INFLAMMATION AND REPAIR
Lecture 5
Tissue Repair and Regeneration

Foundation Block, pathology

2016

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Objectives

Upon completion of this lecture, the student should:

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

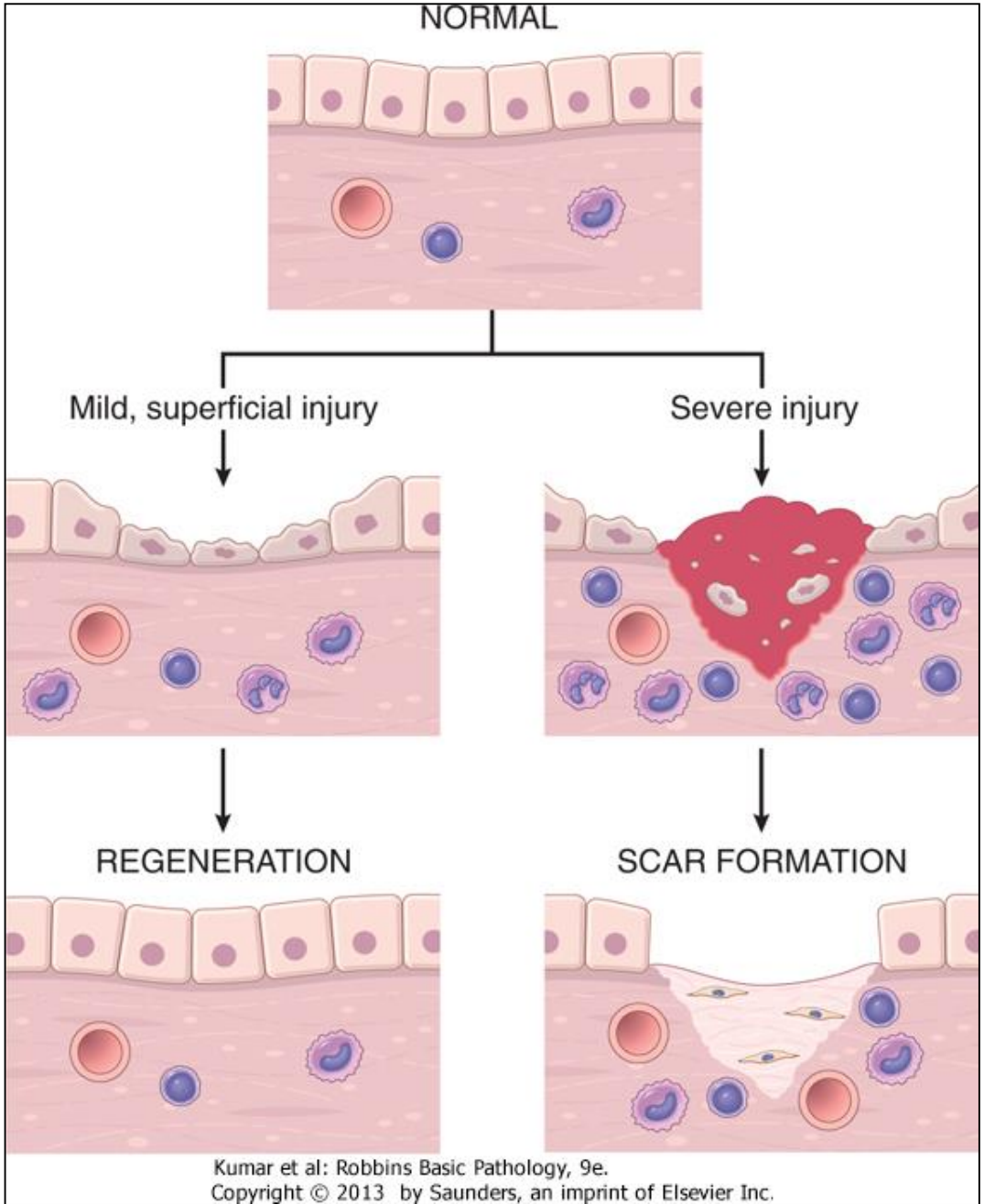
