

# Inflammation and Repair L5

{ وَقُلْ رَبِّ زِدْنِي عِلْمًا }

## Objectives:

- Describe the difference between repair processes: regeneration, healing and fibrosis. List examples of each cell type.
- Know the difference between the various cell in regenerative abilities types.
- Know the mechanism of repair and formation of granulation tissue.
- List the three main phases of cutaneous wound healing.
- Compare and contrast the difference between healing by primary intention and healing by secondary intention.
- List factors which are associated with delayed wound healing.
- List complication of wound healing.

Color Index:  
Girl's Slides  
**Important**  
Male's Notes  
Female's Notes  
Extra information

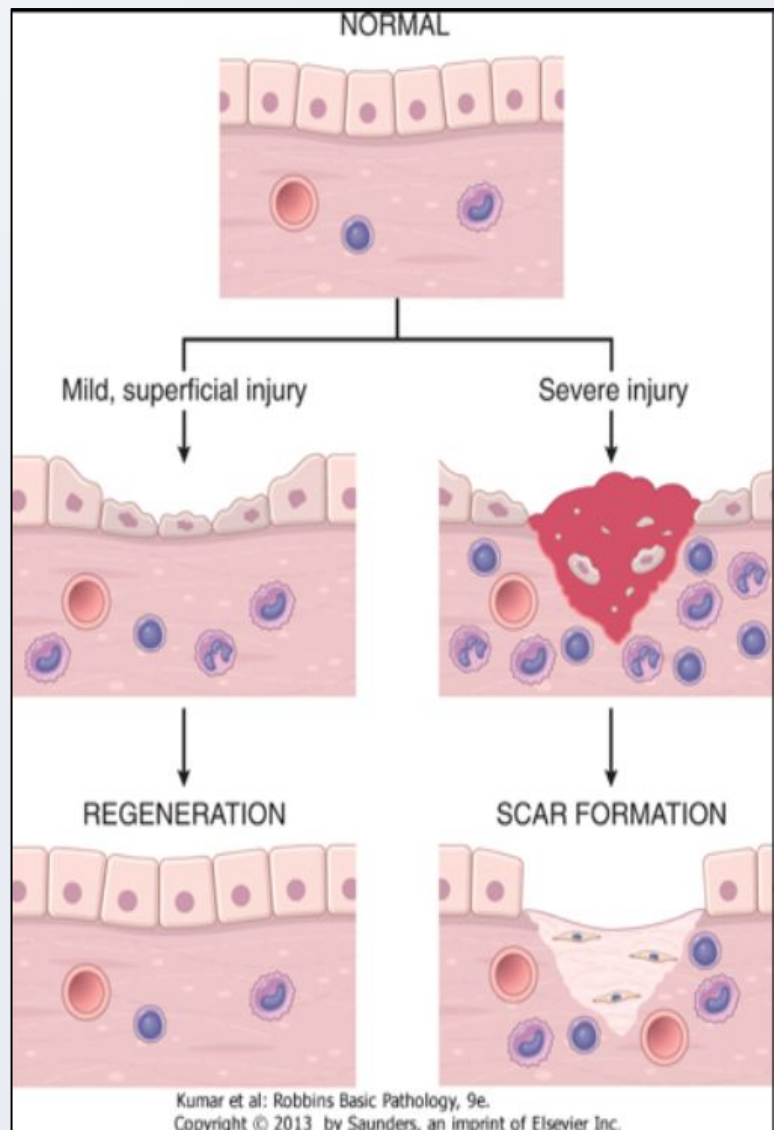


# Goal of the repair process

To restore the tissue to its original state after inflammatory reaction.

Some tissues can be **completely reconstituted** after injury, such as the repair of bone after a fracture or the regeneration of the surface epithelium in a cutaneous wound.

For tissues that are **incapable of regeneration**, repair is accomplished by connective tissue deposition, producing a **scar**.

