

PATHOLOGY TEAMWORK

MED 444



Tissue repair & regeneration

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.

Editing file

COLOR INDEX:

MAIN TEXT (BLACK)

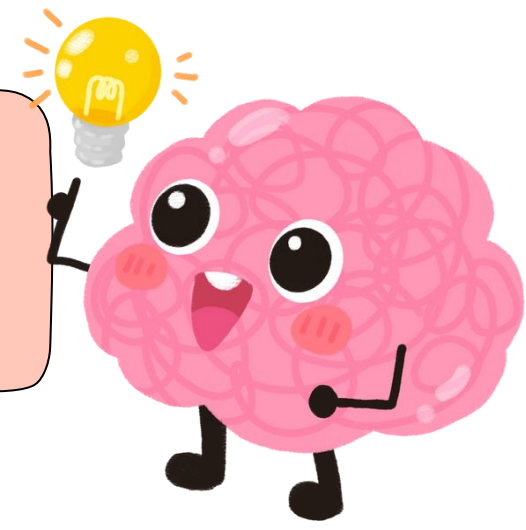
FEMALE SLIDES (PINK)

MALE SLIDES (BLUE)

IMPORTANT (RED)

DR'S NOTE (GREEN)

EXTRA INFO (GREY)



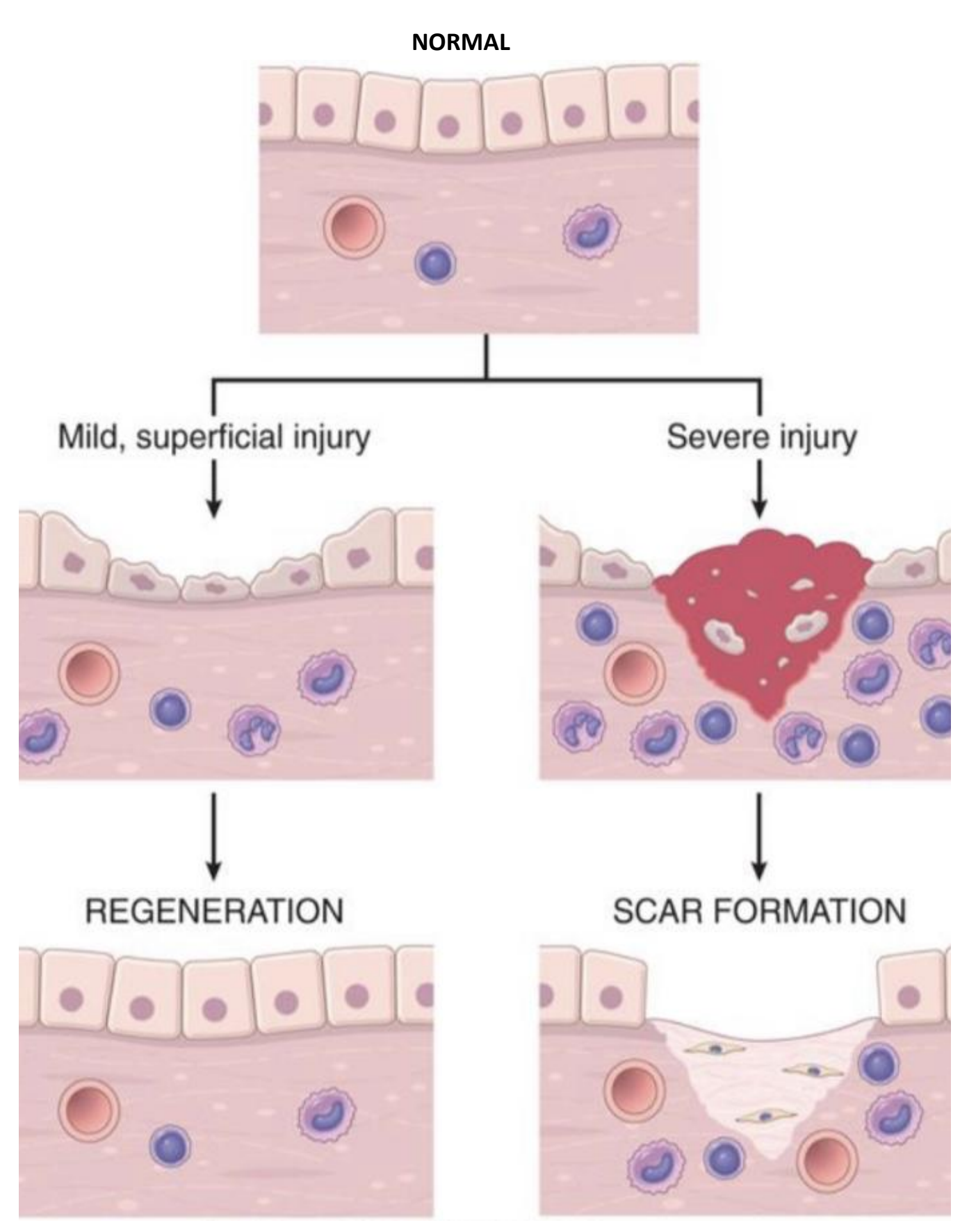
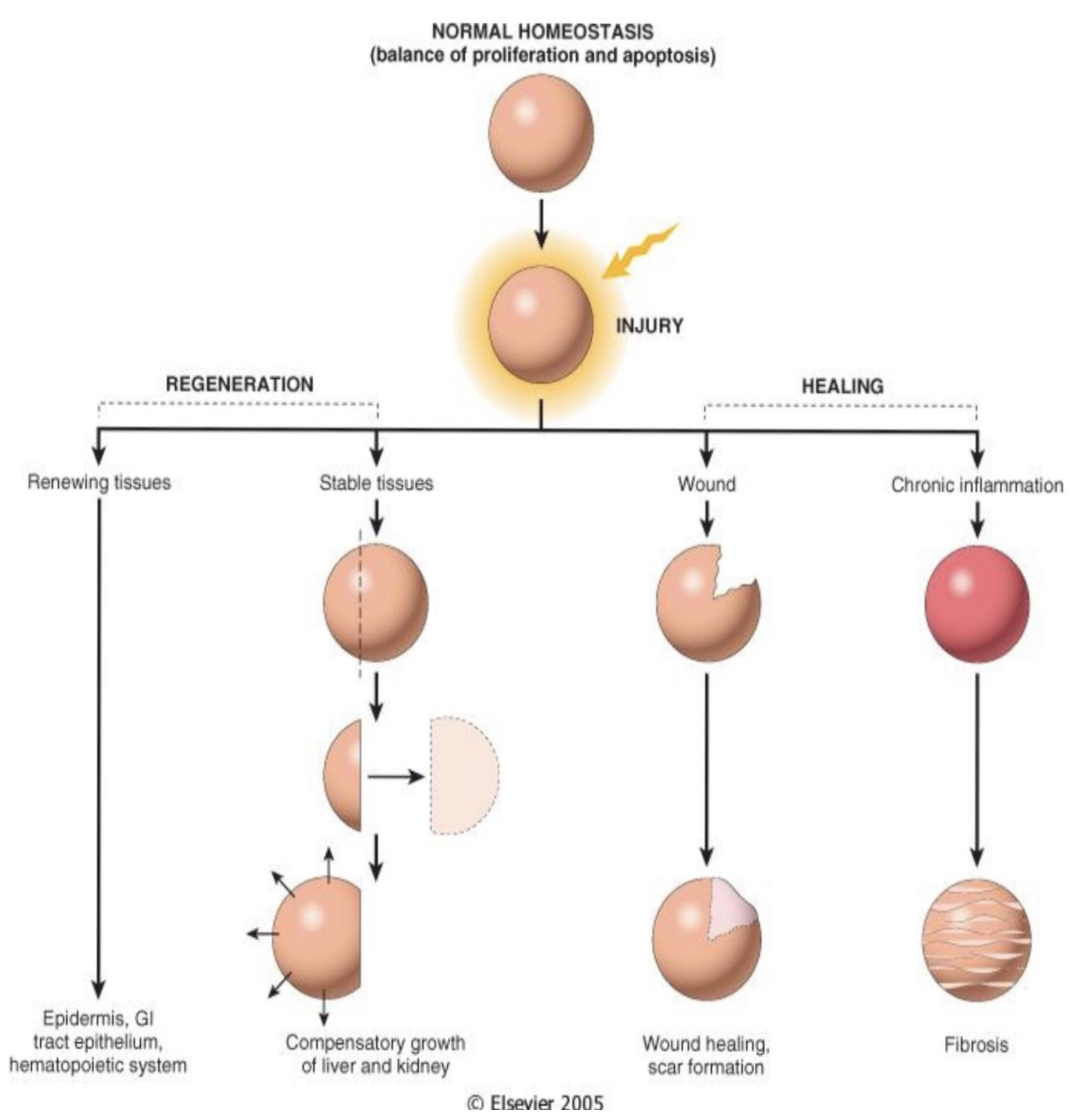
Goal of the repair process

