

# INFLAMMATION AND REPAIR

Editing File

## Lecture 5:

# Mechanisms and factors affecting repair

Objectives:

- ★ Describe the differences between repair processes: regeneration, healing and fibrosis. List examples of each cell type.
- ★ Know the differences 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 Code:

Female's Notes

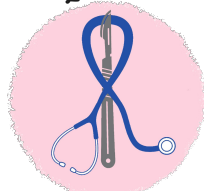
Male's Notes

Important

Extra



Revised & Reviewed  
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Fay.e Wael Sendi



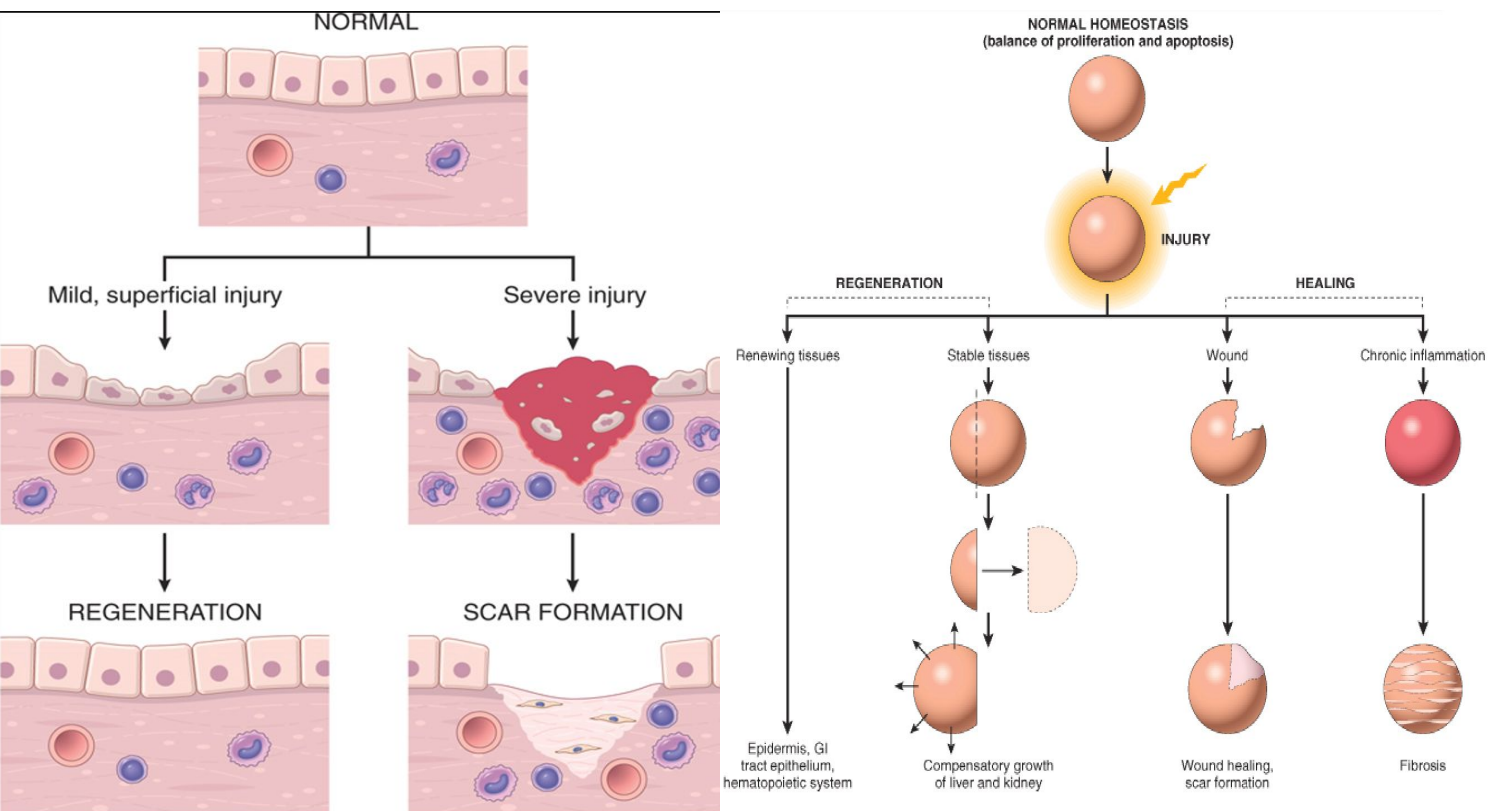
# Goal of the repair process

To restore the tissue to its original state after inflammatory reaction

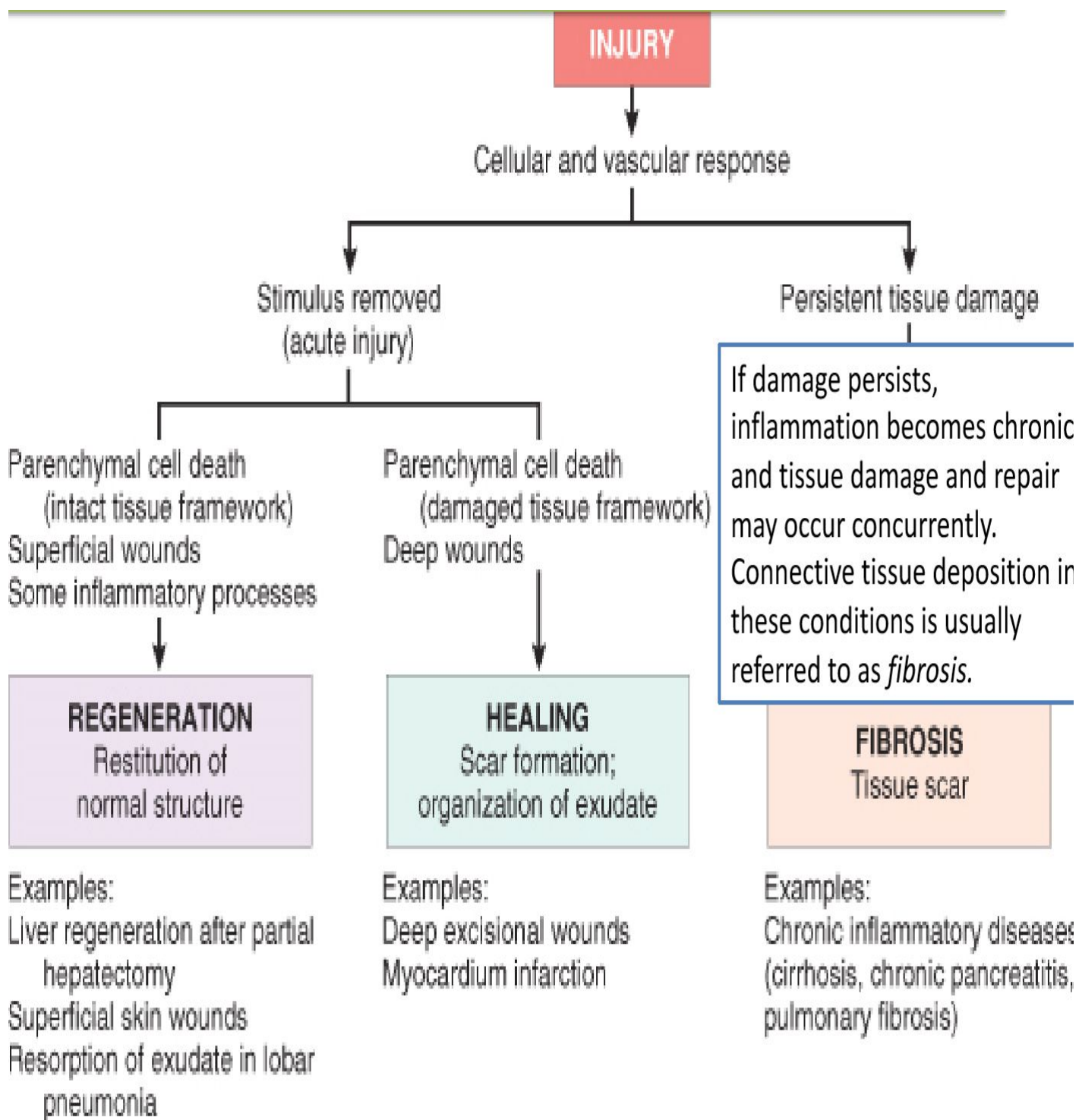
Some tissues can be completely reconstituted after injury, such as the repair of bone after a fracture or the regeneration of the surface epithelium in a cutaneous wound.