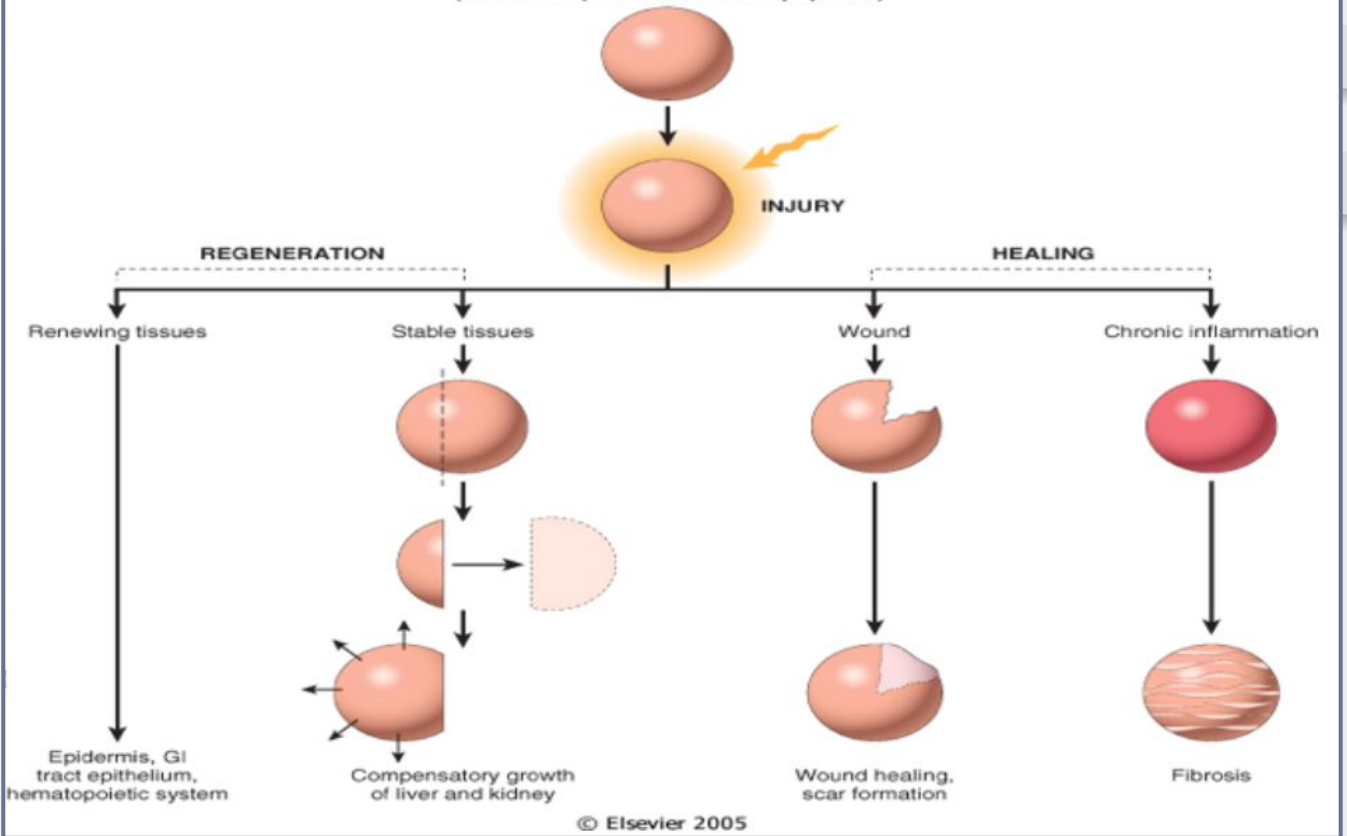


## Fibrosis:

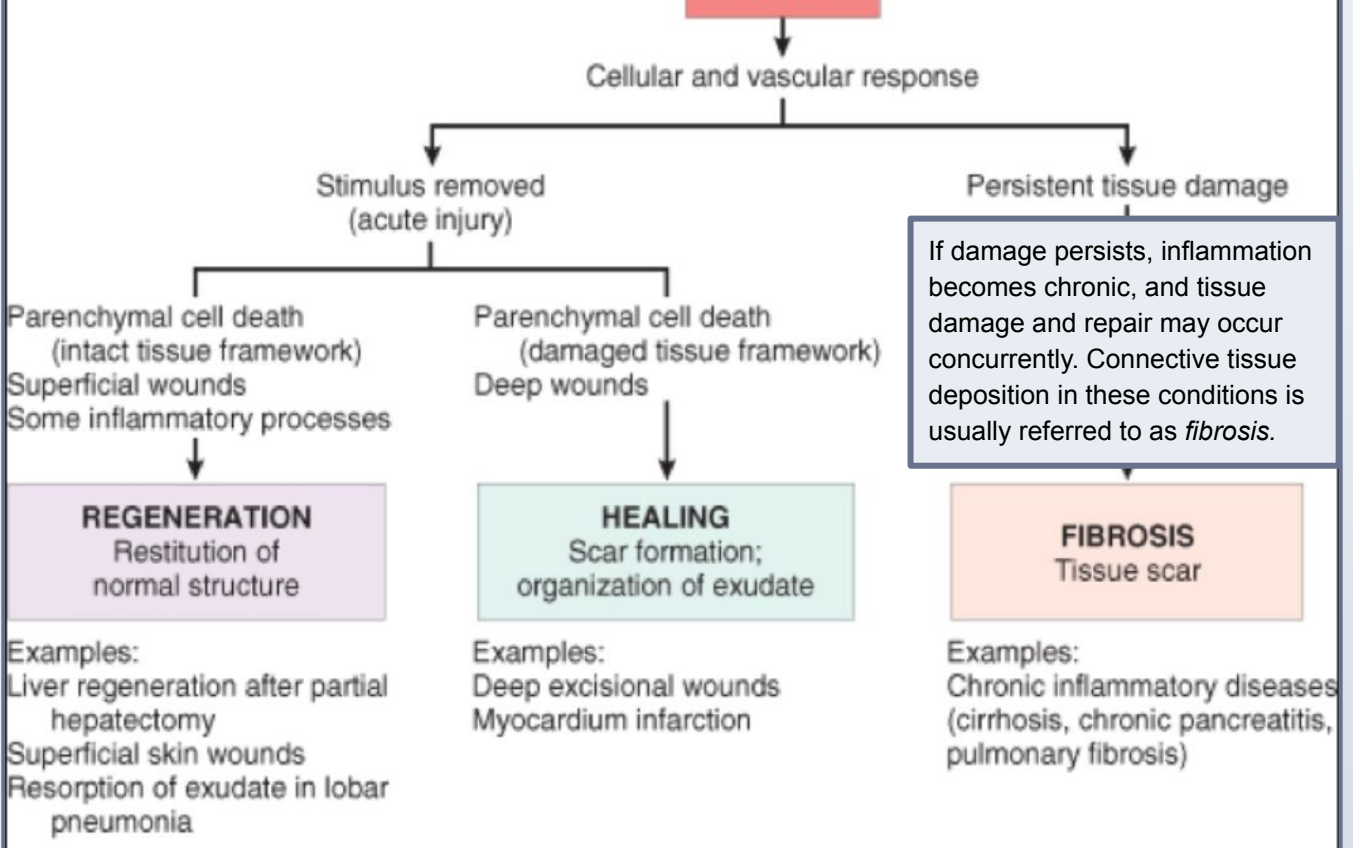
Is an increase in extracellular matrix (ECM) → formed of **collagen** and **may have proteoglycan**, but the most important is the collagen (Connective Tissue).

- Chronic inflammation **always** leads to fibrosis
- Fibrosis causes **loss** of function.

**NORMAL HOMEOSTASIS**  
(balance of proliferation and apoptosis)



**INJURY**



# Repair by tissue regeneration or healing depend on cell type

## Labile cells

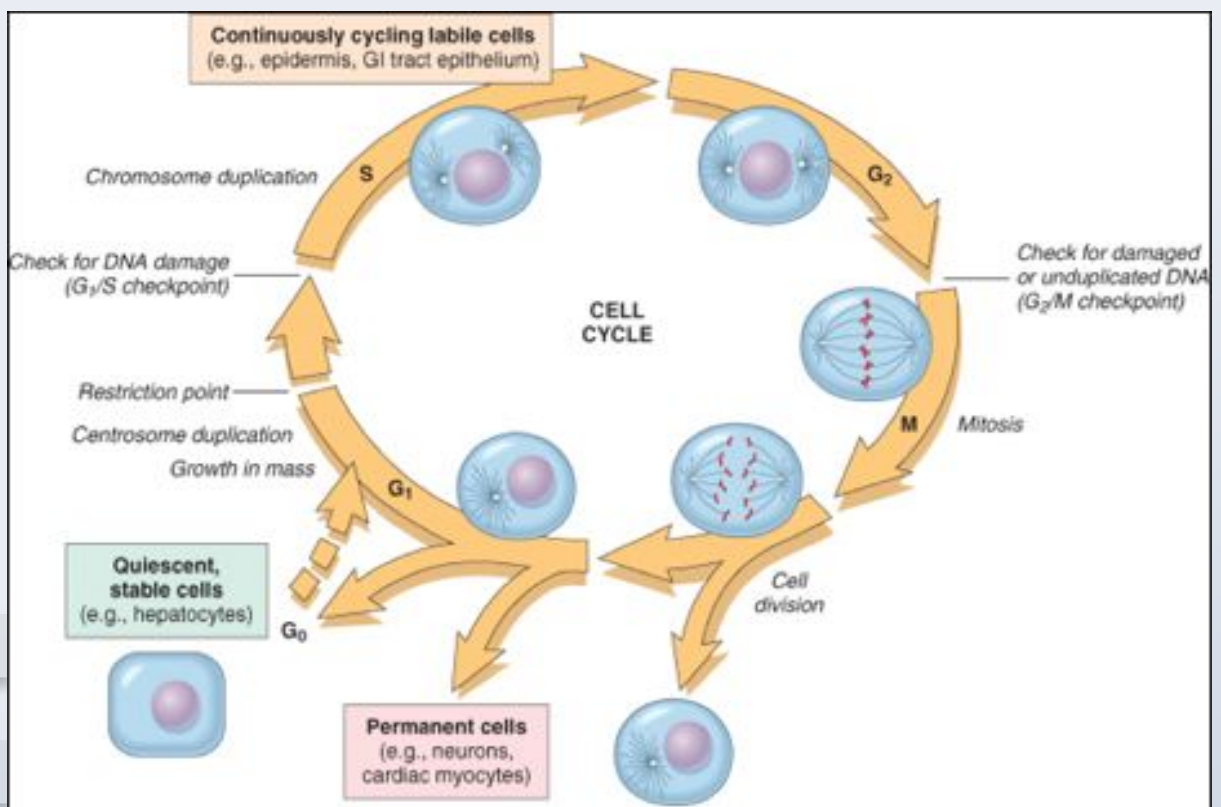
continue to proliferate throughout life: squamous, columnar, transitional epithelia; hematopoietic and lymphoid tissues. (skin, mucous membrane, G.I tract and urogenital system mucosa)