01 To **restore** the tissue to its **original state** after inflammatory reaction

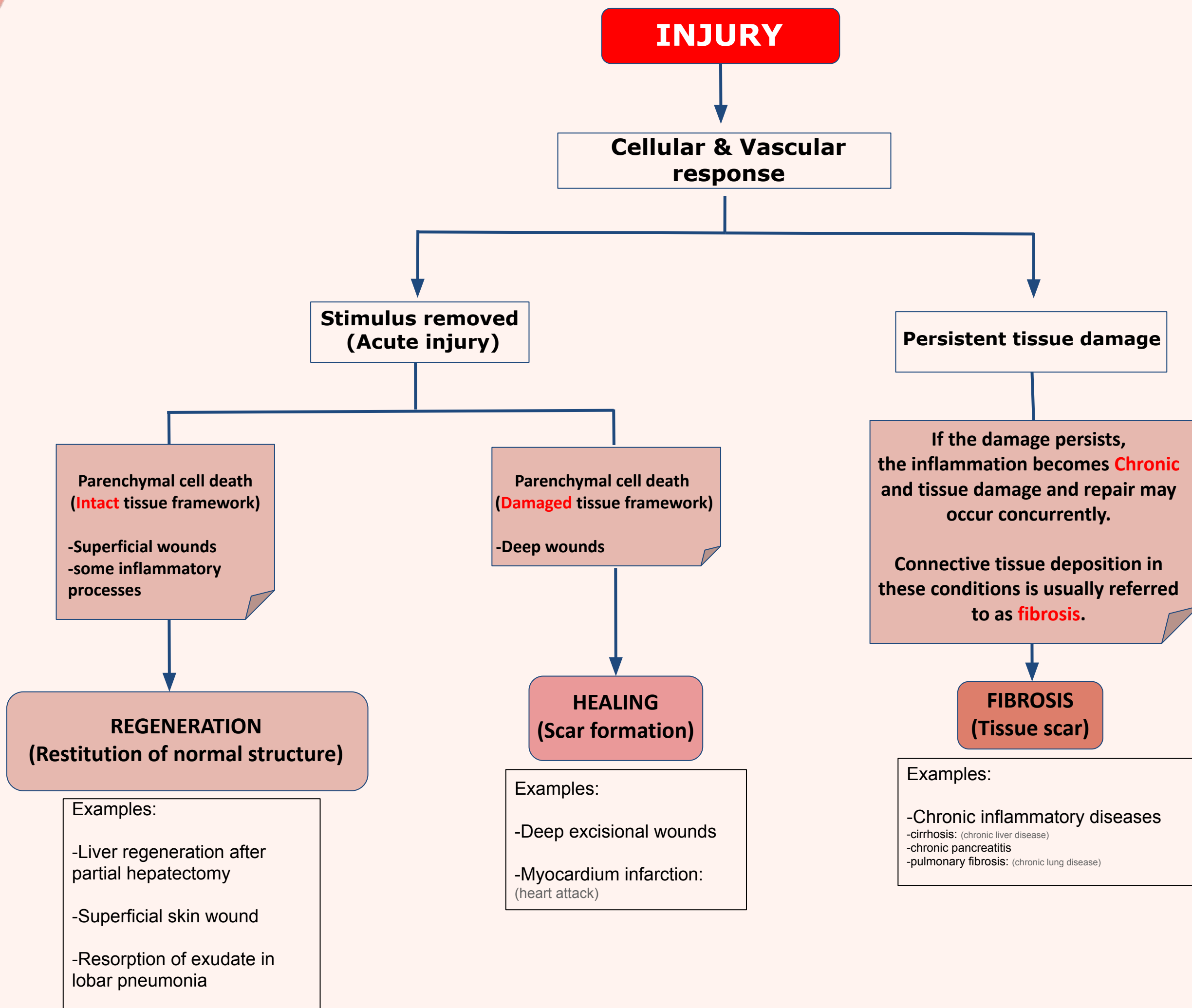
02 Some tissues can be completely **reconstituted** after injury, such as the repair of bone after a fracture or the regeneration of the surface epithelium in a cutaneous wound.

03 For tissues that are **incapable** of regeneration, repair is accomplished by **connective tissue deposition** → (**Scar formation**)

The differences between regeneration, healing and fibrosis



Cont. the differences between regeneration, healing and fibrosis



Repair by tissue regeneration or healing depend on cell type

Labile cells

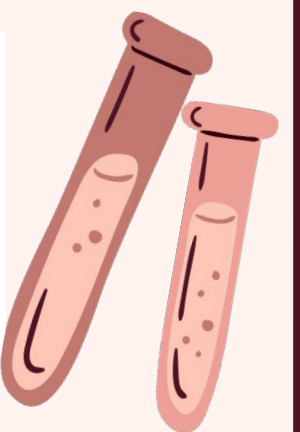
Continue to proliferate (grow rapidly) throughout life : squamous, columnar, transitional epithelia; hematopoietic (formation of blood cells) and lymphoid tissues

Stable cells

Retain the capacity of proliferation but they don't replicate normally: parenchymal cells (the main functional cells of an organ or a tissue) of all glandular organs & mesenchymal cells, e.g. hepatocytes & renal tubular cells

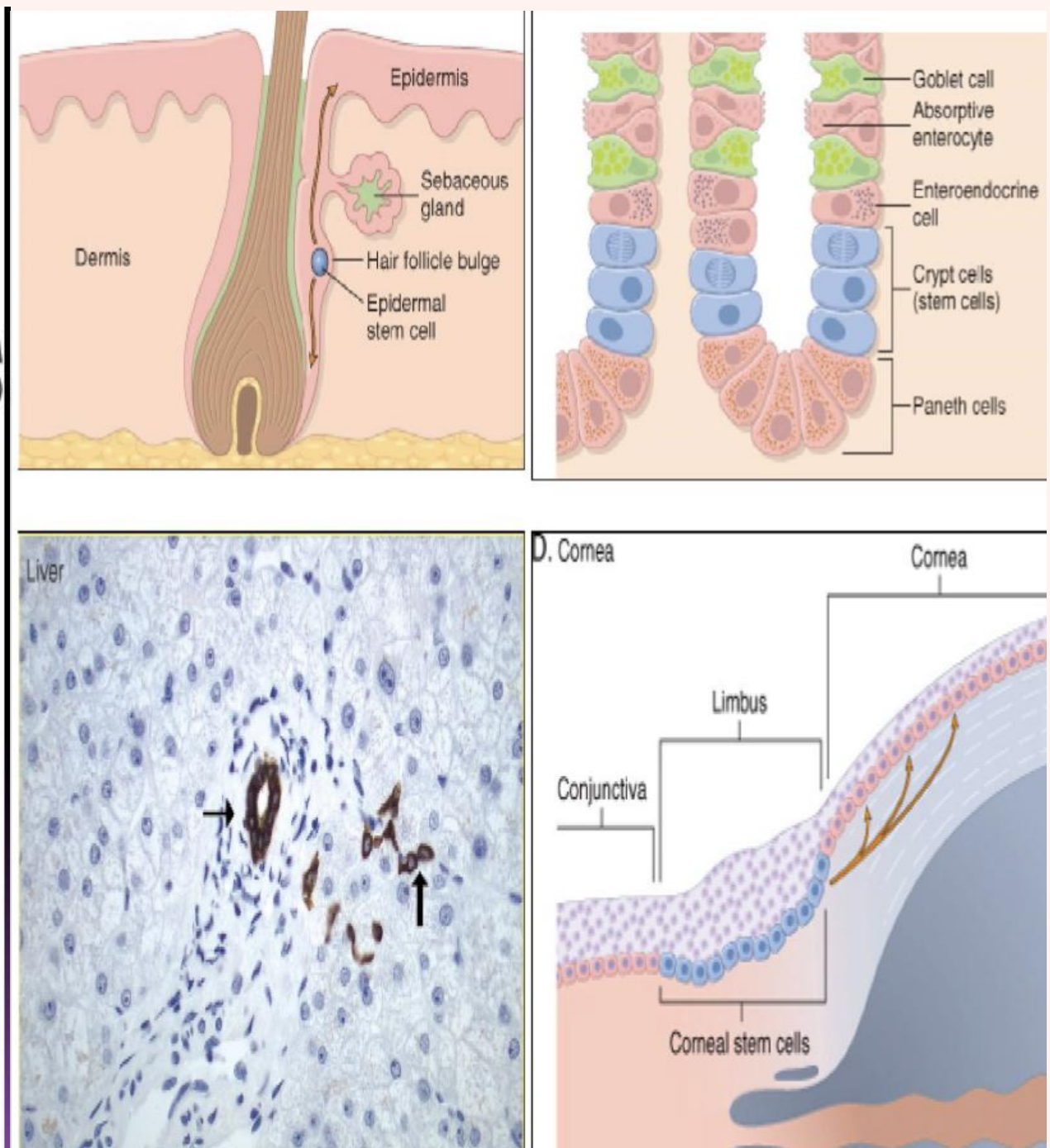
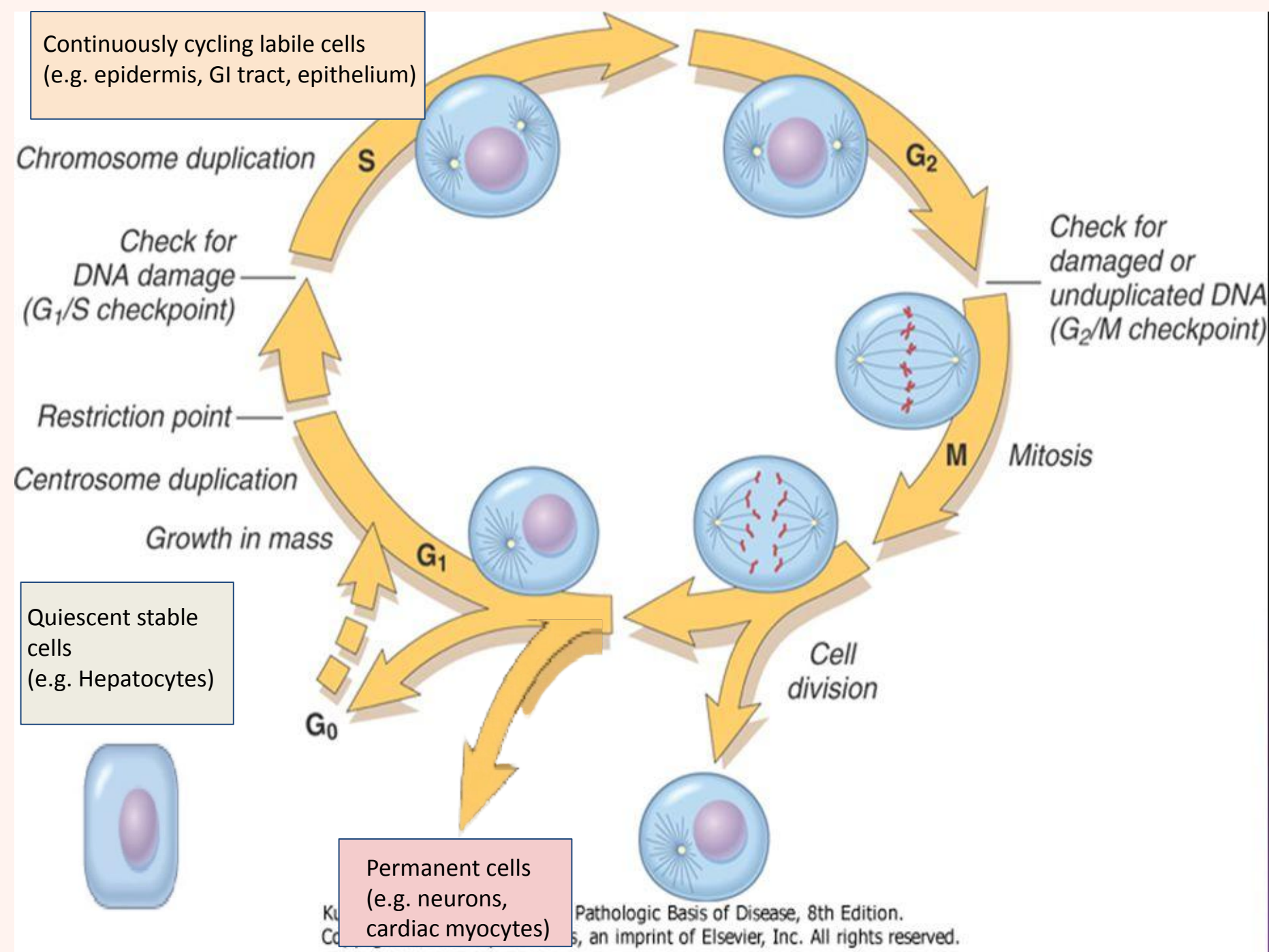
Permanent cells