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

## Describe the differences between regeneration, healing and fibrosis



# Describe the differences between regeneration, healing and fibrosis



# 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

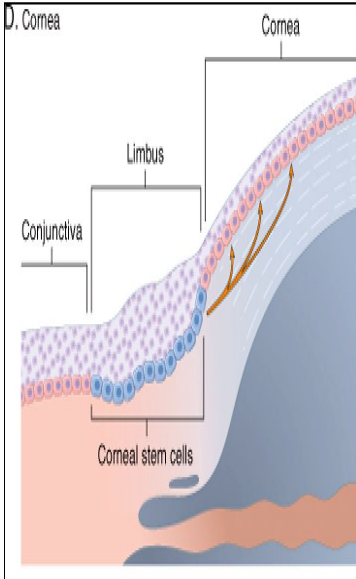
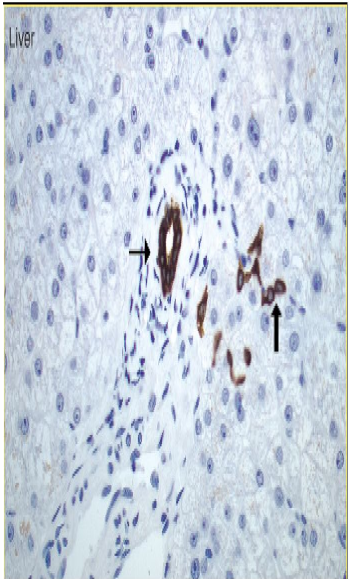
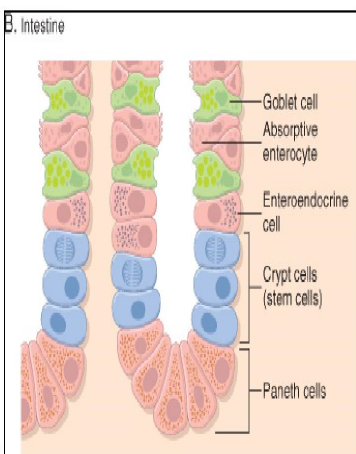
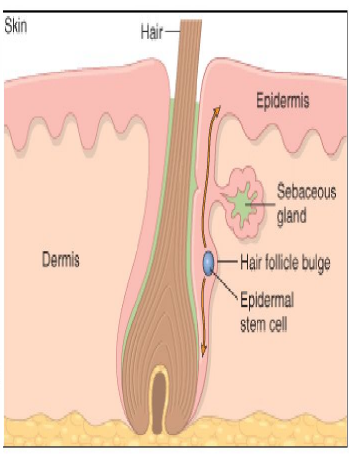
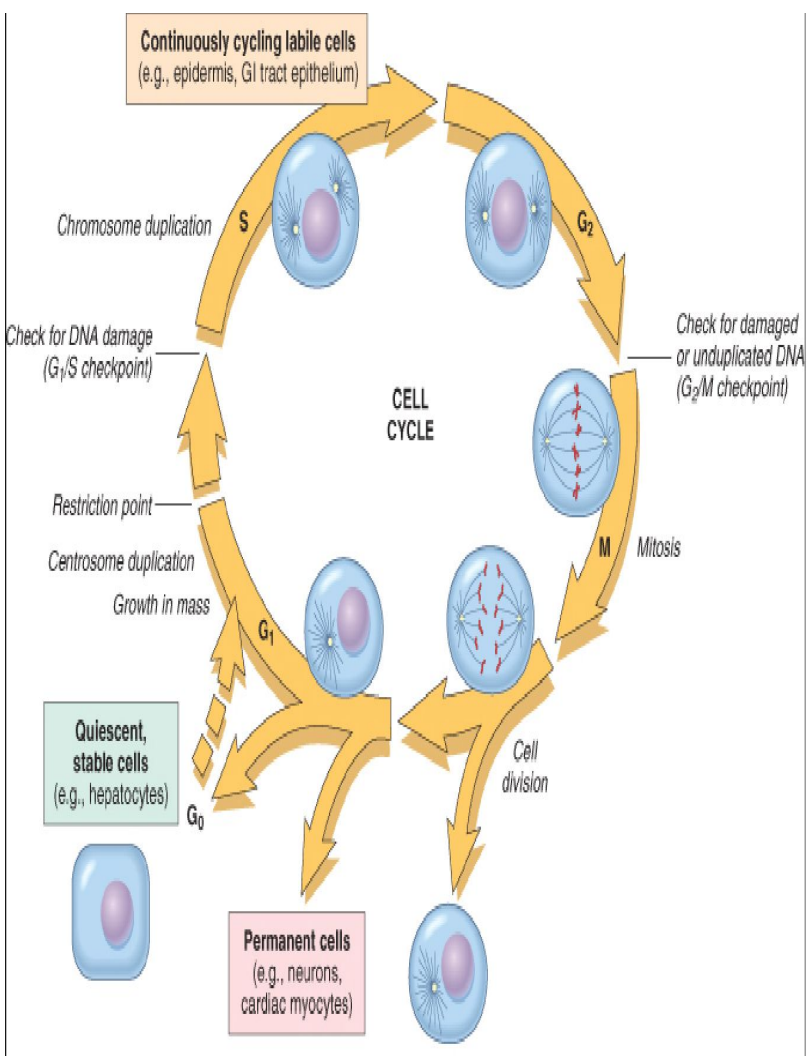
## Stable cells

retain the capacity of proliferation but they don't replicate normally: parenchymal cells of all glandular organs & mesenchymal cells e.g. hepatocytes and renal tubular cells

## Permanent cells

cannot reproduce themselves after birth: neurons, cardiac muscle cells

# The differences between the various cell in regenerative abilities types





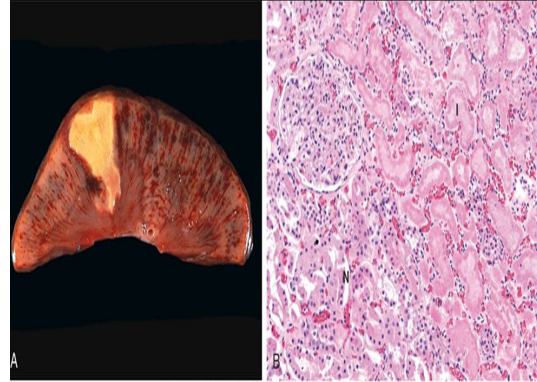
# Healing

Healing is usually a tissue response

to a wound (commonly in the skin)

to inflammatory processes in internal organs

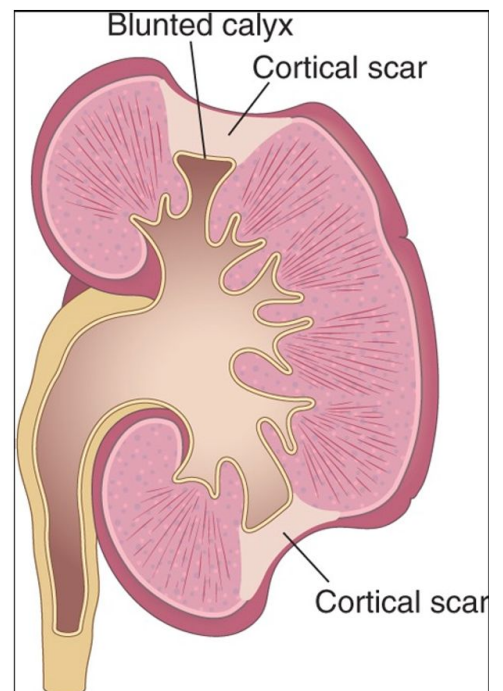
to cell necrosis in organs incapable of regeneration



Kumar et al; Robbins Basic Pathology, 9e.  
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**Know the mechanism of repair and formation of granulation tissue**

Healing occur as a response to inflammatory processes in internal organs



# Mechanism of repair

Repair begins early in inflammation.