Goal of the repair process

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

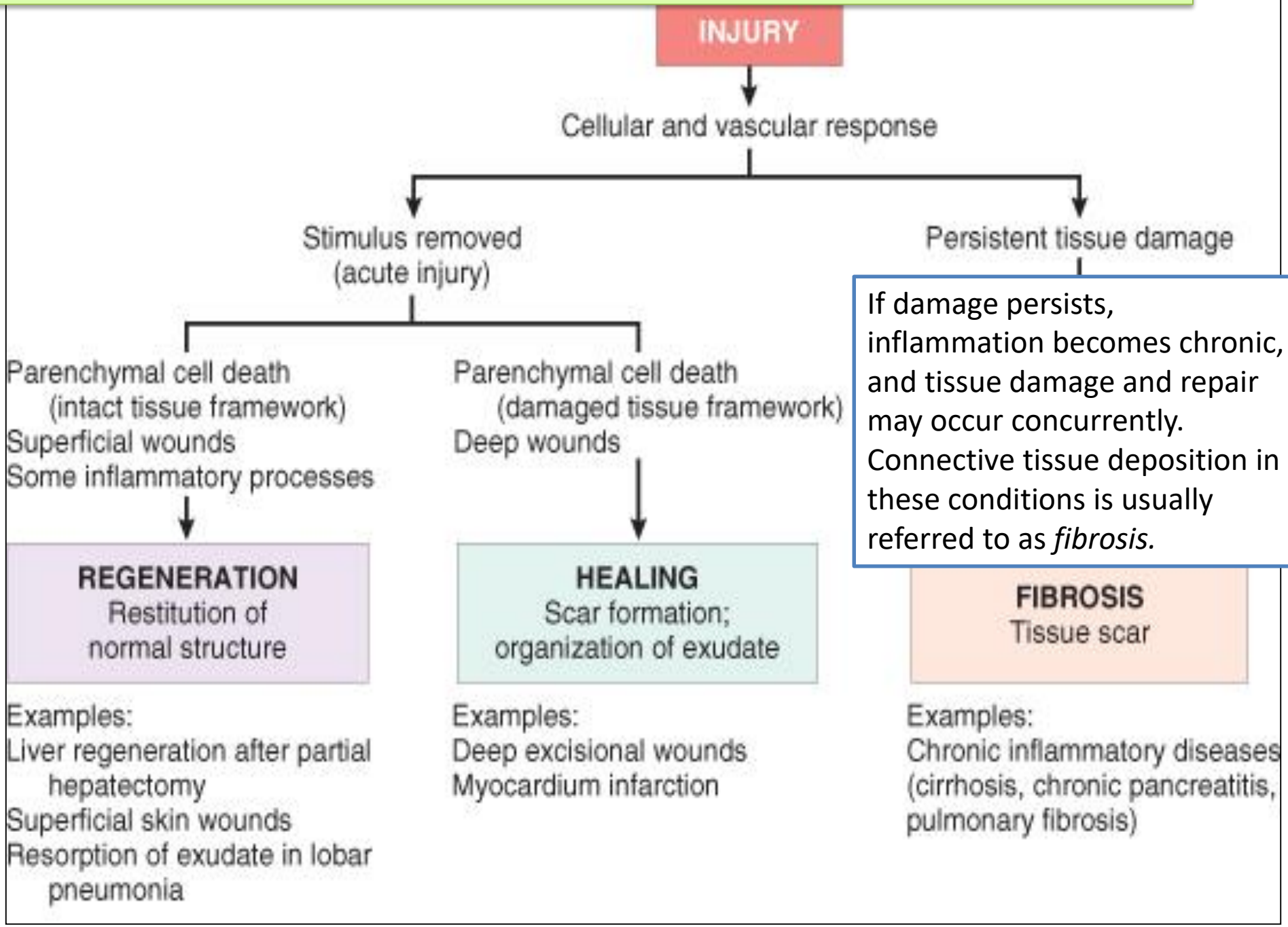
Some tissues can be completely reconstituted after injury, such as the repair of bone after a fracture or the regeneration of the surface epithelium in a cutaneous wound.