Cannot reproduce themselves after birth: neurons, cardiac muscle cells



The differences between the various cell in regenerative abilities types

Examples of labile cells : stem cells



Healing

Healing is usually a tissue response to:

1

a wound (commonly in the skin)

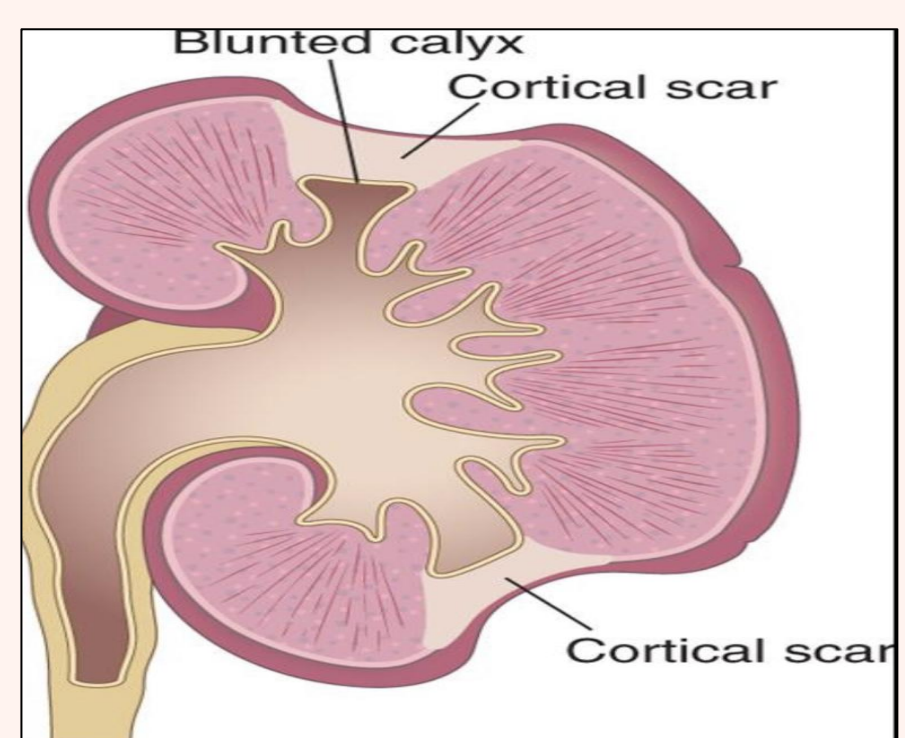
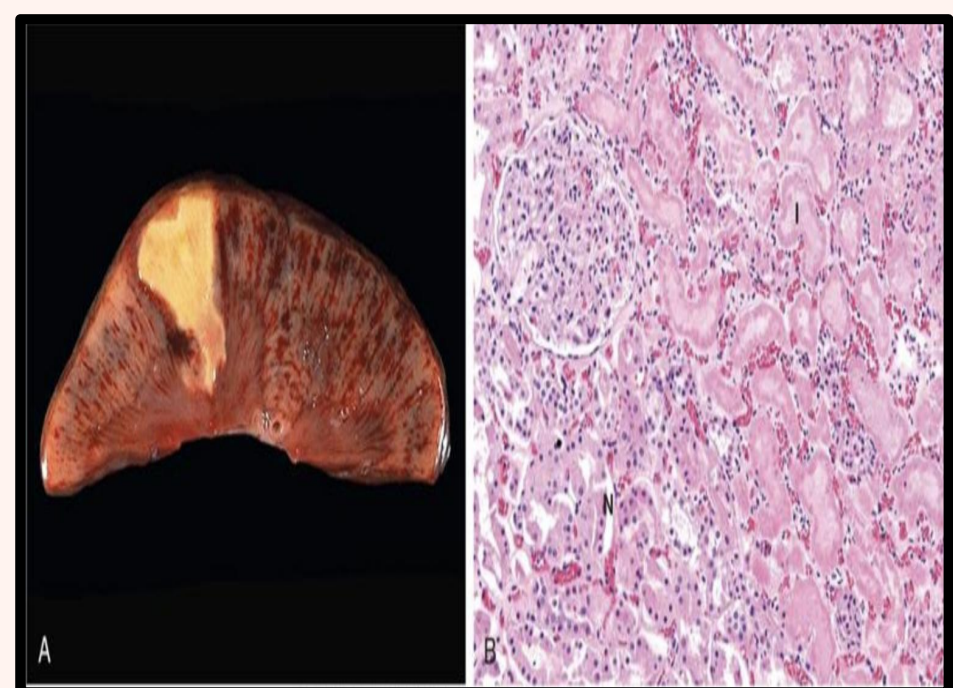
2

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.

• **Organization:** the name of the process of (granulation tissue formation)