## Stable cells

retain the capacity of proliferation but they don't replicate normally: parenchymal cells (e.g. Liver) of all glandular organs & mesenchymal cells. (e.g. renal tubules, bone/osteoblast and smooth muscle cells)

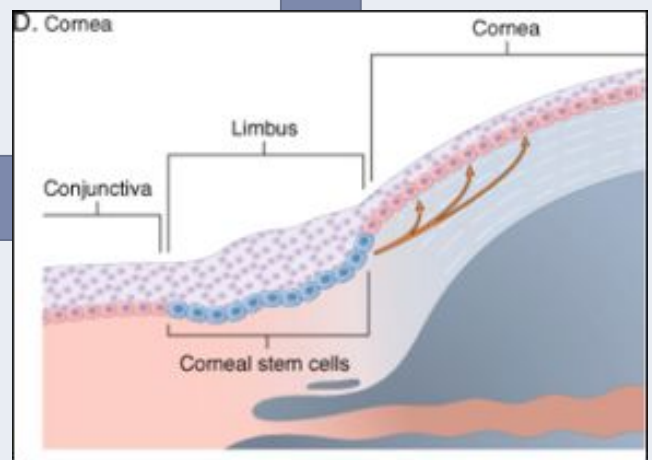
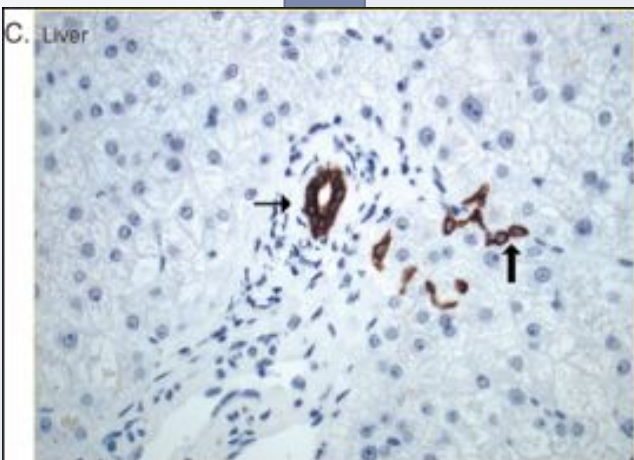
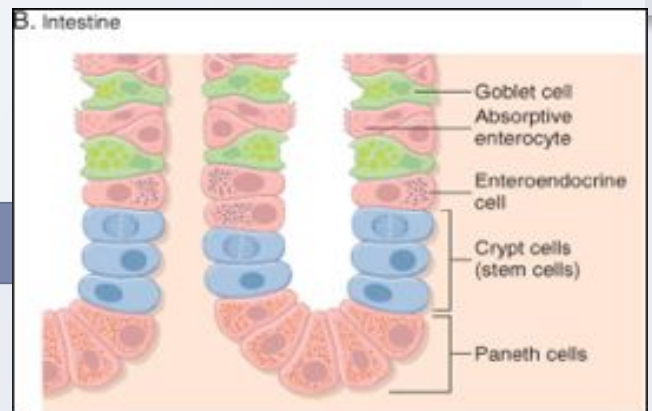
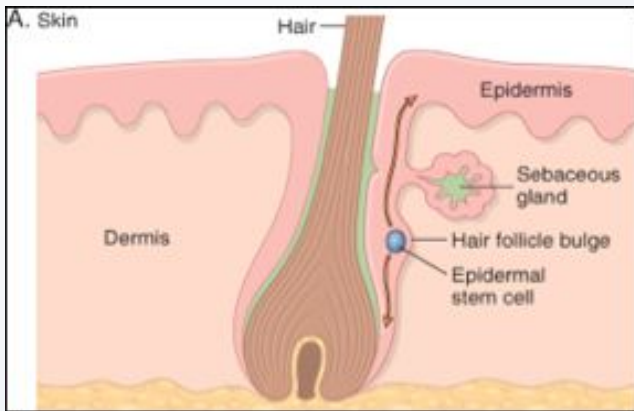
## Permanent cells

cannot reproduce themselves after birth: neurons, cardiac muscle cells (myocardial fibres) and retina cells