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

1. Describe the differences between regeneration, healing and fibrosis.

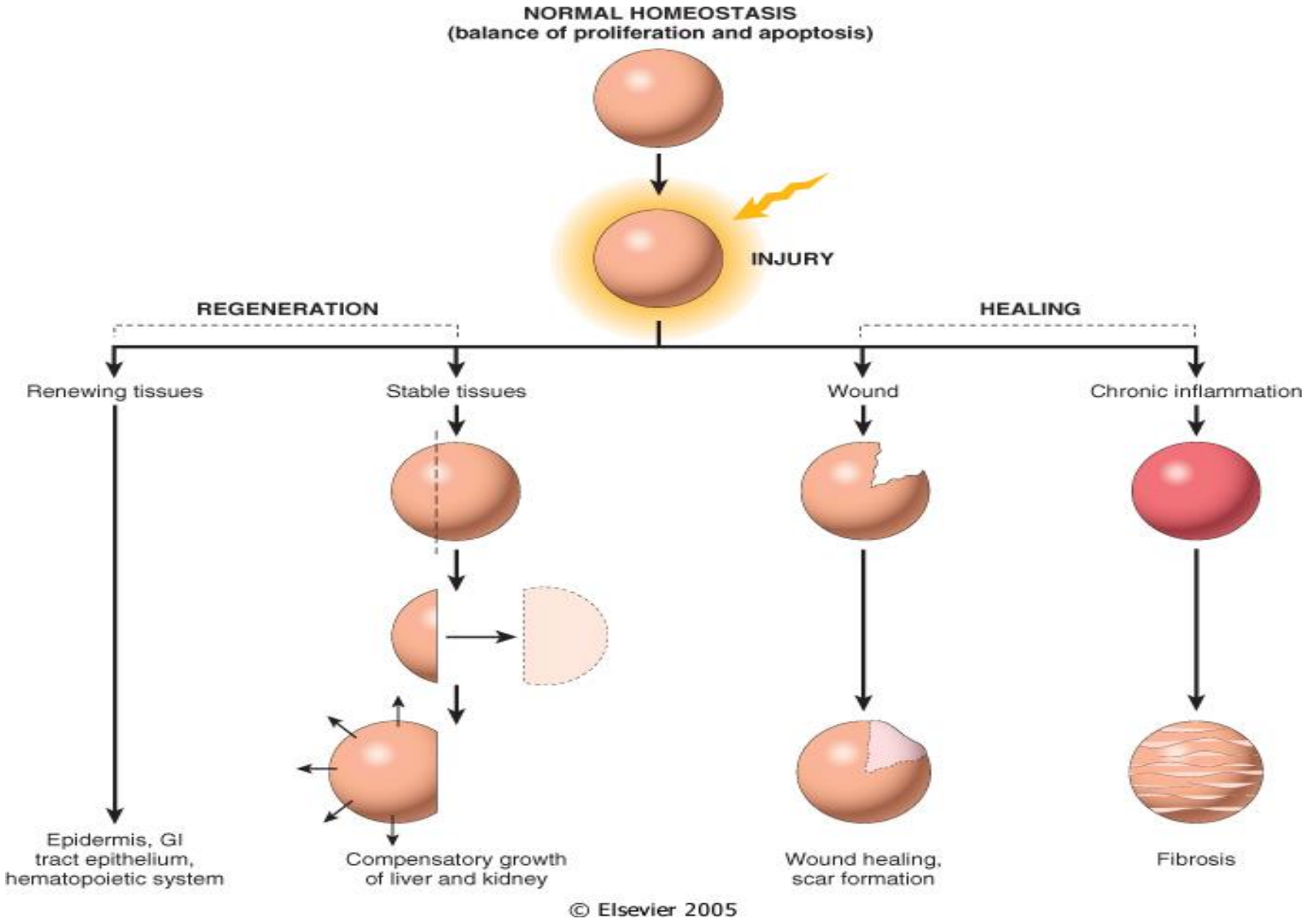


1. Describe the differences between regeneration healing and fibrosis.



If damage persists, inflammation becomes chronic, and tissue damage and repair may occur concurrently. Connective tissue deposition in these conditions is usually referred to as *fibrosis.*