The process is called organization

At site of inflammation, fibroblasts and vascular endothelial cells begin proliferating to form a specialized type of tissue (hallmark of healing) called: **granulation tissue**

# Mechanism of repair

Fibroblasts

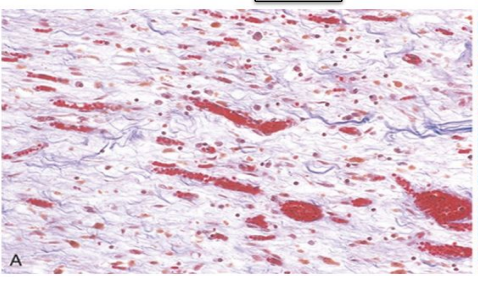
Vascular connective tissue

Inflammatory Cells

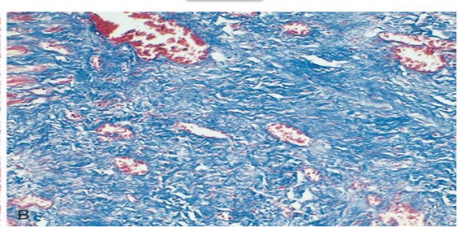
**Granulation tissue consists of:**

## Granulation tissue

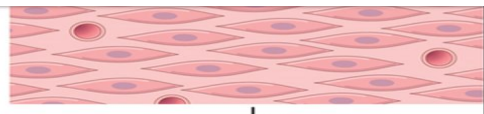
Early



Late



NORMAL



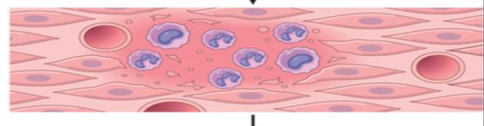
Infection or injury

TISSUE INJURY

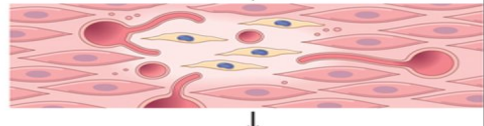


Area of injury

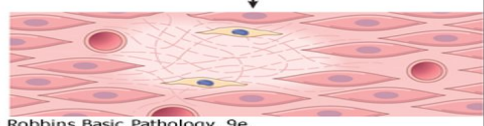
INFLAMMATION



FORMATION OF GRANULATION TISSUE

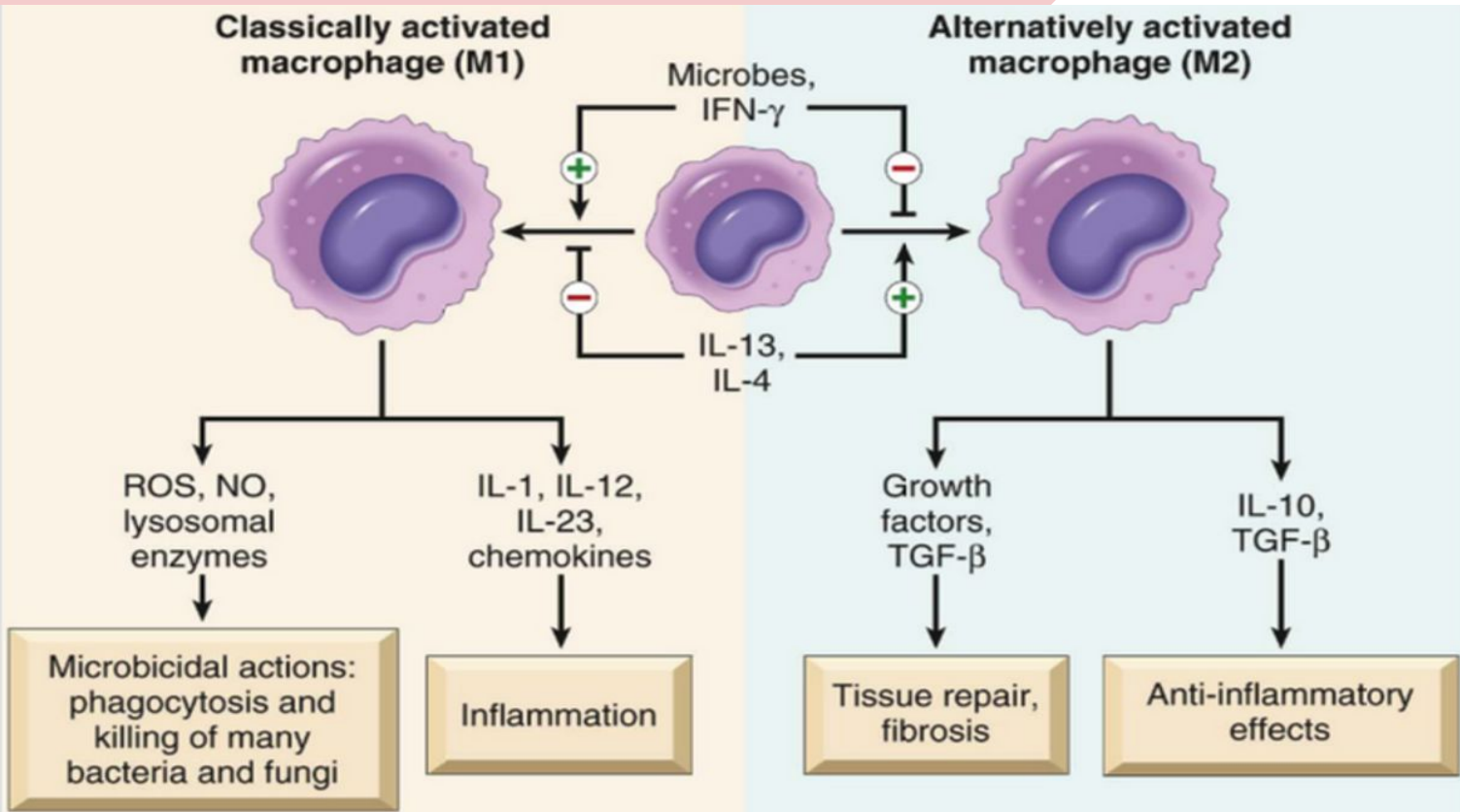


SCAR FORMATION



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# Role of macrophages in wound healing



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

- 1 Cleanup of debris, fibrin, and other foreign material at the site of repair.
