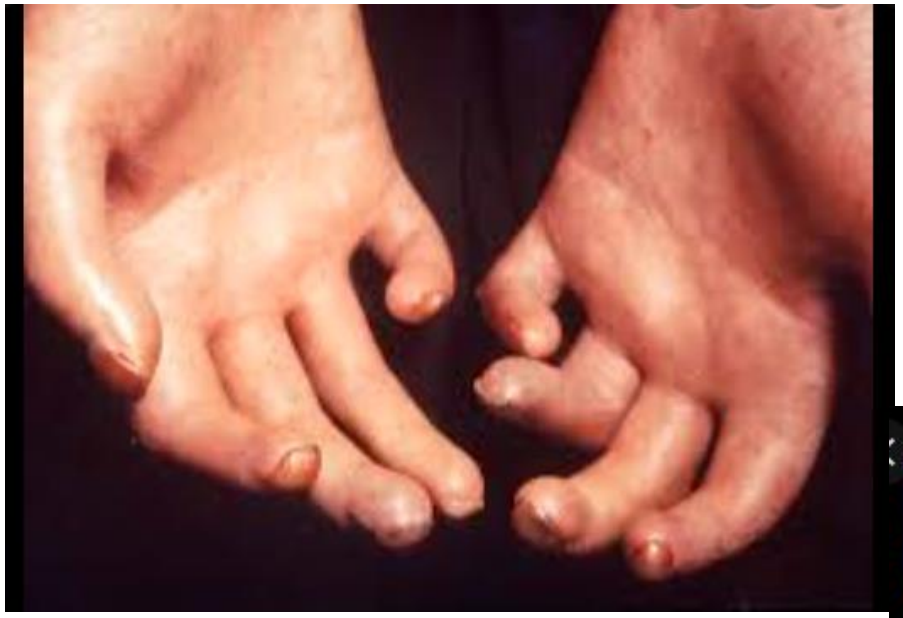
Examples of Fibrotic disorders

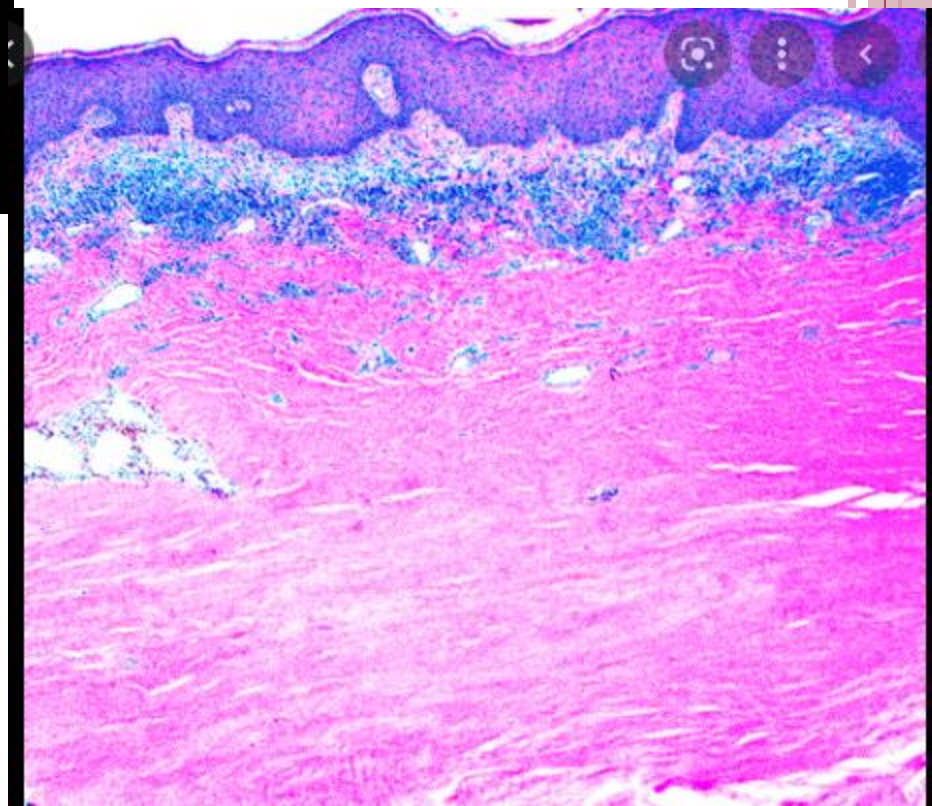
- 1. liver cirrhosis.