1. Describe the differences between regeneration healing and fibrosis.



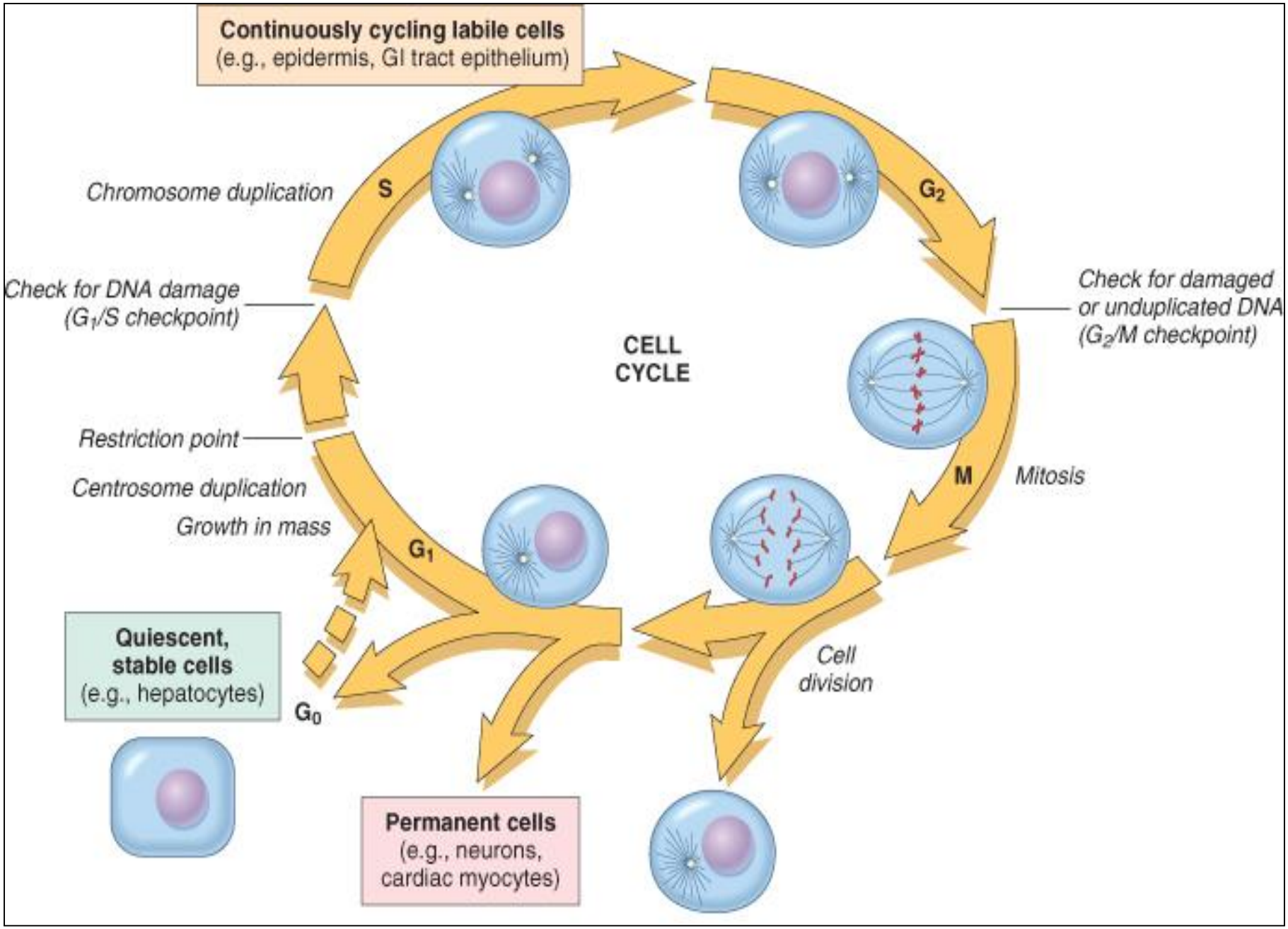
Repair by tissue regeneration or healing depend on cell type.

- Labile cells: continue to proliferate throughout life : squamous, columnar, transitional epithelia; hematopoitic and lymphoid tissues

- Stable cells: retain the capacity of proliferation but they don't replicate normally: parenchymal cells of all glandular organs & mesenchymal cells

- Permanent cells: cannot reproduce themselves after birth: neurons, cardiac muscle cells