- 2 Macrophages recruit other cells: fibroblasts and angioblasts
- 3 Stimulation of matrix production, interleukins that stimulate fibroblasts and angioblasts to produce the extracellular matrix.
- 4 Remodeling of the scar. They secrete collagenases
- 5 Secretion of transforming growth factor beta (TGF-B)
- 6 TGF-beta has anti inflammatory action and plays a role in tissue repair and fibrosis

# 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 lead to:**

1. Increased synthesis of collagen and fibronectin
2. Decreased degradation of extracellular matrix (ECM) by metalloproteinases

# ECM Deposition and Scar Formation

\*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.

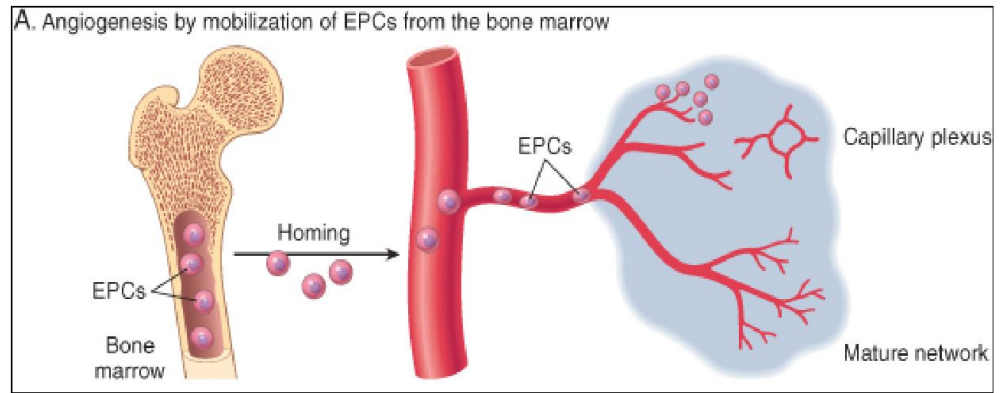
**Histologically:** granulation tissue is composed of :

- proliferation of new small blood vessels and
- proliferation of fibroblasts with deposition of type III collagen (begin third day in wound healing) · macrophags



# Angiogenesis

Sprouting of new capillaries



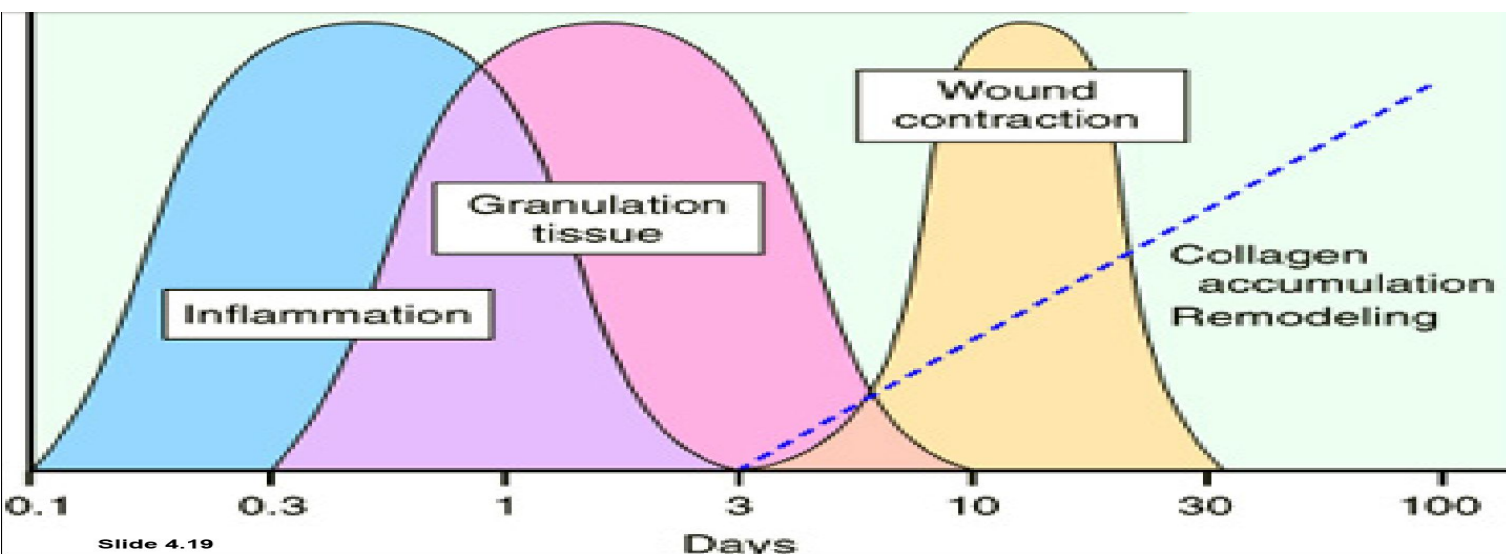
Angiogenesis from Endothelial Precursor Cells