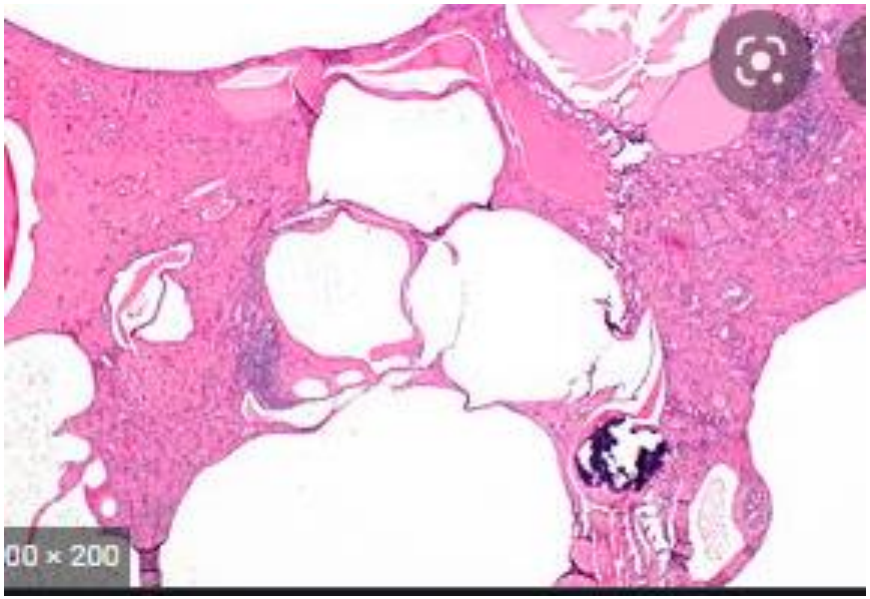


2.SYSTEMIC SCLEROSIS (SCLERODERMA).



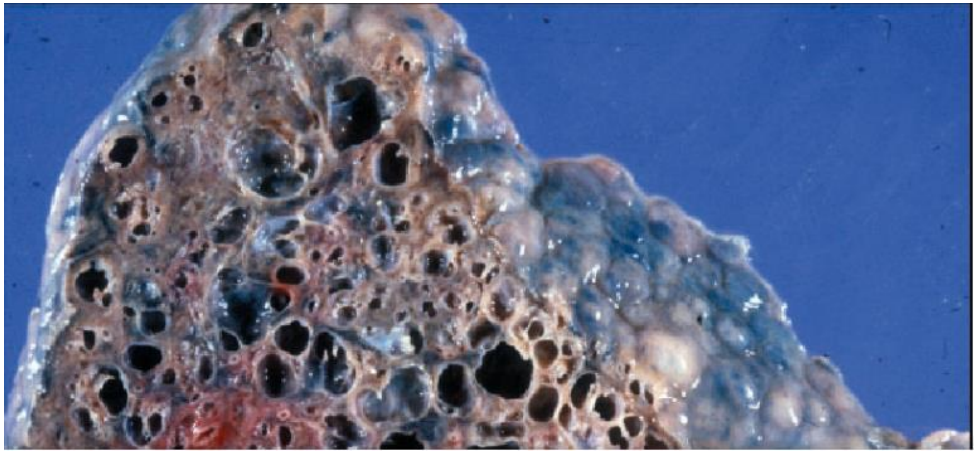


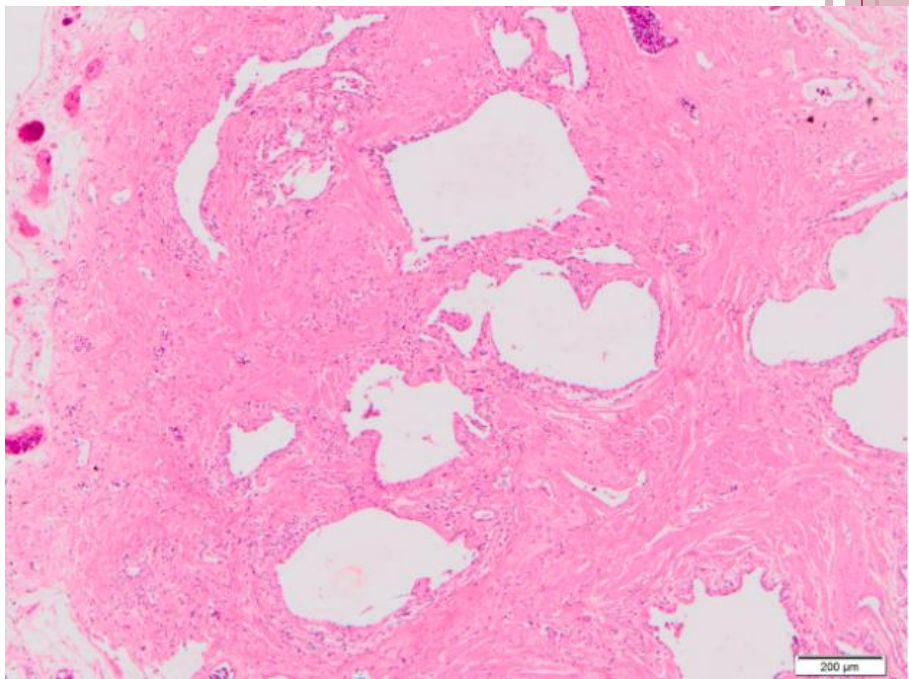
3. END-STAGE KIDNEY DISEASE.



❖fibrosing diseases of the lung.

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






QUESTIONS?
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