2. The differences between the various cell in regenerative abilities types



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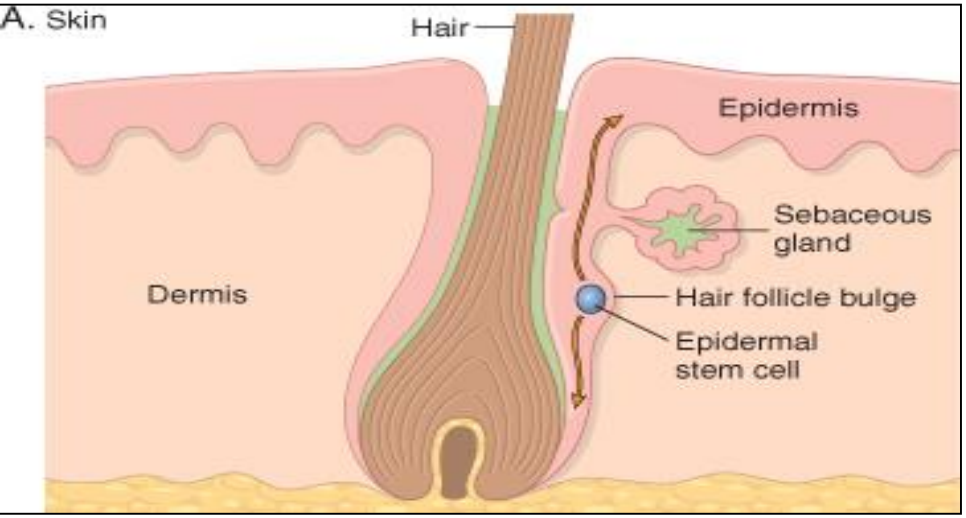
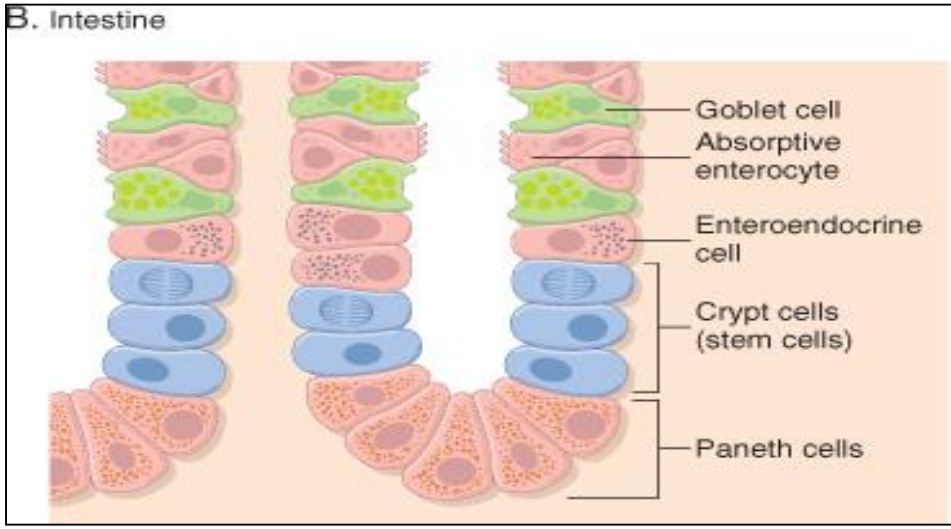
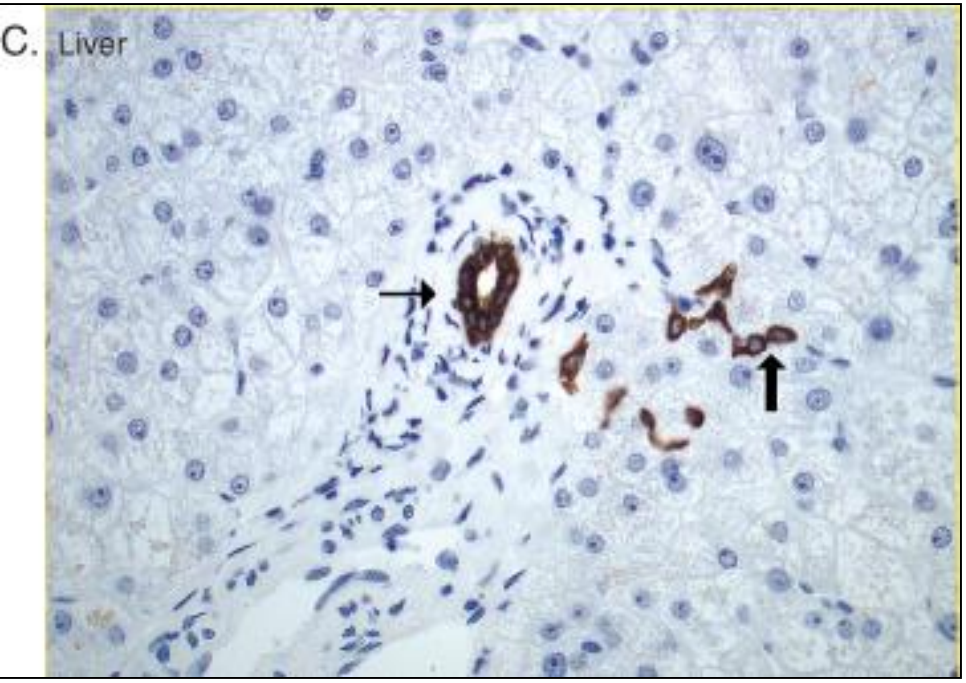
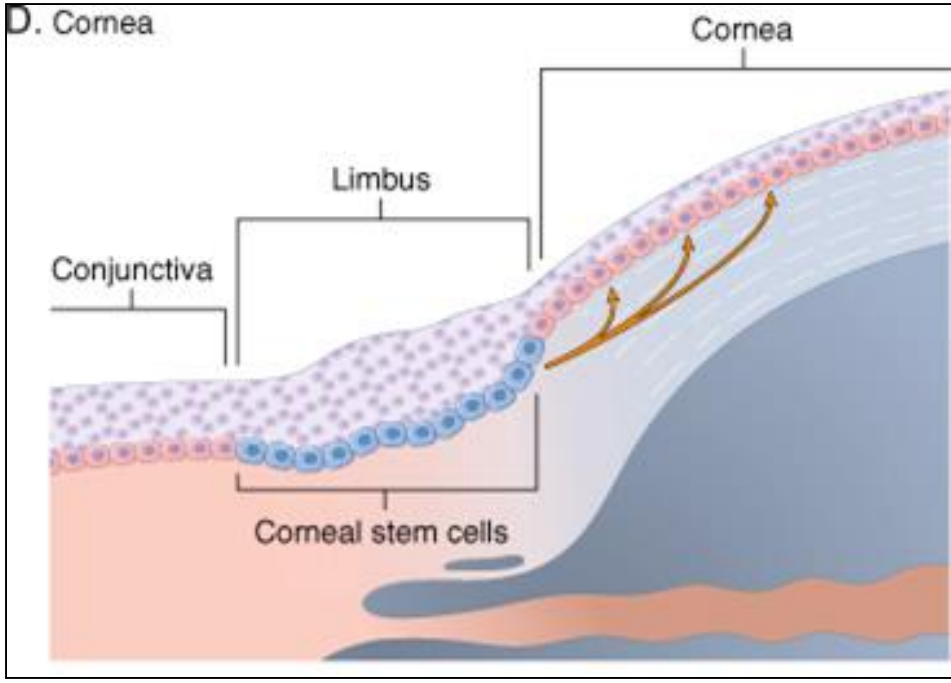