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

• **Granulation tissue consists of:**

Dr's note: Granulation tissue is temporary till the fibrosis occurs

1

Vascular connective tissue

2

Fibroblasts

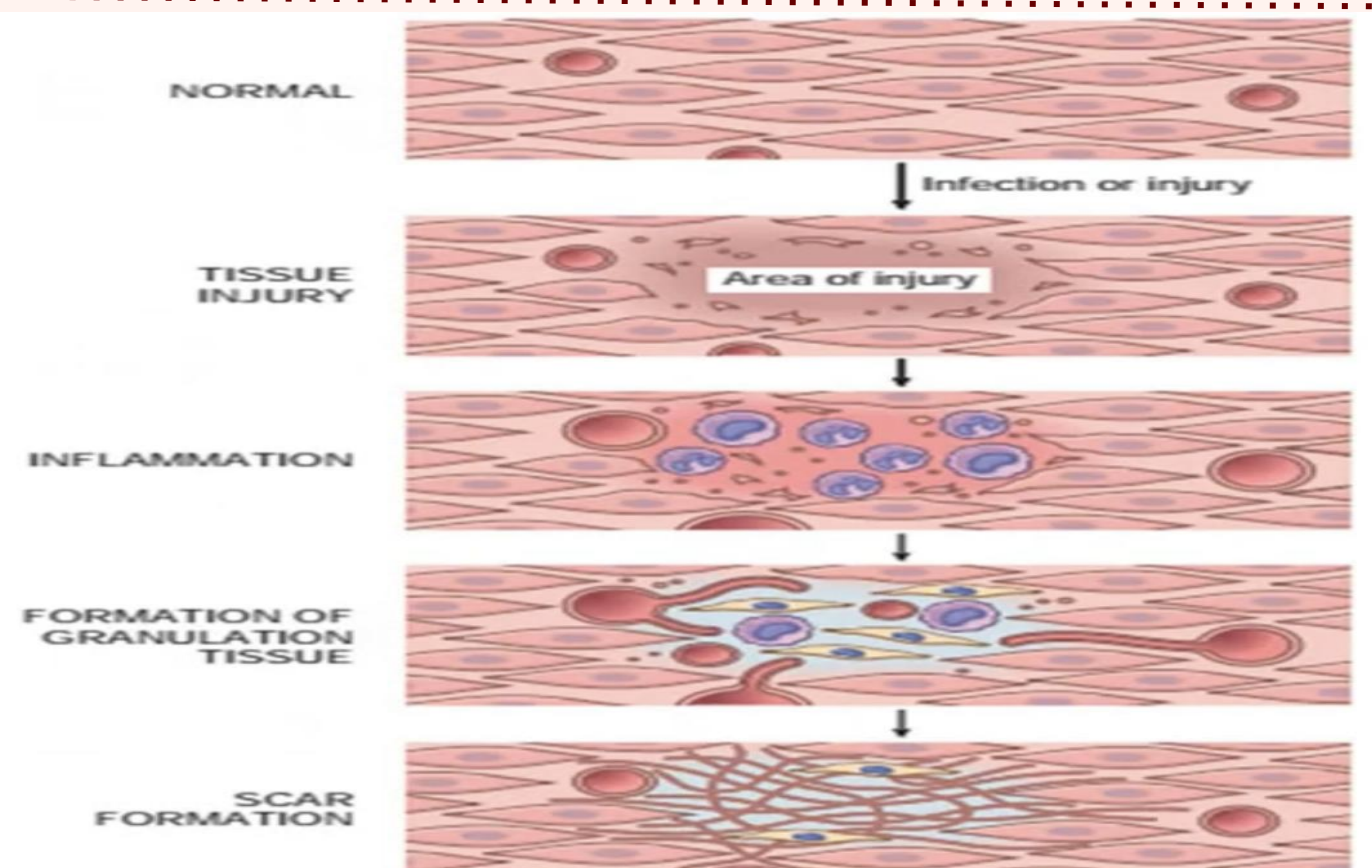
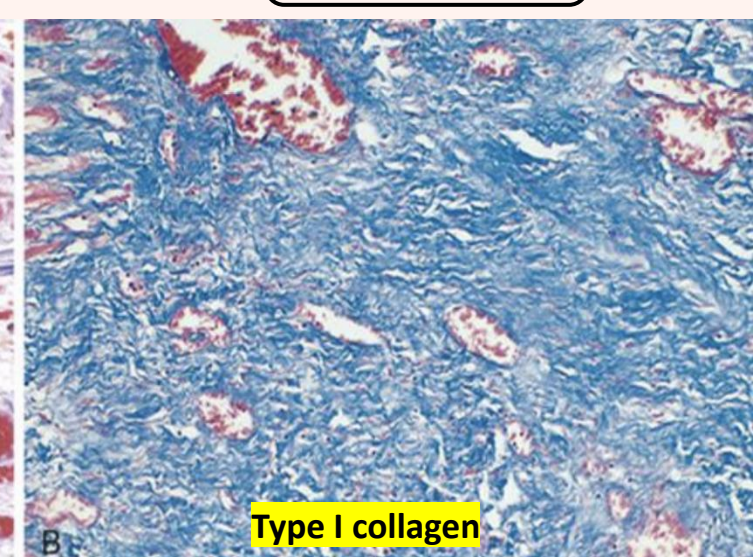
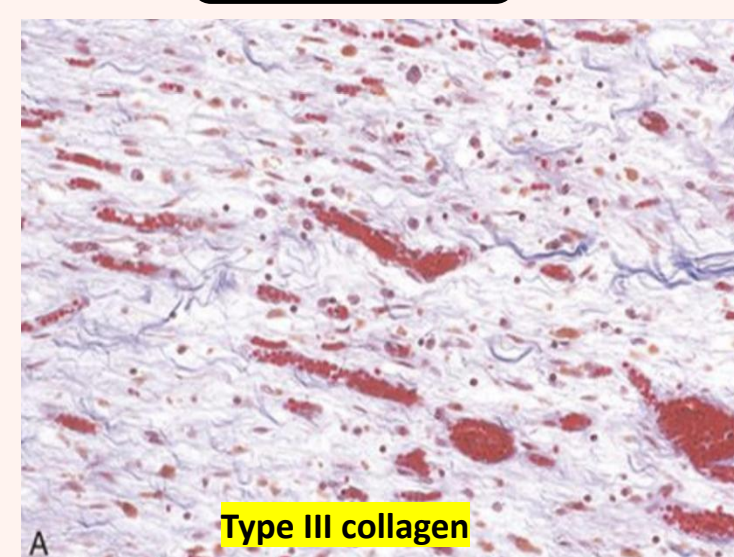
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Inflammatory Cells (like macrophages)

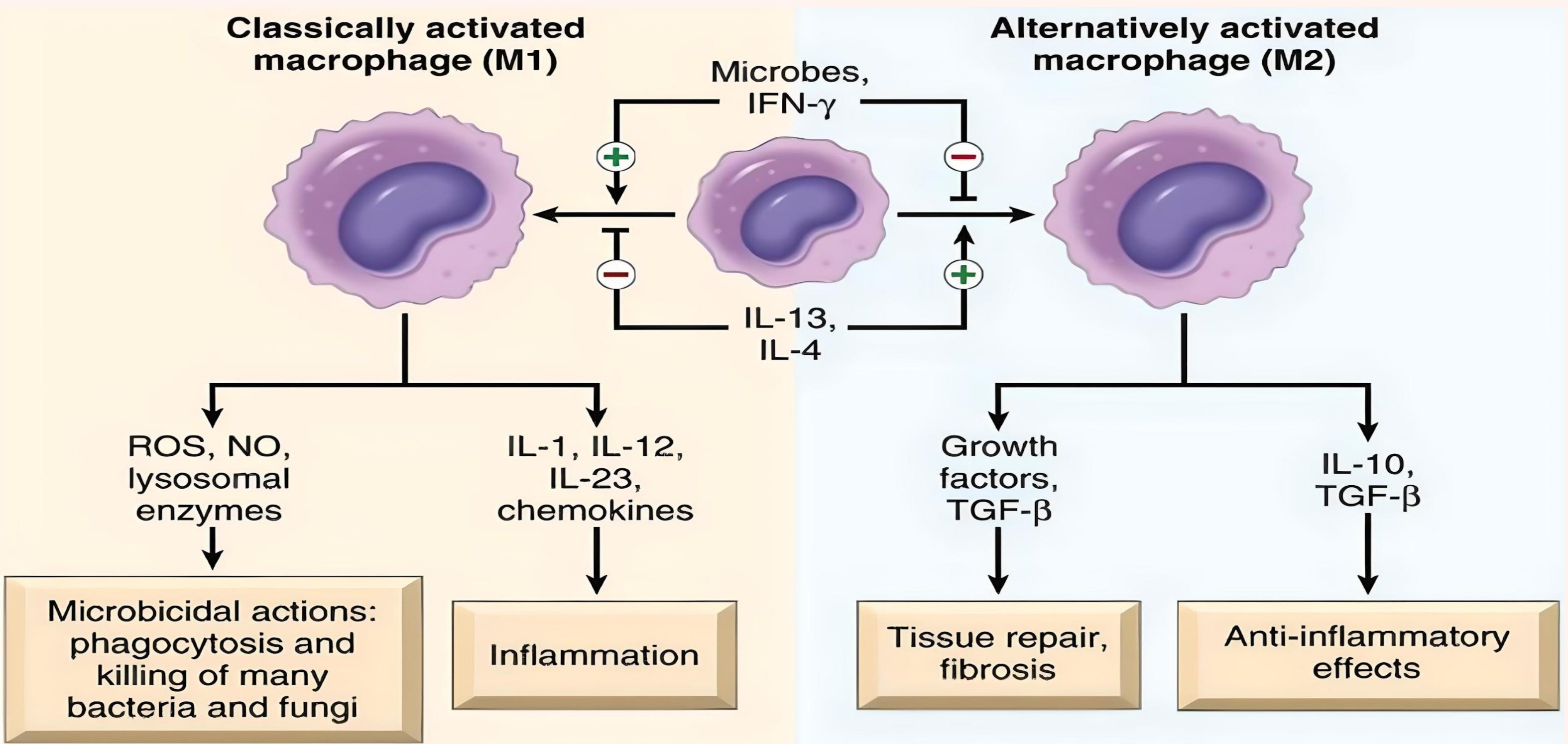
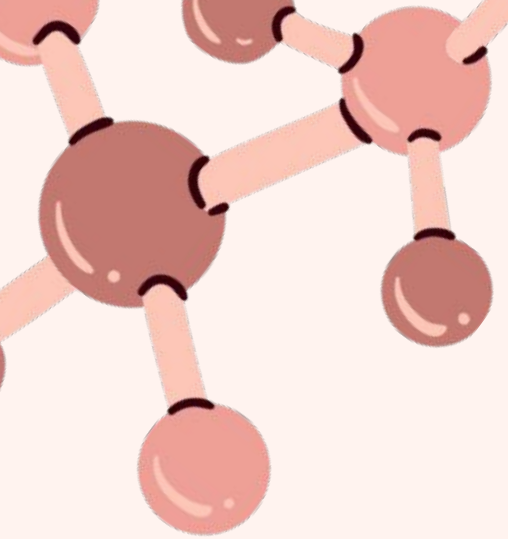
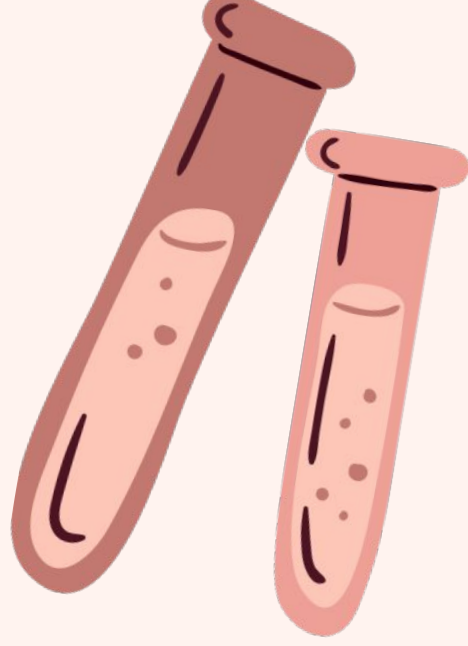
Granulation tissue