# Examples of labile cells: STEM CELLS

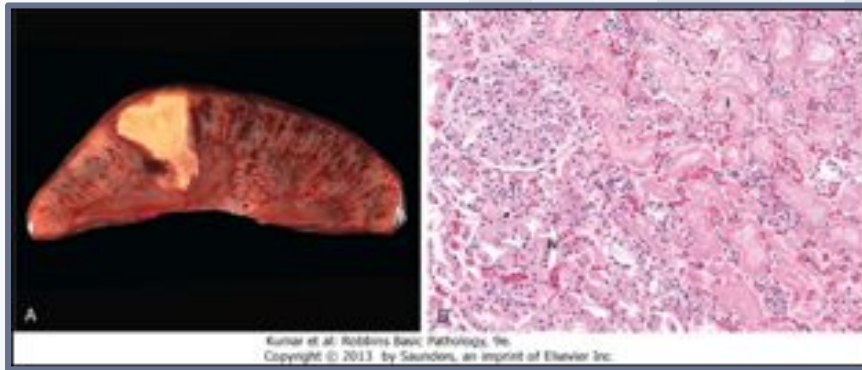


## Healing

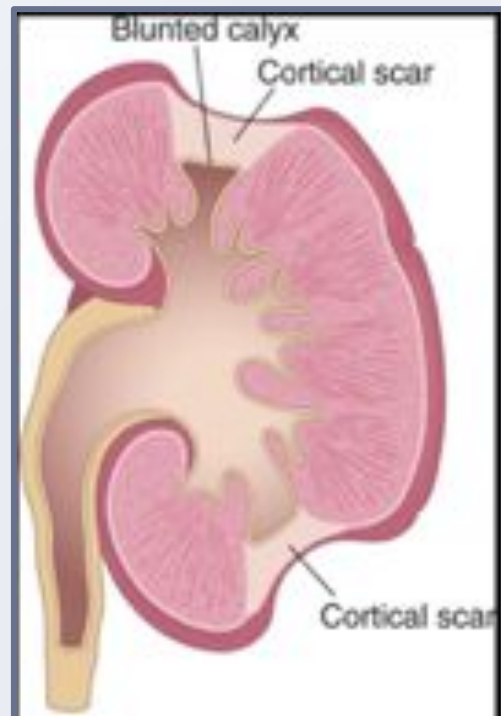
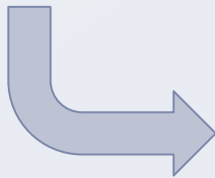
Normal framework → regenerated  
Destroyed framework → Scar formation

Healing is usually a tissue response to:

- 1) A wound (commonly in the skin)
- 2) Inflammatory processes in internal organs
- 3) Cell necrosis in organs incapable of regeneration



Healing occur as a response to inflammatory processes in internal organs



## Mechanism of repair

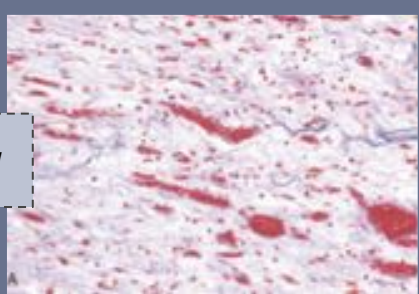
- Repair begins early in inflammation.
- **At site of inflammation**, fibroblasts and vascular endothelial cells begin proliferating to form a specialized type of tissue (hallmark of healing) called:

### **Granulation tissue**

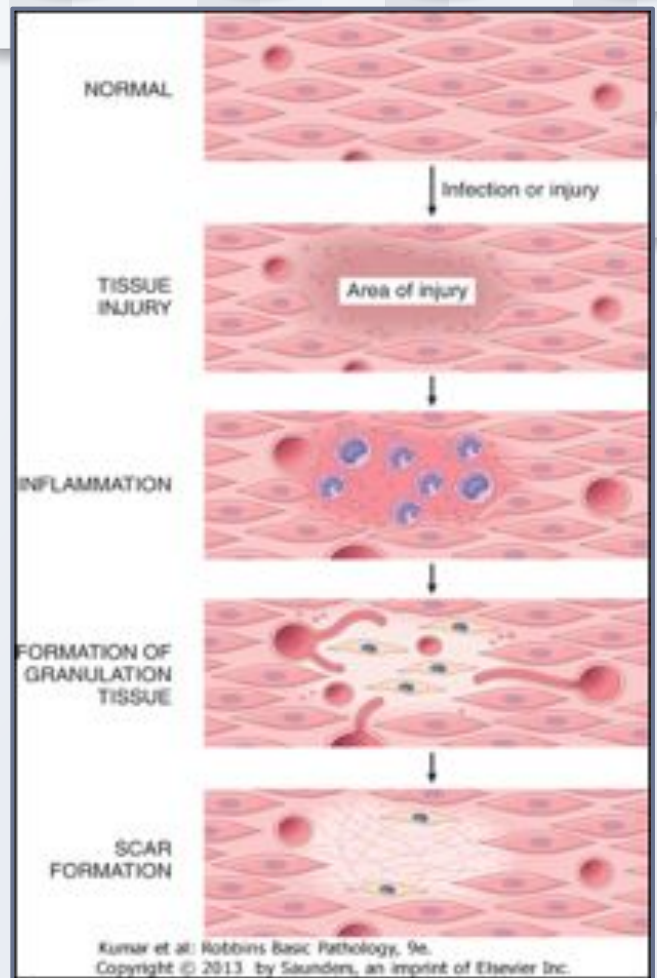
- The process is called **organization**

## Granulation tissue

Early



Late



## Repair by connective tissue (granulation tissue)

It consists of:

1

Fibroblasts surrounded by abundant extracellular matrix.

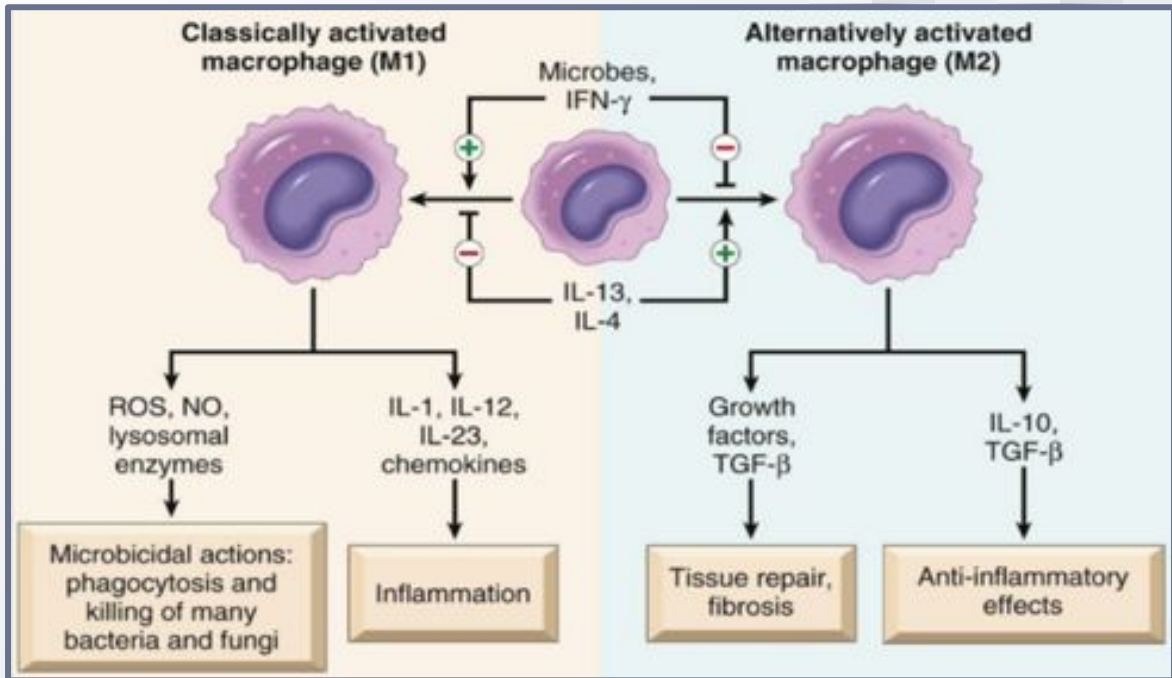
2

Newly formed blood vessels (sprouting of new capillaries).