★ 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

• The ECM is much more than a space filler around cells. Its various functions:



Mechanical support



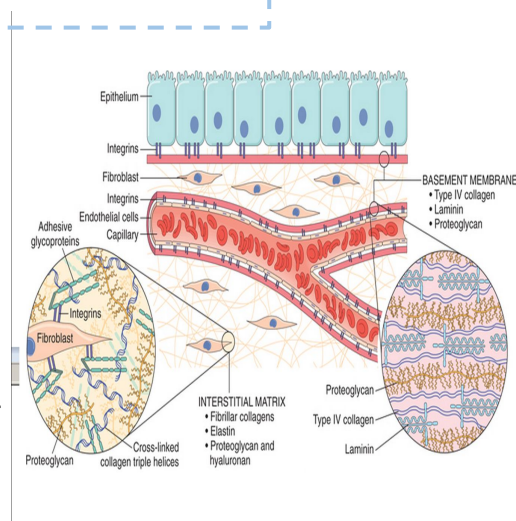
Control of cell proliferation



Scaffolding for tissue renewal



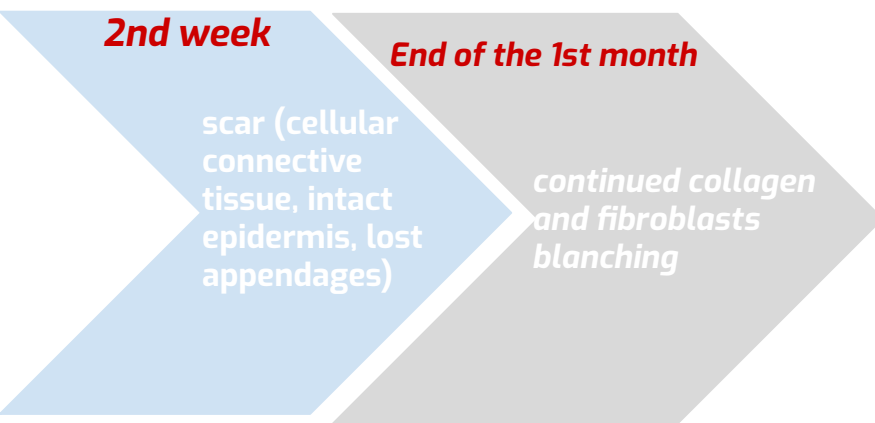
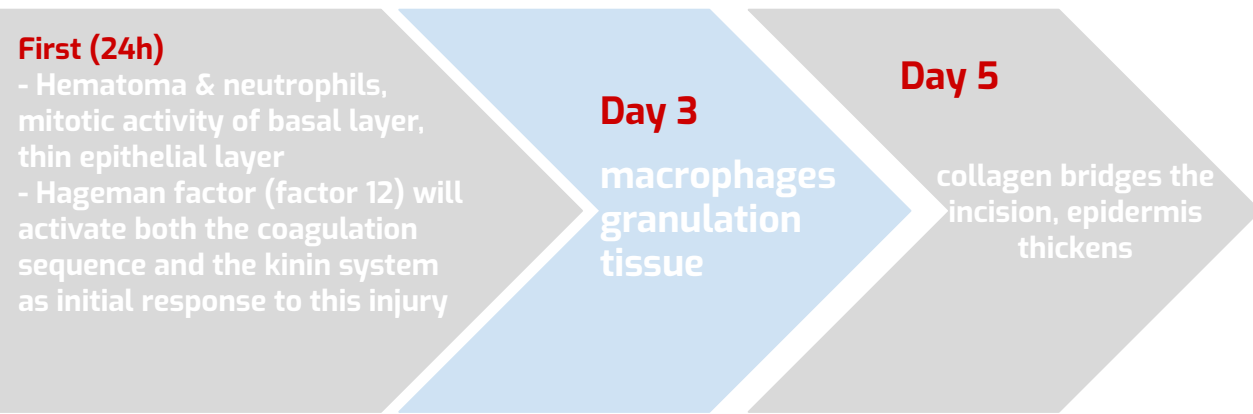
Establishment of tissue microenvironments