Early

Late



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 angioblast

3

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

4

Remodeling of the scar. They secrete collagenases (to break down extra collagen)

5

Secretion of transforming growth factor beta (TGF- β)

6

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

Q: what is the cells that produce TGF- β
A: Macrophages



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- β** and others e.g. PDGF, EGF, FGF, and the cytokines IL-1 and TNF.**

TGF- β 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



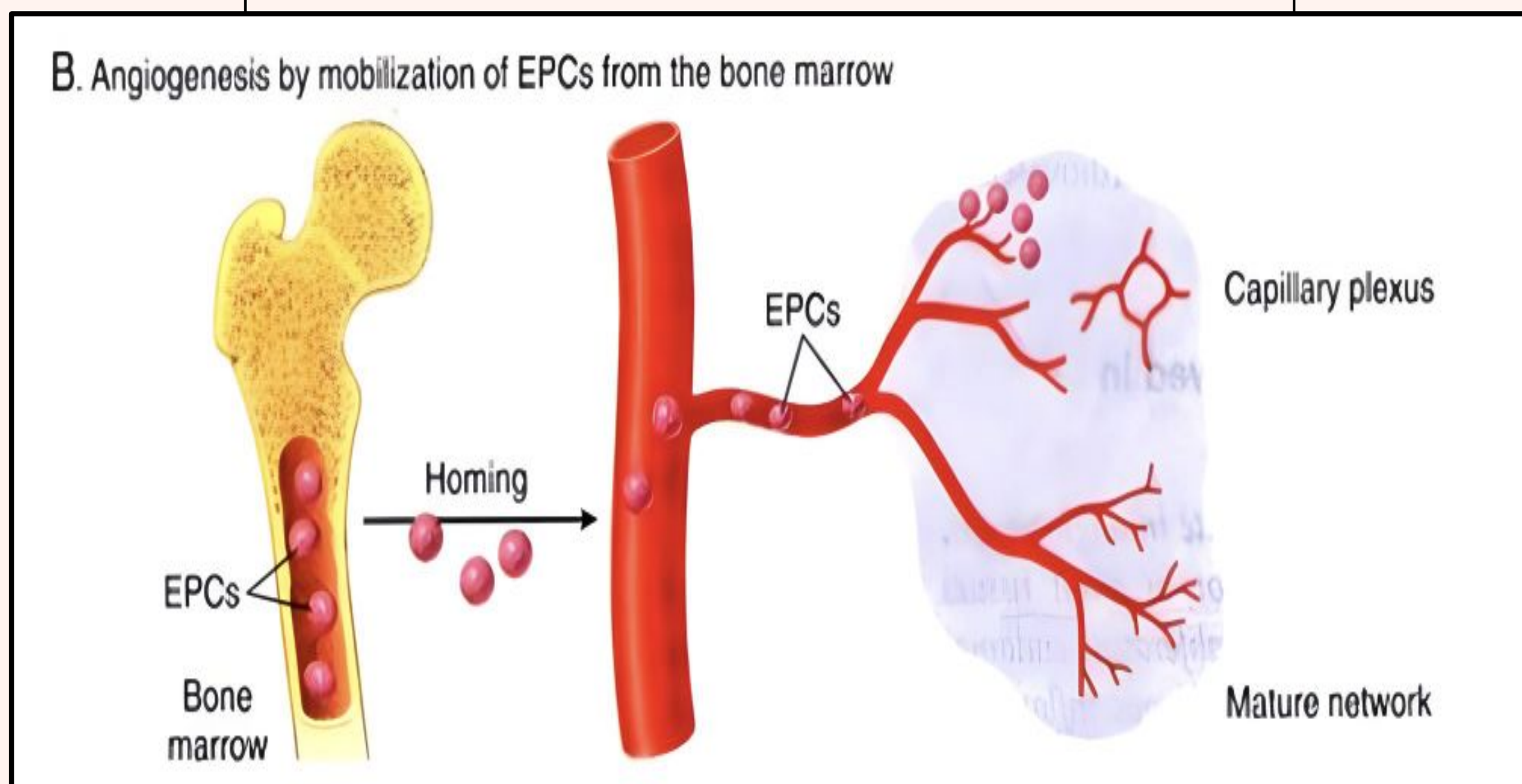
***As early as 24 hr. After injury, fibroblasts and vascular endothelial cells begin proliferating to form (by 3-5 days) granulation tissue - **pink soft granular appearance on the surface of the wound**.**

***New granulation tissue is often edematous.**

- ★ Histologically : granulation tissue is composed of :**
- proliferation of new small blood vessels**
 - proliferation of fibroblasts with deposition of type III collagen (begin **third day** in wound healing)**
 - macrophages**

Angiogenesis

The sprouting of new capillaries



Angiogenesis from Endothelial Precursor Cells

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

Scar Formation

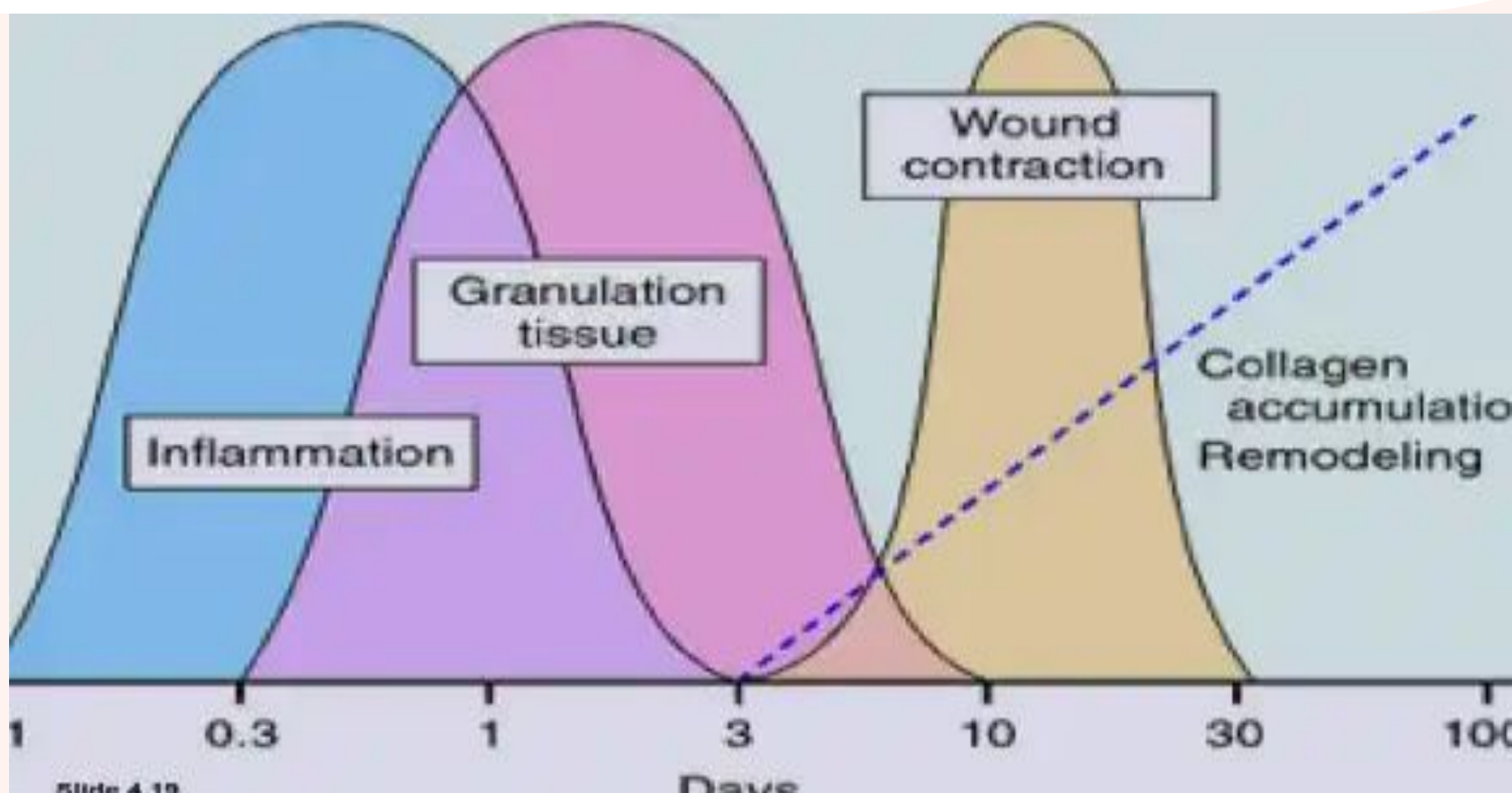
Further Healing:

Increased collagen + decreased active fibroblasts + new vessels (thrombosis -clotting- and degeneration)

Maturation and reorganization of the connective tissue (remodelling reduce the stable fibrosis score)

At the end:

Scar (inactive fibroblasts, dense collagen, fragments of elastic tissue, extracellular matrix, few vessels).