3

Scattered macrophages and some other inflammatory cells.

# Role of macrophages in wound healing



**Cleanup** of debris, fibrin, and other foreign material at the site of repair.

Stimulation of **matrix production**, interleukins that stimulate fibroblasts and angioblasts to produce the extracellular matrix.

Macrophages **recruit other cells**: fibroblasts and angioblasts

TGF-beta has anti-inflammatory action and plays a role in tissue repair and fibrosis.

**What is the role of macrophages in wound healing?**

**Remodeling** of the scar. They secrete collagenases which digest collagen

Secretion of transforming growth factor beta (**TGF-B**), Role:-

- Activation of fibroblasts
- Lay down of collagen fiber



## Fibroblast\* Migration and Proliferation

Migration of fibroblasts to the site of injury and their subsequent proliferation are triggered by multiple growth factors, including mainly **TGF- $\beta$**  and others e.g. PDGF, EGF, FGF, and the cytokines **IL-1** and **TNF**.

**This leads to:**

1

**Increased** synthesis of collagen and fibronectin.

2

**Decreased** degradation of extracellular matrix (ECM) by metalloproteinases.

## ECM Deposition and Scar Formation

ECM= connective tissue = collagen = interstitial tissue. these all have the same meaning

As repair continues, the number of proliferating endothelial cells and fibroblasts decreases.

Net collagen accumulation, however, depends not only on increased collagen synthesis but also on decreased degradation.

# Granulation tissue morphology

- As early as 24 hr. after injury, fibroblasts and vascular endothelial cells begin proliferating to form (by 3-5 days) granulation tissue - pink soft granular appearance on the surface of the wound
- *New granulation tissue is often edematous (has Edema).*

**Histologically:** granulation tissue is composed of:

1

proliferation of **new small blood vessels**

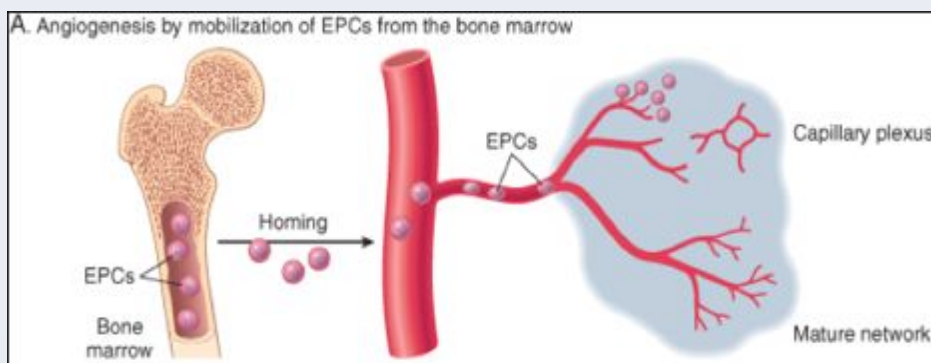
2

proliferation of **fibroblasts**

3

**Macrophages**

## Angiogenesis Sprouting of new capillaries



It Brings more blood to site of the injury → more chemical mediators

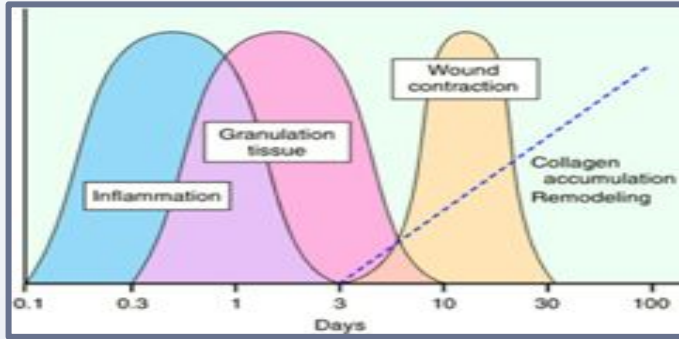
**Angiogenesis from Endothelial Precursor Cells**

**Angiogenesis plays a major role in granulation tissue formation during wound healing**

# SCAR FORMATION

**Further healing:** increased collagen, decreased active fibroblasts and new vessels (thrombosis and degeneration).

**At the end:** scar (inactive fibroblasts, dense collagen, fragments of elastic tissue, extracellular matrix, few vessels).



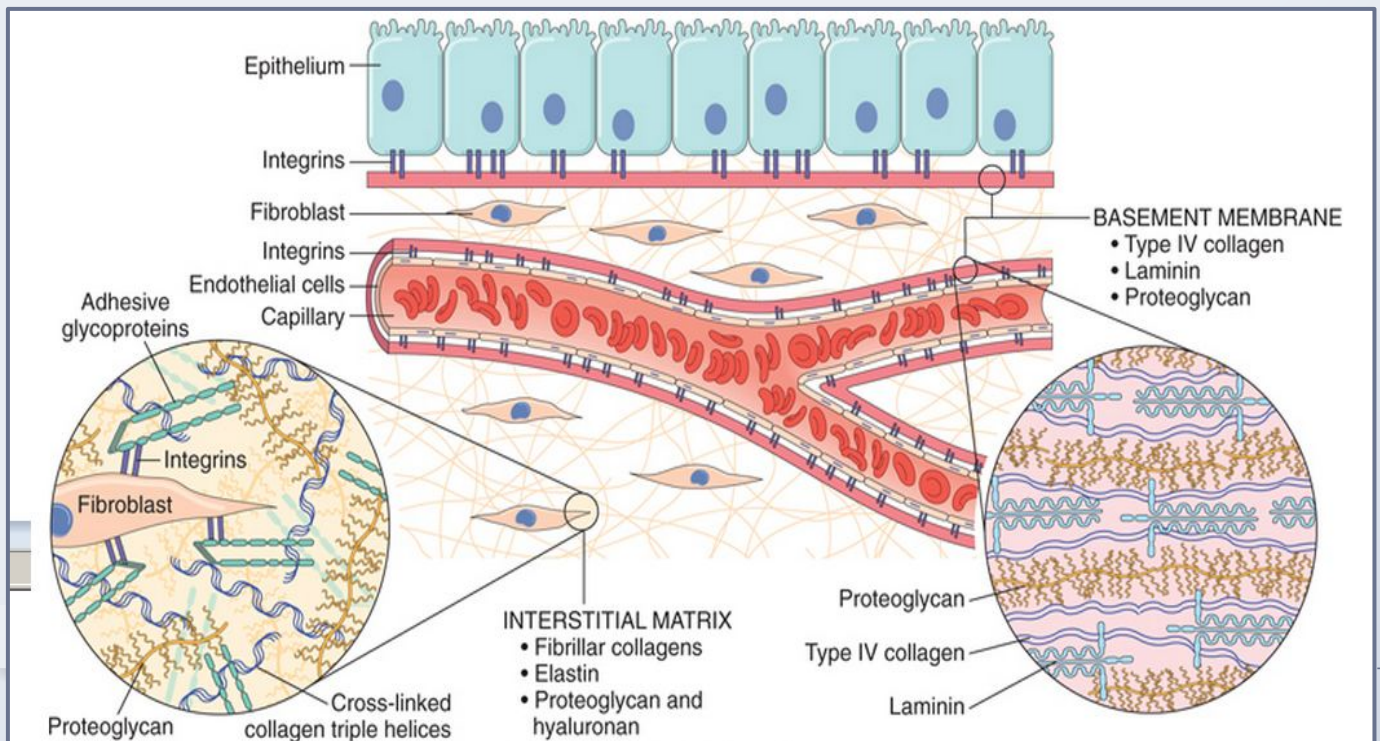
## Functions of the Extracellular Matrix