## Cutaneous Wound healing

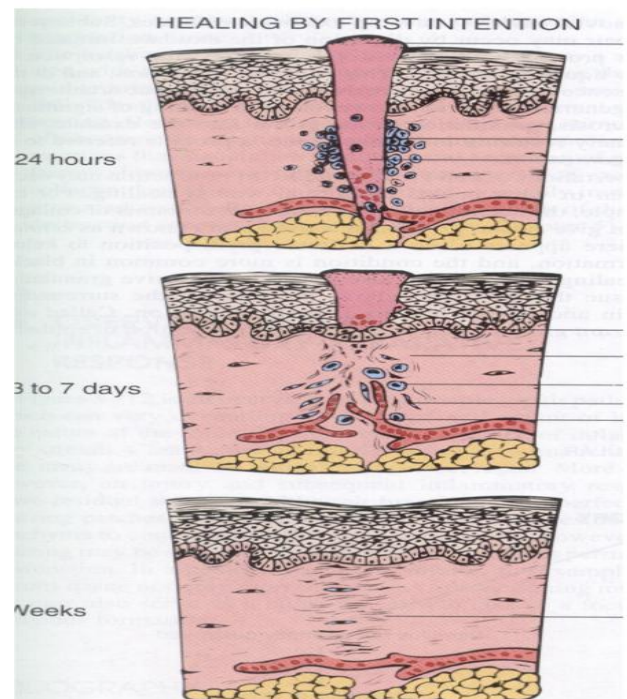
Primary union (Healing by 1st Intention/ <i>ideal condition</i> )	Secondary union (healing by 2nd intention)
clean surgical incision	surface wound with large defect
no significant bacterial contamination	large tissue defect that must be filled
minimal loss of tissue	more extensive loss of cells and tissues E.g( - <i>Bacterial infection</i> - <b>inflammatory ulceration</b> - <b>infarction</b> - <b>abscess formation</b> )
clot, scab formation	

# Primary union (healing by first intention)



## Primary union (healing by 1st intention):

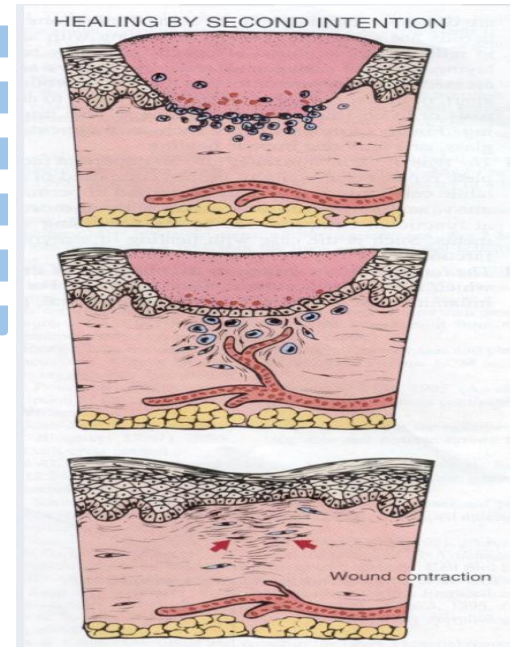
- Later, **collagen type III** is slowly replaced by **collagen type I** and the wound acquires tensile Strength.
- By the end of third month, the tissue has approximately **80%** of its original strength.



# Secondary union (healing by 2nd intention)

Occur in:

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



## What makes secondary intention different from primary intention?

Require more time to close because the edges are far apart

wound contraction (5 to 10%), caused by myofibroblasts

Show a more prominent inflammatory reaction in & around the wound

Contain more copious granulation tissue inside the tissue defect

**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

## \*the most common causes of delayed wound healing:

### Mechanical factors

Suture help healing of wound

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

### infection

the most important cause of delay in healing it prolongs inflammation and potentially increases the local tissue injury.

### Nutritional deficiencies

protein deficiency and **vitamin C** Deficiency **inhibit collagen synthesis** and retard healing Zinc and copper deficiency

### Poor perfusion

due either to Arteriosclerosis and diabetes or to obstructed venous drainage (**not enough blood supply**)

### Excess corticosteroid

### Foreign bodies in the wound

## Excess corticosteroid

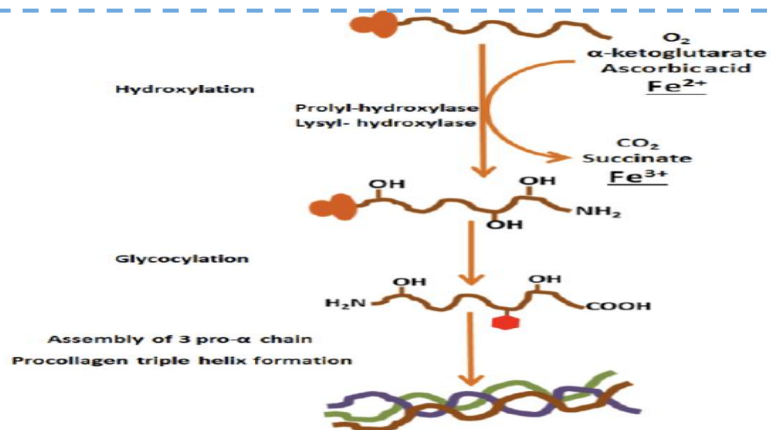
- Have well-documented anti-inflammatory effects, and their administration may result in weakness of the scar. **i.e. reduced healing of wound**