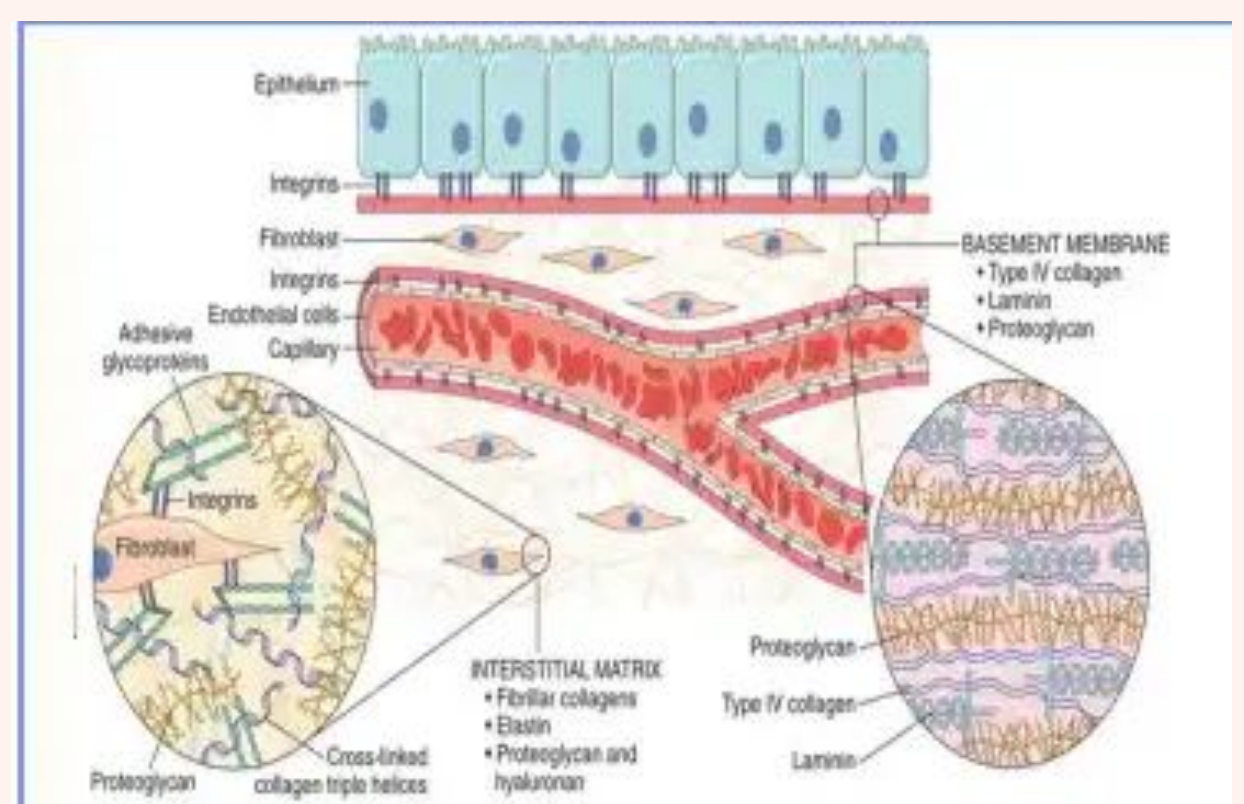


In granulation tissue phase: new blood vessels and fibroblasts disappear of fibroblasts and they get replaced by new collagen fibers and increased **in wound contraction phase.**

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 microenvironment**



Cutaneous Wound healing

1. Primary union (healing by 1st intention)	2. Secondary union (healing by 2nd intention)
<ul style="list-style-type: none"> • clean surgical incision 	<ul style="list-style-type: none"> • more extensive loss of cells and tissue: <ul style="list-style-type: none"> -infarction -inflammatory ulceration -abscess formation
<ul style="list-style-type: none"> • no significant bacterial contamination 	<ul style="list-style-type: none"> • surface wound with large defect
<ul style="list-style-type: none"> • minimal loss of tissue 	<ul style="list-style-type: none"> • large tissue defect that must be filled
<ul style="list-style-type: none"> • clot, scab formation 	-

Primary union (healing by first intention)

24 hr

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

Day 3

macrophages, granulation tissue

Day 5

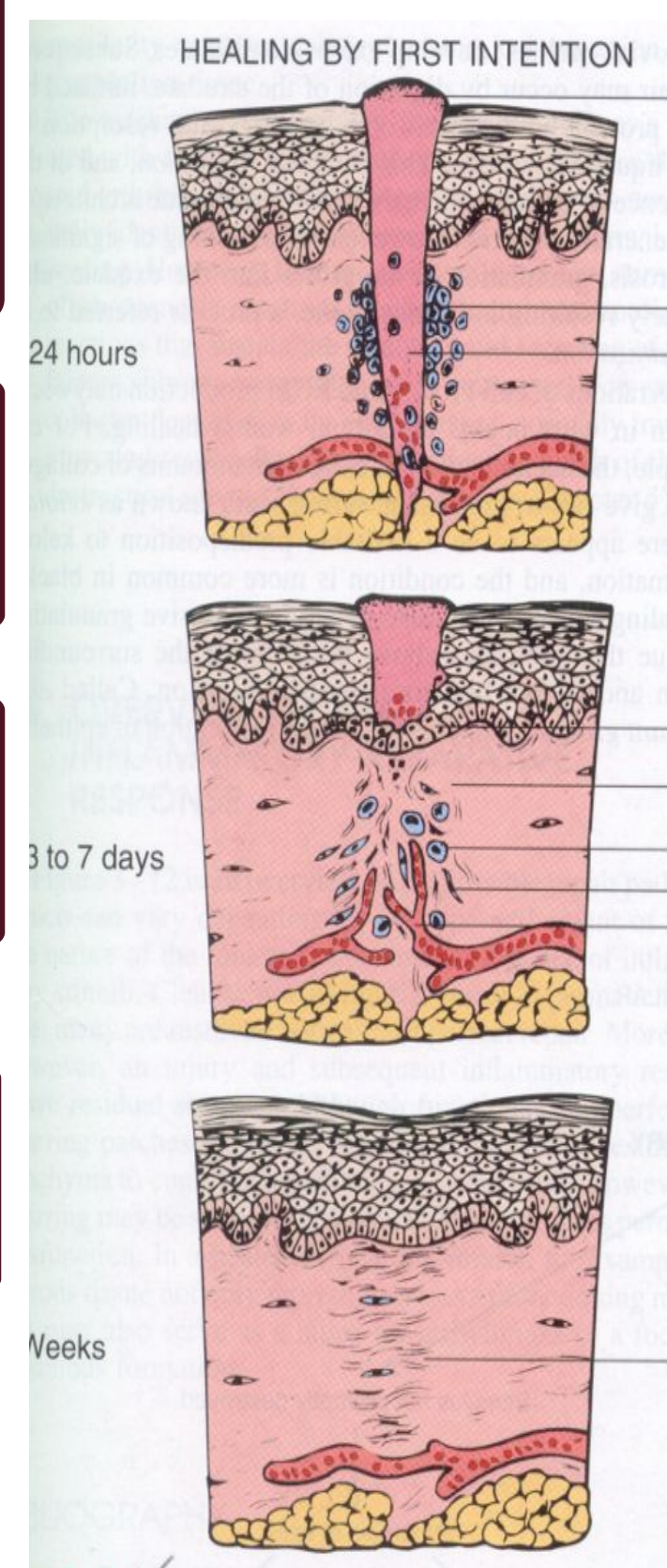
collagen bridges the incision, epidermis thickens

2nd week

continued collagen accumulation and fibroblasts proliferation (**blanching**)