Mechanical support

Scaffolding for tissue renewal

Establishment of tissue microenvironments.

Control of cell proliferation



# Cutaneous Wound healing

## Primary union (Healing by 1st Intention/*ideal condition*)

clean surgical incision

no significant bacterial contamination

minimal loss of tissue

clot, scab formation

*Approximation of ends*

*the amount of the scar and fibrosis is minimal*

*better healing with sutures*

## Secondary union (healing by 2nd intention)

surface wound with large defect

large tissue defect that must be filled

*the area may be depressed because of fibro myoblasts*

*more extensive loss of cells and tissues and more extensive scarring.*

E.g

*Bacterial infection*

inflammatory ulceration

infarction

abscess formation



# Primary union (healing by first intention)

## Linear scar formation

- Hematoma & neutrophils, mitotic activity of basal layer, thin epithelial layer  
- Hageman factor (factor 12) will activate both the coagulation sequence and the kinin system as an initial response to this injury

macrophages, granulation tissue

collagen bridges the incision, epidermis thickens

continued collagen and fibroblasts, blanching

scar (cellular connective tissue, intact epidermis, lost appendages)

24h

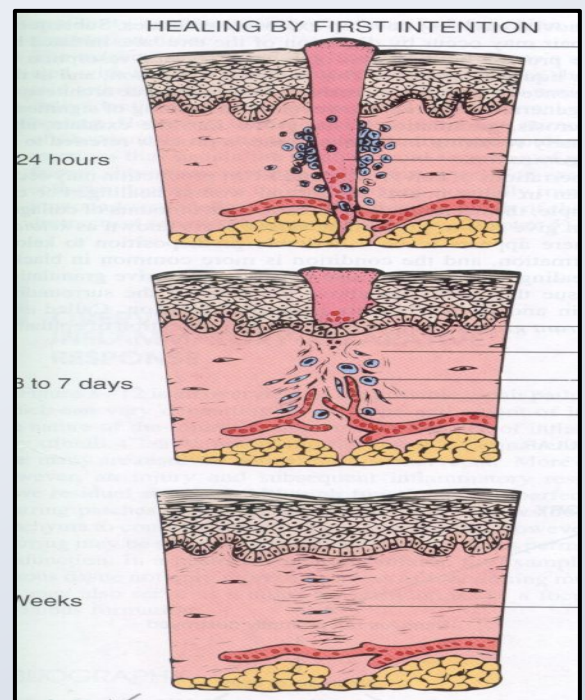
Day 3

Day 5

2nd week

End of 1st month

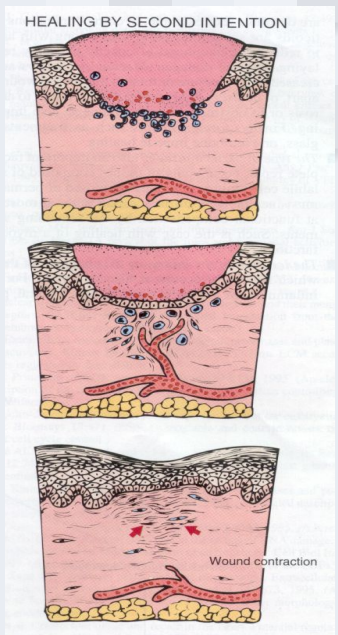
- Later, **collagen type III** is slowly replaced by **collagen type I** and the wound acquires tensile Strength.
- By the end of third month, the tissue has approximately **80%** of its original strength.



# Secondary union (healing by 2nd intention)

Occur in:

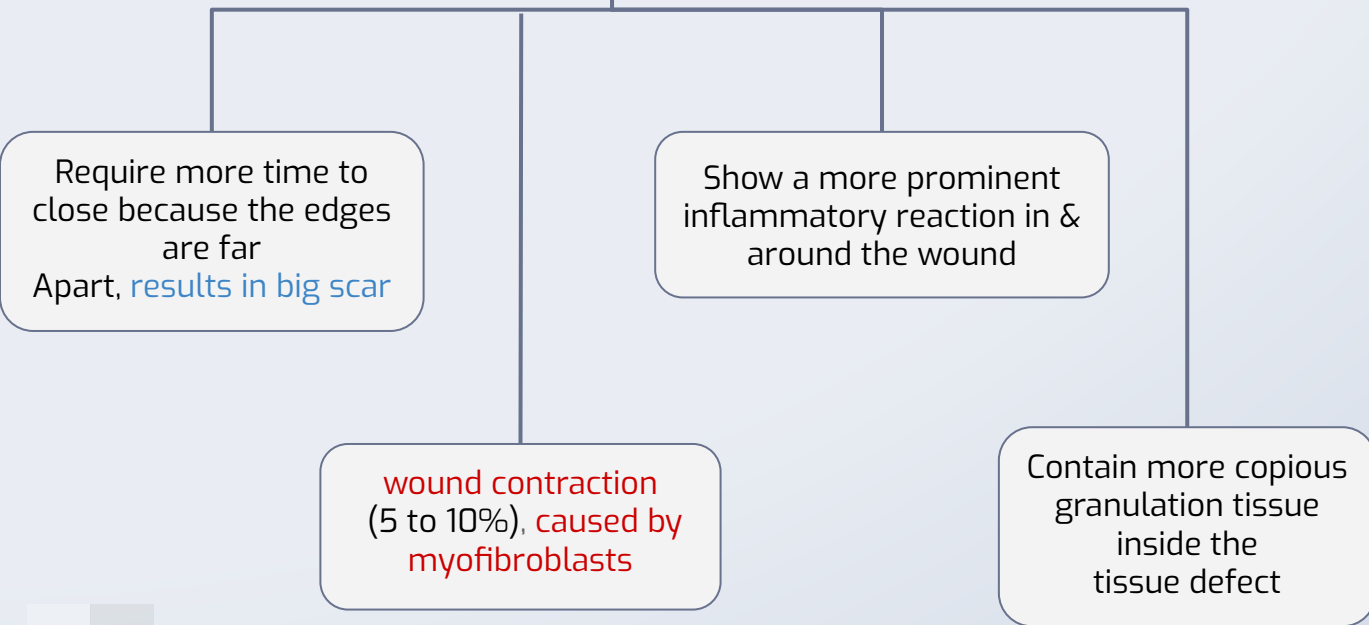
- Large gaping wounds
- Infected wounds
- Wounds that contain foreign material