- 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.**

1

Deficient scar formation

2

Formation of contractures (myofibroblast)

3

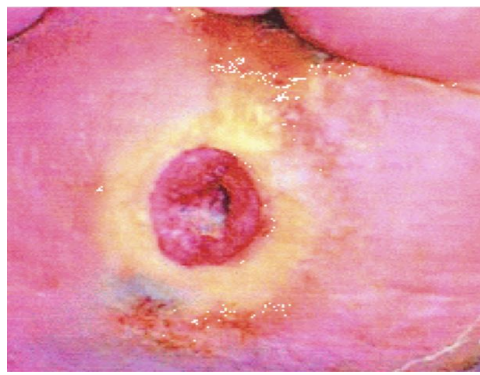
Excessive formation of the repair components and connective tissue

**Types of aberrations (abnormalities)**

## Examples of complications in wound healing



Wound dehiscence



Wound ulceration



Keloid



Contracture

Source: Wounds © 2003 Health Management Pu

# Keloid

## Keloid

**An Excessive scars composed of irregular deposit of thick hyalinized collagen bands. They may appear as bulging masses.**

### **\*Difference between keloid & hypertrophic scar**

Keloids	Hypertrophic scars
- Result of an overgrowth of dense fibrous tissue that usually develops after healing of a skin injury.	<u>Characterized by:</u> erythematous, pruritic, raised fibrous lesions.
- The tissue extends beyond the borders of the original wound	- Do not expand beyond the boundaries of the initial injury
- Does not usually regress spontaneously, and tends to <u>recur</u> after excision.	- May undergo partial spontaneous resolution.
	- common after thermal injuries.

## Formation of contractures

1

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

2

- Commonly seen after **serious burns**

3

- It can compromise the movement of joints.

4

- it is caused by **myofibroblasts**

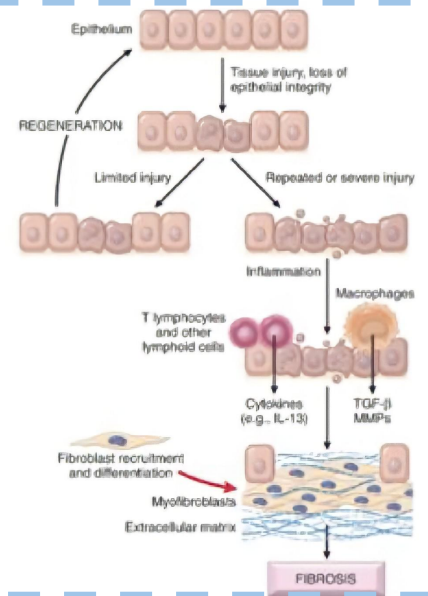
# Fibrosis in Parenchymal Organs

- 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***

# ★ MCQs

**Q1) In primary union collagen type III is replaced by ..... ?**

- |            |                     |                    |              |
|------------|---------------------|--------------------|--------------|
| A) elastin | B) Reticular Fibers | C) collagen type I | D) cartilage |
|------------|---------------------|--------------------|--------------|

**Q2) Secondary union occurs in....?**

- |                      |                   |                        |                   |
|----------------------|-------------------|------------------------|-------------------|
| A) surgical incision | B) aseptic wounds | C) Large gaping wounds | D) fresh injuries |
|----------------------|-------------------|------------------------|-------------------|

**Q3) ..... deficiency and .....deficiency inhibit collagen synthesis ?**

- |                         |                   |                        |                    |
|-------------------------|-------------------|------------------------|--------------------|
| A) vitamin b12& protein | B) zinc & calcium | C) vitamin C & protein | D) omega 3& copper |
|-------------------------|-------------------|------------------------|--------------------|

**Q4) ..... continue to proliferate throughout life : squamous, columnar, transitional epithelia; hematopoietic and lymphoid tissues**

- |                 |                 |                    |
|-----------------|-----------------|--------------------|
| A) Labile cells | B) Stable cells | c) Permanent cells |
|-----------------|-----------------|--------------------|

**Q5) Granulation tissue consists of:**

- |                               |                |                       |                |
|-------------------------------|----------------|-----------------------|----------------|
| A) Vascular connective tissue | B) Fibroblasts | C) Inflammatory cells | D) All of them |
|-------------------------------|----------------|-----------------------|----------------|

**Q6) At site of inflammation, fibroblasts and vascular endothelial cells begin proliferating to form a specialized type of tissue (hallmark of healing) called:**

- |                       |              |                      |
|-----------------------|--------------|----------------------|
| A) granulation tissue | B) Granuloma | C) connective tissue |
|-----------------------|--------------|----------------------|

# ★ SAQ

**Q1) give three examples of complications in wound healing : Answer (slide 14)**

**Q2) What is the role of macrophages in wound healing? Answer (slide 7)**



### **Leaders:**

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Layan Alhelal  
Taif alshehri  
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laila almeshariy  
Alanoud Albawardi  
Reema Alrashedi

Shouq Alhathal  
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