End of 1st month

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

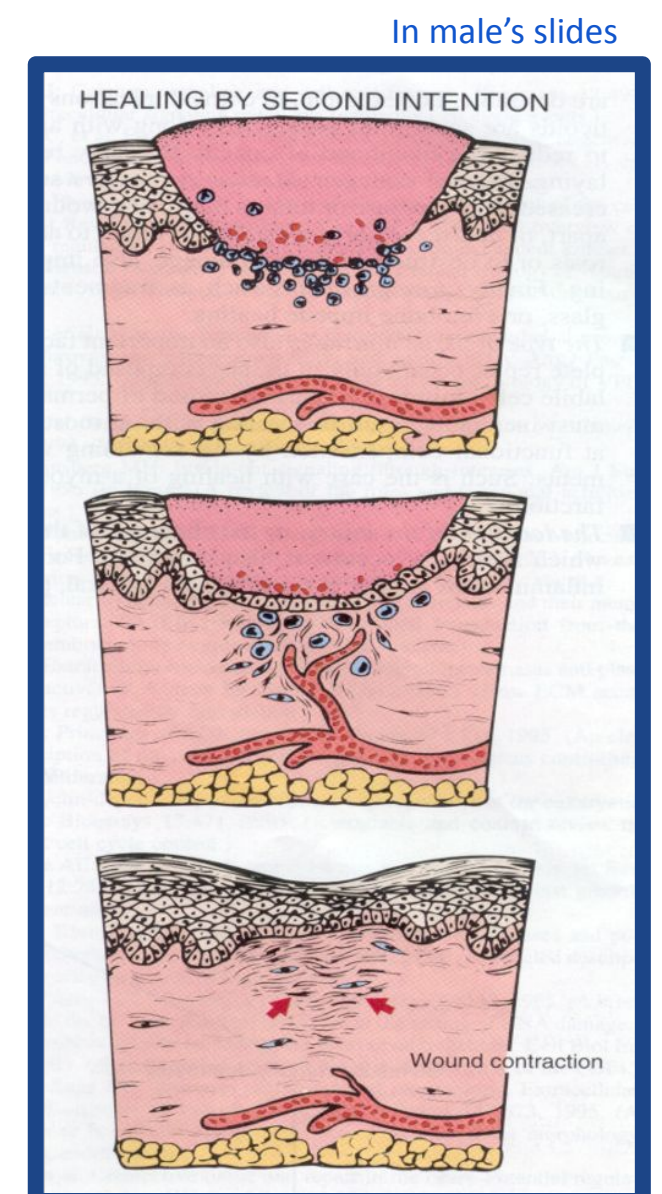
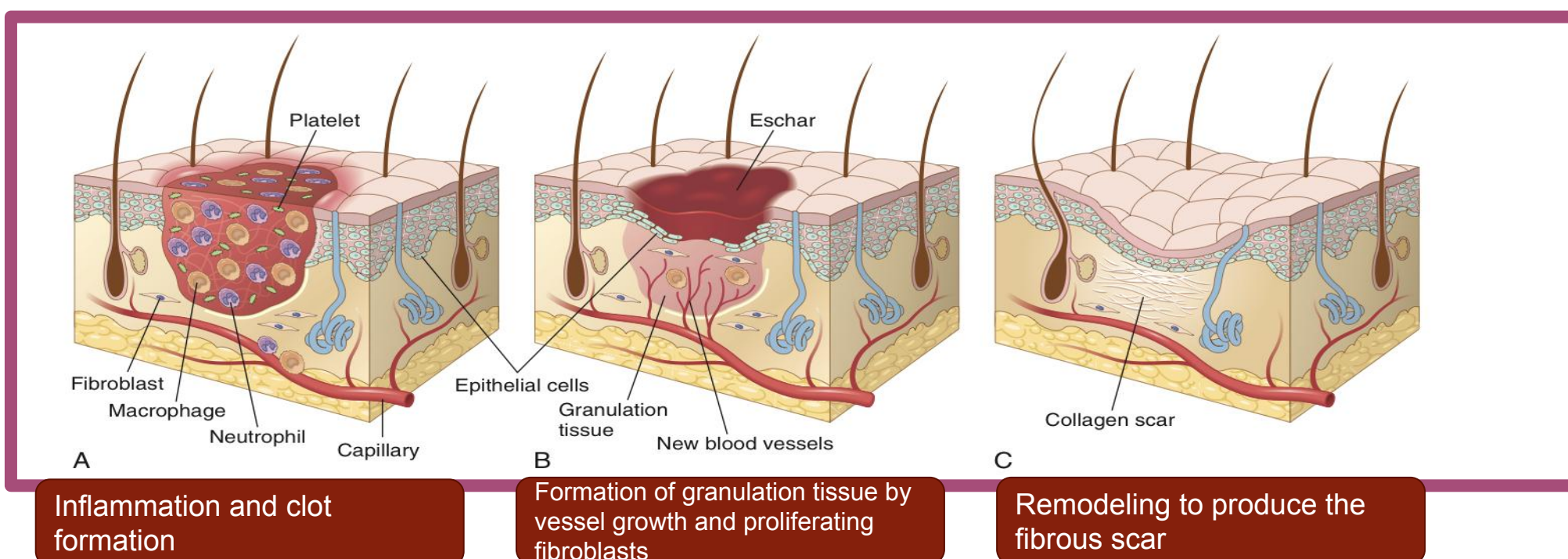


cutaneous wound healing

Secondary union (healing by 2nd intention)

It occur in:
-large, gaping wounds,
-as well those that are infected or contain foreign material

In female's slides



Difference between **primary intention** and **secondary intention**

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

- Require more time to close because the edges are far apart
- Show a more prominent inflammatory reaction in and around the wound
- Contain more copious granulation tissue inside the tissue defect
- wound contraction (5 to 10%), caused by myofibroblasts

Wound Strength

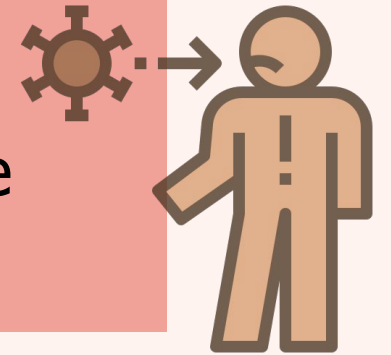
- At first a provisional matrix containing fibrin, plasma fibronectin, and type III collagen is formed
- In about 2 weeks, collagen type III is slowly replaced by collagen type I and the wound acquires tensile strength
- By the end of third month, the tissue has approximately 80% of its original strength.

Delayed wound healing

most common cause of delayed wound healing?

01 Infection

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

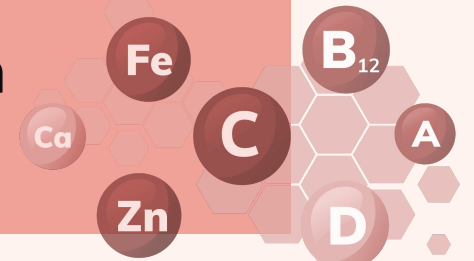


02 Mechanical factors

Suture help healing of wound

03 Nutritional deficiencies

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



04 Poor perfusion

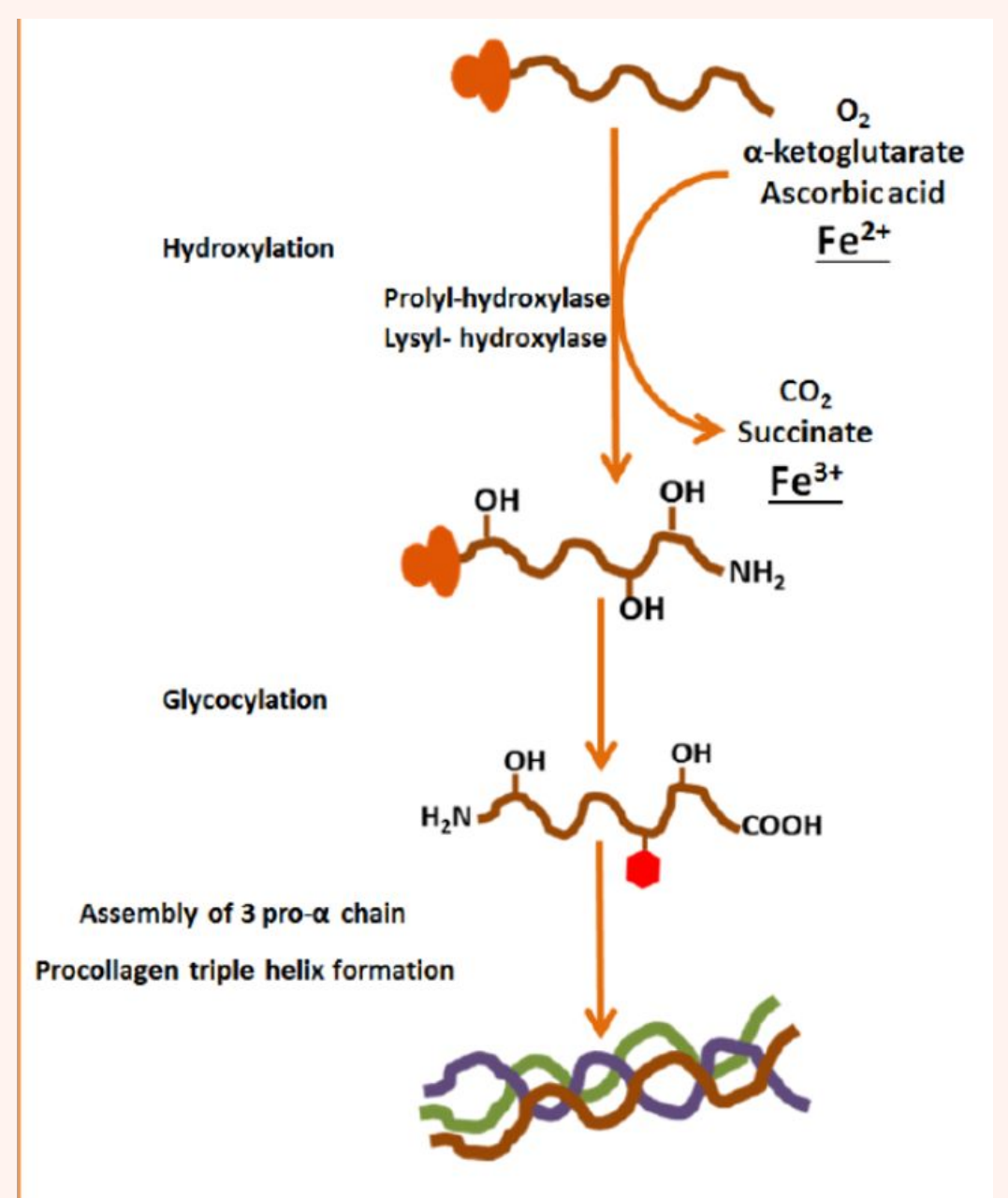
due either to arteriosclerosis and diabetes or to obstructed venous drainage

05 Foreign bodies in the wound

06 Excess corticosteroid

Collagen synthesis

Proline hydroxylation by vitamin C.