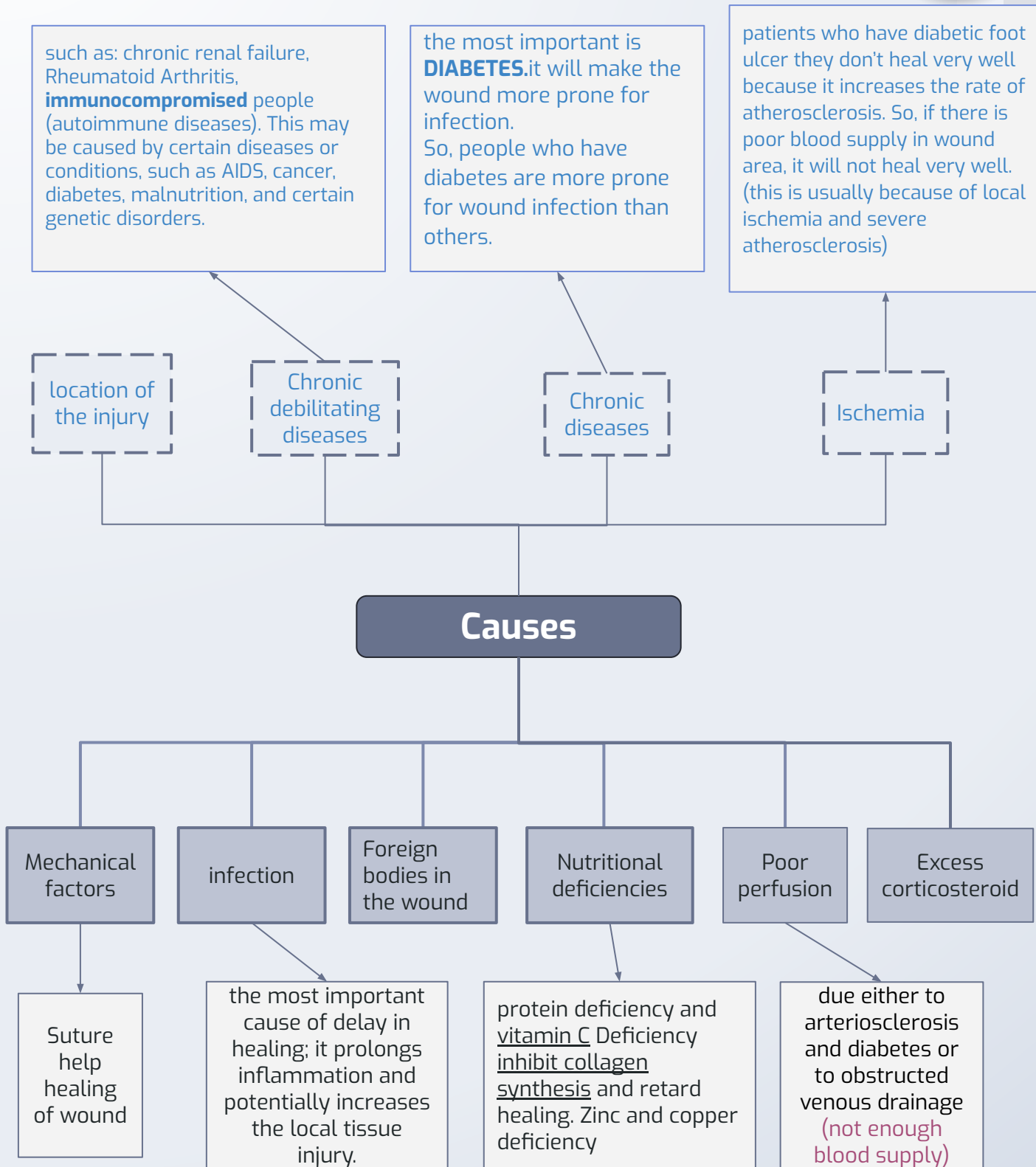
\*Scar is due to tissue contraction

What makes secondary intention different from primary intention?

The basic process of healing is the same in all wounds. In contrast to healing by primary intention, wounds healing by secondary intention



# Delayed wound healing



Example for mechanical factors : woman need to rest after c. section

Arteriosclerosis: The thickness & stiffness of blood vessels which lead to an inadequate blood supply.

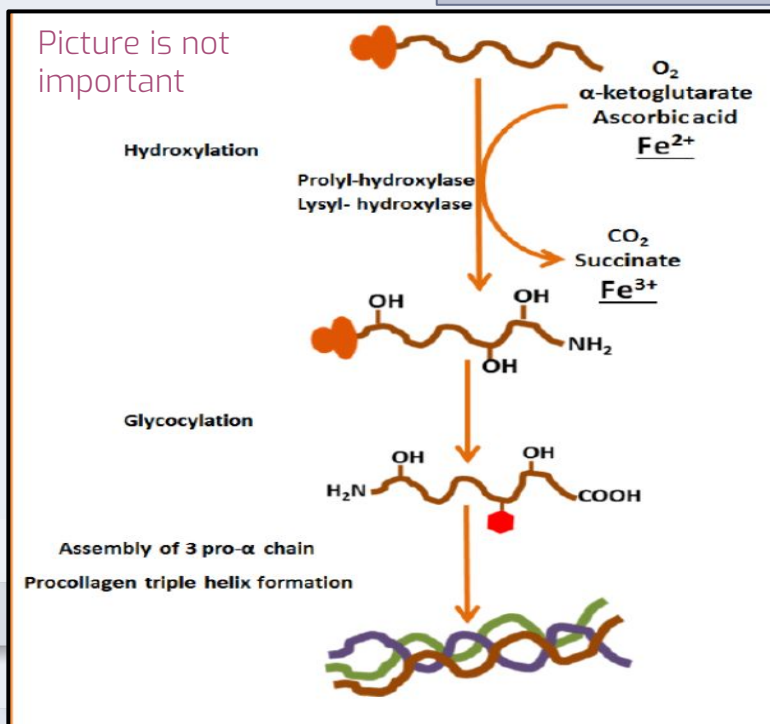
# Delayed wound healing

## Excess corticosteroid

- Have well-documented anti-inflammatory effects, and their administration may result in weakness of the scar. *i.e. reduced healing of wound*
- However, the anti-inflammatory effects of glucocorticoids are sometime desirable E.g. corneal infections

*Fibrous tissue is not desirable in this case, it has to be translucent to allow light to come in. So cortisone is given only *briefly* to reduce inflammation. If anti-inflammatory are given for too long it may cause viral infection.*

## Collagen Synthesis



- Proline hydroxylation by vitamin C.



# Complications In Cutaneous Wound Healing

Complications in wound healing can arise from abnormalities in any of the basic components of the repair process.

## Types of aberrations (abnormalities)

Deficient scar formation

Formation of contractures (myofibroblast).

Excessive formation of the repair components and connective tissue

## Examples of complications in wound healing



Contracture



Fibrin adhesion



Wound dehiscence



Keloid



Hypertrophic scar



Wound ulceration

# Keloid

- An Excessive scars composed of irregular deposit of thick hyalinized collagen bands. They may appear as bulging masses.
- more prone in people with dark skin, It can occur at the site of burn or sometimes it is just Minor trauma like ear piercing in girls.
- Microscope of keloid : dermis is all collagen ( Type III ) and its color is eosinophilic called **hyalinized collagen** : it is one of the histopathological features of keloid .



## Difference between keloid & hypertrophic scar

### Keloids

- Result of an overgrowth of dense fibrous tissue that usually develops after healing of a skin injury.
- The tissue extends beyond the borders of the original wound
- Does not usually regress spontaneously, and tends to recur after excision.

### Hypertrophic scars

#### Characterized by:

- erythematous, pruritic, raised fibrous lesions.
- Do not expand beyond the boundaries of the initial injury
- May undergo partial spontaneous resolution.
- common after thermal injuries.



# Formation of contractures

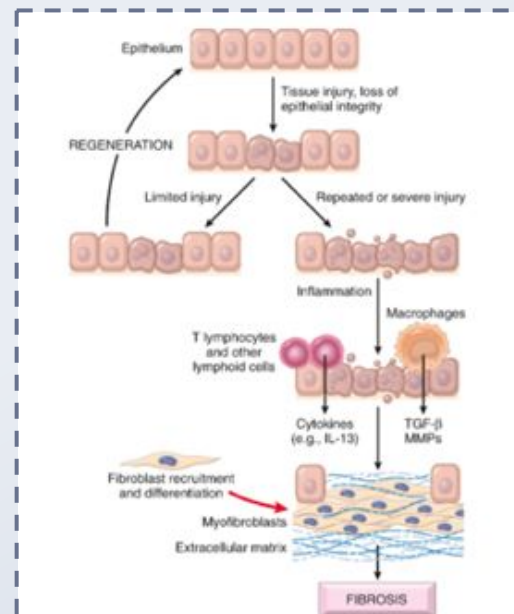
- Common on:
  - 1) Palms
  - 2) Soles
  - 3) Anterior aspect of the thorax.



- Commonly seen after serious burns
- It can compromise the movement of joints.
- it is caused by myofibroblasts

## Fibrosis in Parenchymal Organs Not important

- A pathologic process induced by persistent injurious stimuli such as:
  - 1) Chronic infections
  - 2) immunologic reactions
- Associated with loss of tissue
- E.g. liver cirrhosis after chronic hepatitis or pancreatic insufficiency after chronic pancreatitis.



## Take home messages

The various cell types (ie, labile, stable, and permanent cells) affect the outcome of healing.

Three main phases of cutaneous wound healing: (1) inflammation, (2) formation of granulation tissue, and (3) ECM deposition and remodeling

Healing by primary intention occur in surgical clean wound and healing by secondary intention occur when excessive tissue damage is present

Several factors are associated with delayed wound healing.

Complication of wound healing include failure of healing, contracture and excessive scar formation



1- A 17-year old female receiving corticosteroid therapy for an autoimmune disease has an abscess on her upper outer left arm. She undergoes a drainage procedure but the wound heals poorly over the next month. Which of the following aspects of wound healing is most likely to be deficient in this patient?

- |                            |                        |                         |                           |
|----------------------------|------------------------|-------------------------|---------------------------|
| A- neutrophil infiltration | B- collagen deposition | C- re-epithelialization | D- fibroblast elaboration |
|----------------------------|------------------------|-------------------------|---------------------------|

2- All of these can lead to a delayed wound healing except:

- |                           |                    |              |             |
|---------------------------|--------------------|--------------|-------------|
| A- Excess corticosteroids | B- Heavy perfusion | C- Infection | D- Ischemia |
|---------------------------|--------------------|--------------|-------------|

3-Which of the following is associated with primary union (healing by first intention)?

- |                                   |                        |                   |                            |
|-----------------------------------|------------------------|-------------------|----------------------------|
| A- happens in large cell injuries | B- large tissue defect | C- Scab formation | D- more extensive scarring |
|-----------------------------------|------------------------|-------------------|----------------------------|

4-What happens in first 24 hours in healing by first intention?

- |                                  |              |                                    |         |
|----------------------------------|--------------|------------------------------------|---------|
| A- Collagen bridges the incision | B- Blanching | C- Mitotic activity of basal layer | D- Scar |
|----------------------------------|--------------|------------------------------------|---------|

5-Wound healing by Secondary intention:

- |                                    |                             |                                       |                            |
|------------------------------------|-----------------------------|---------------------------------------|----------------------------|
| A- Shows low inflammatory reaction | B- Needs less time to close | C- contains little granulation tissue | D- shows wound contraction |
|------------------------------------|-----------------------------|---------------------------------------|----------------------------|

6-Which of the following is a function of ECM?

- |                                   |                    |                         |                         |
|-----------------------------------|--------------------|-------------------------|-------------------------|
| A- Scaffolding for tissue renewal | B- Provides Energy | C- Control of diffusion | D- Rigidity of the cell |
|-----------------------------------|--------------------|-------------------------|-------------------------|

## SAQs

- 1- There are many factors that stand behind a delayed wound healing, can you mention one?
- 2- Complications in wound healing can arise from an abnormality of the basic components of the repair process, can you mention one type of those abnormalities?
- 3- Can you give an example of a complication in wound healing?
- 4- In what kind of wound secondary union usually occurs?

1. (page 16)
- 2.(page 18)
- 3.(page 18)
- 4.(page 15)

## Inflammation Lectures Quiz

Thanks for everyone who participated in this Teamwork <3

**INFLAMMATION LECTURES COMPLETED**  
Good Luck!

● ماجد العسكر

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- |                      |                  |
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