Delayed wound healing

Excess corticosteroid

have well-documented anti-inflammatory effects, and their administration may result in weakness of the scar

however, the anti-inflammatory effects of glucocorticoids are sometime desirable. For example, in corneal infections

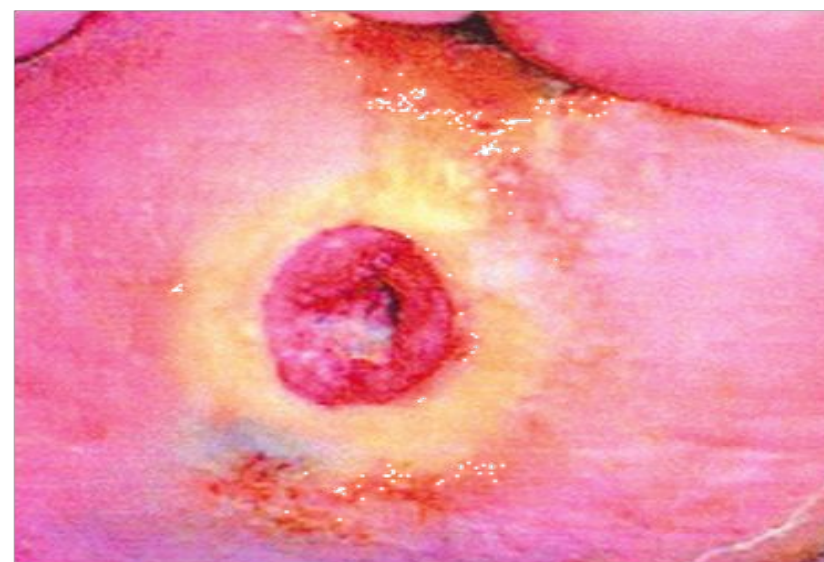
COMPLICATIONS IN CUTANEOUS WOUND HEALING

Complications in wound healing can arise from abnormalities in any of the basic components of the repair process. These aberrations can be grouped into three general categories:

- (1) *deficient scar formation*
- (2) *excessive formation of the repair components and connective tissue*
- (3) *formation of contractures (myofibrblast).*



Wound dehiscence



Wound ulceration



Keloid



Contracture



WHAT IS KELOID?

Keloids are excessive scars composed of irregularly deposited **thick hyalinized collagen bands**. They may appear as **bulging masses**.



What is the difference between keloid and hypertrophic scar?

Keloids	Hypertrophic scars
are the result of an overgrowth of dense fibrous tissue that usually develops after healing of a skin injury.	characterized by: 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 recur after excision.	<ul style="list-style-type: none">- may undergo partial spontaneous resolution.- Hypertrophic scars are common after thermal injuries.



Complications of wound healing

Formation of contractures

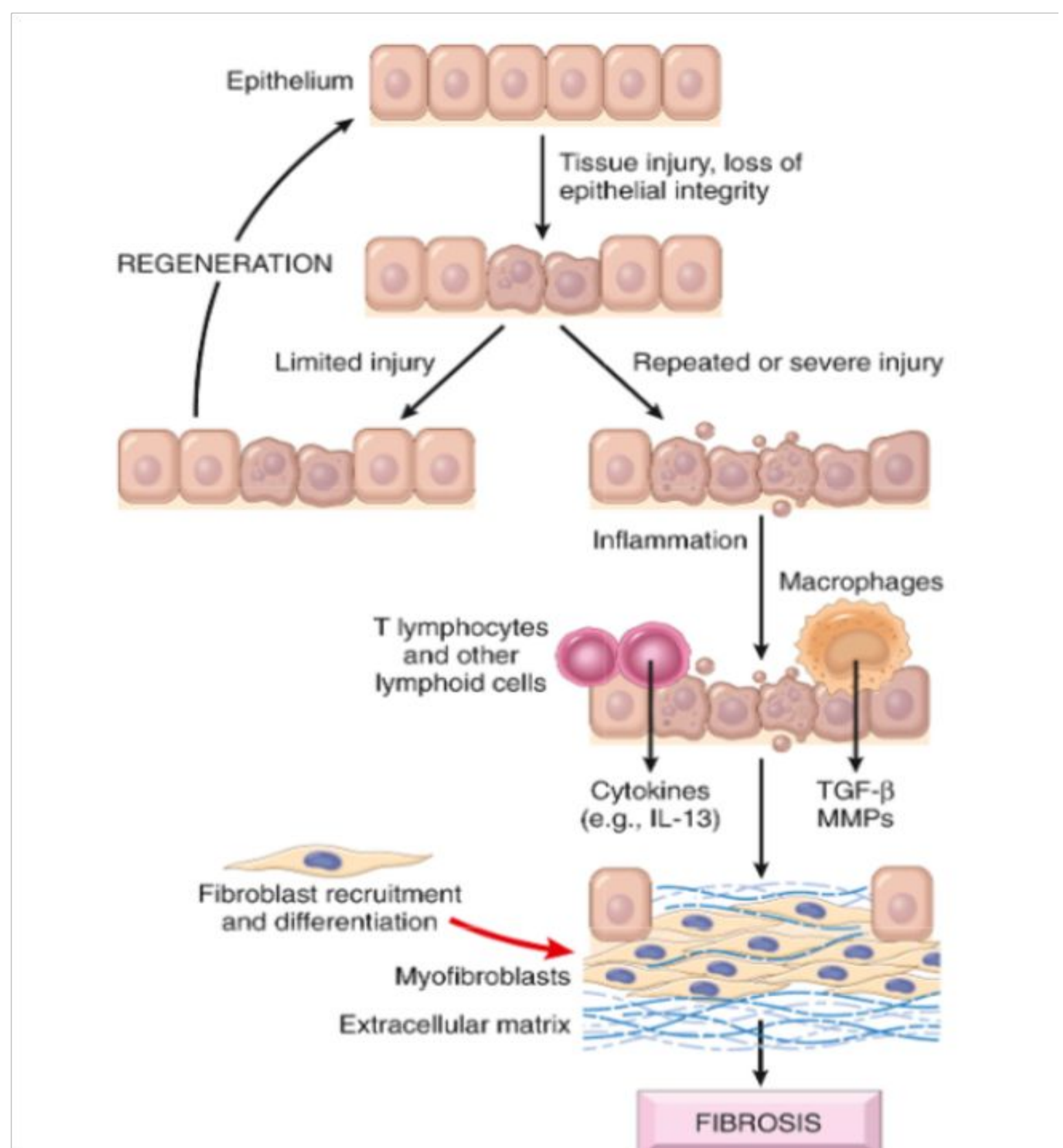
- common on the palms, the soles, and the anterior aspect of the thorax.
- Contractures are commonly seen after serious burns
- It can compromise the movement of joints.
- It is caused by myofibroblasts



Fibrosis in Parenchymal Organs

Fibrosis is a pathologic process induced by persistent injurious stimuli

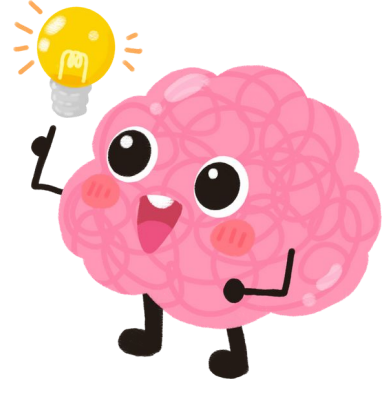
- such as chronic infections and immunologic reactions, and is typically
- associated with loss of tissue
- e.g. **liver cirrhosis** after chronic hepatitis or pancreatic insufficiency after chronic pancreatitis.





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.



KEYWORDS

granulation tissue Consist of	Vascular connective tissue, Fibroblasts and inflammatory cells
scar Contractures	Myofibroblasts
keloid scar	hyalinized collagen
Secondary union	large, gaping wounds

1-When does collagen 3 deposit in injury?

A) 1 day

B) 2 days

C) 3 days

D) 2 weeks

2- which one of the following is one of the characteristics features of a keloid scar?

A) dystrophic calcification

B) granuloma formation

C) dense thick mucus

D) hyalinized collagen

3- which one of the following plays a major role in granulation tissue formation during wound healing?

A) aggregation of cell debris

B) budding of new blood vessels

C) thrombotic blood vessels

D) infiltration of epithelial cells

4- Which of these is associated with granulation tissue?

A) Caseous Granuloma with Giant cells

B) Neutrophils and bacterial products

C) Lymphocytes and fibroblasts

D) Vascular connective tissue, Fibroblasts and inflammatory cells

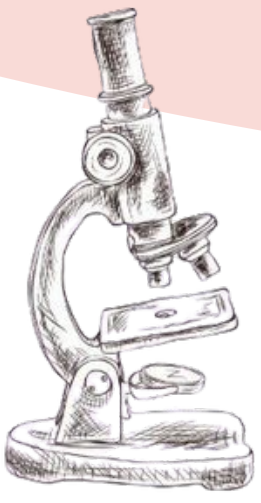
5- A boy had an injury in his left leg with depressed scar, after some time the scar contracted, what is associated with this action?

A) Smooth muscle cells

B) Myofibroblasts

C) Fibroblasts

D) Collagen



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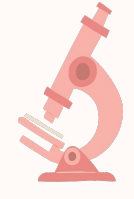
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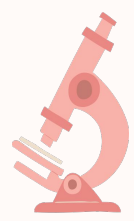
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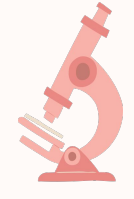
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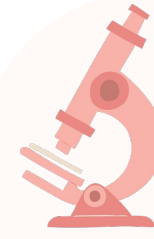
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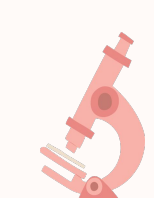
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