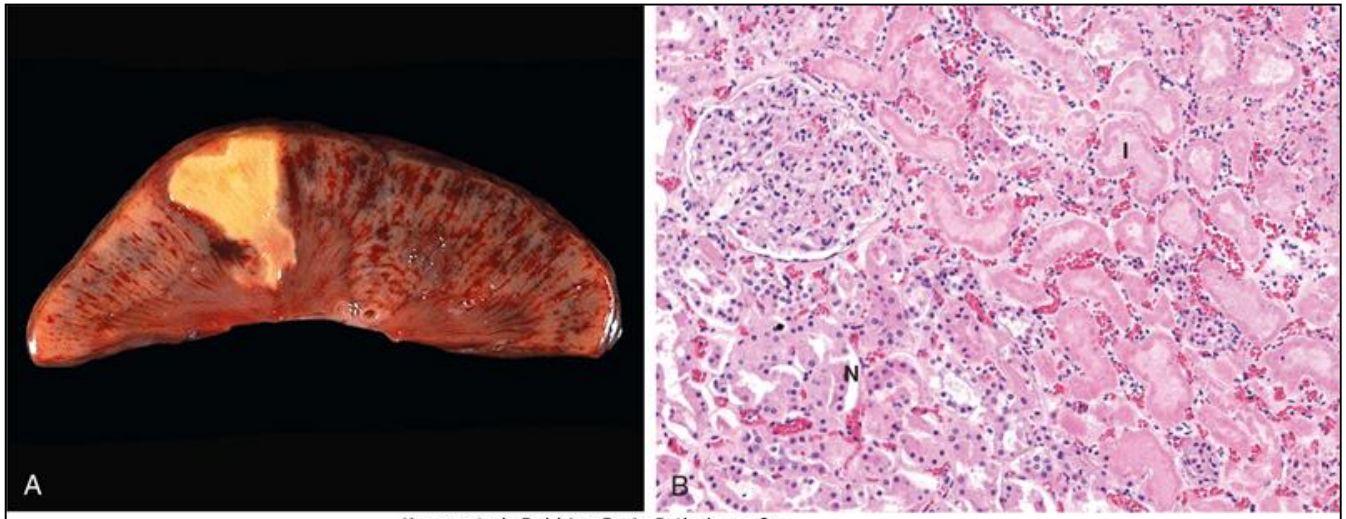




3- Know the mechanism of repair and formation of granulation tissue.

Healing

- *Healing* is usually a tissue response
  - (1) to a wound (commonly in the skin)
  - (2) to inflammatory processes in internal organs
  - (3) to cell necrosis in organs incapable of regeneration



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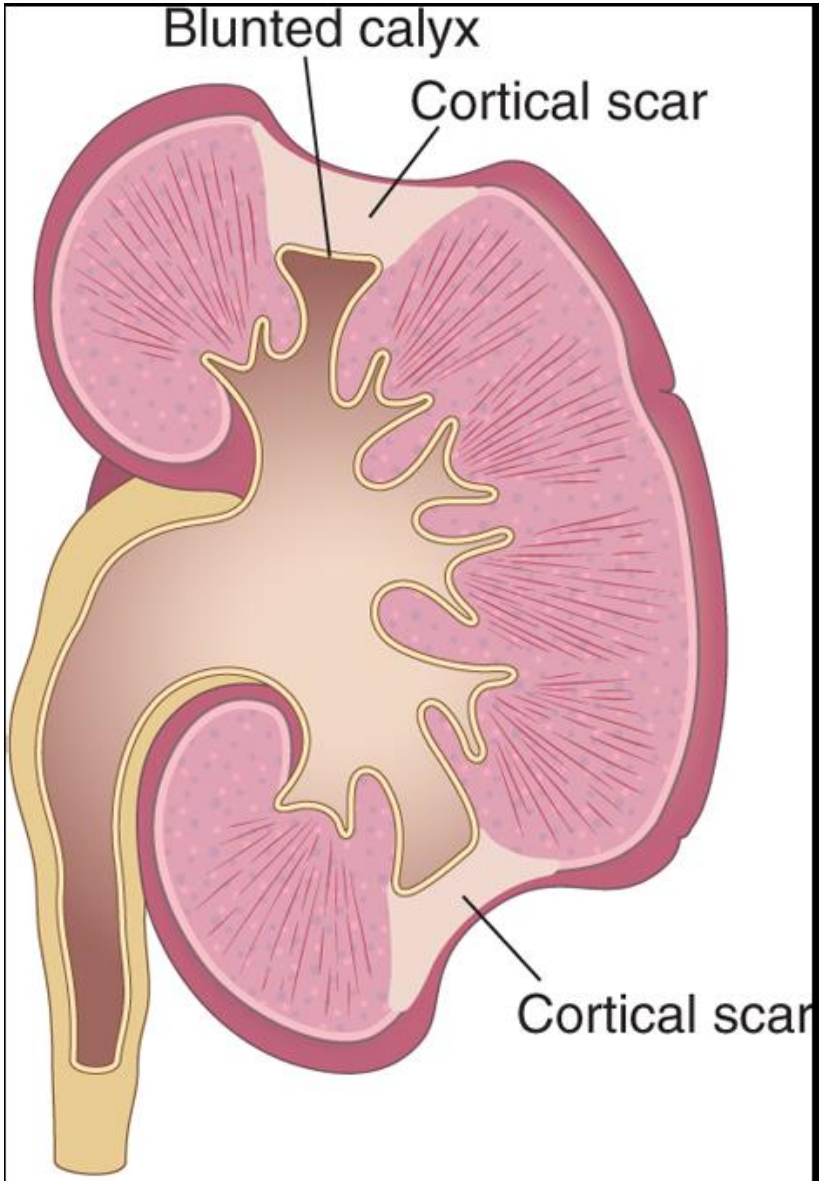


3. Know the mechanism of repair and formation of granulation tissue.

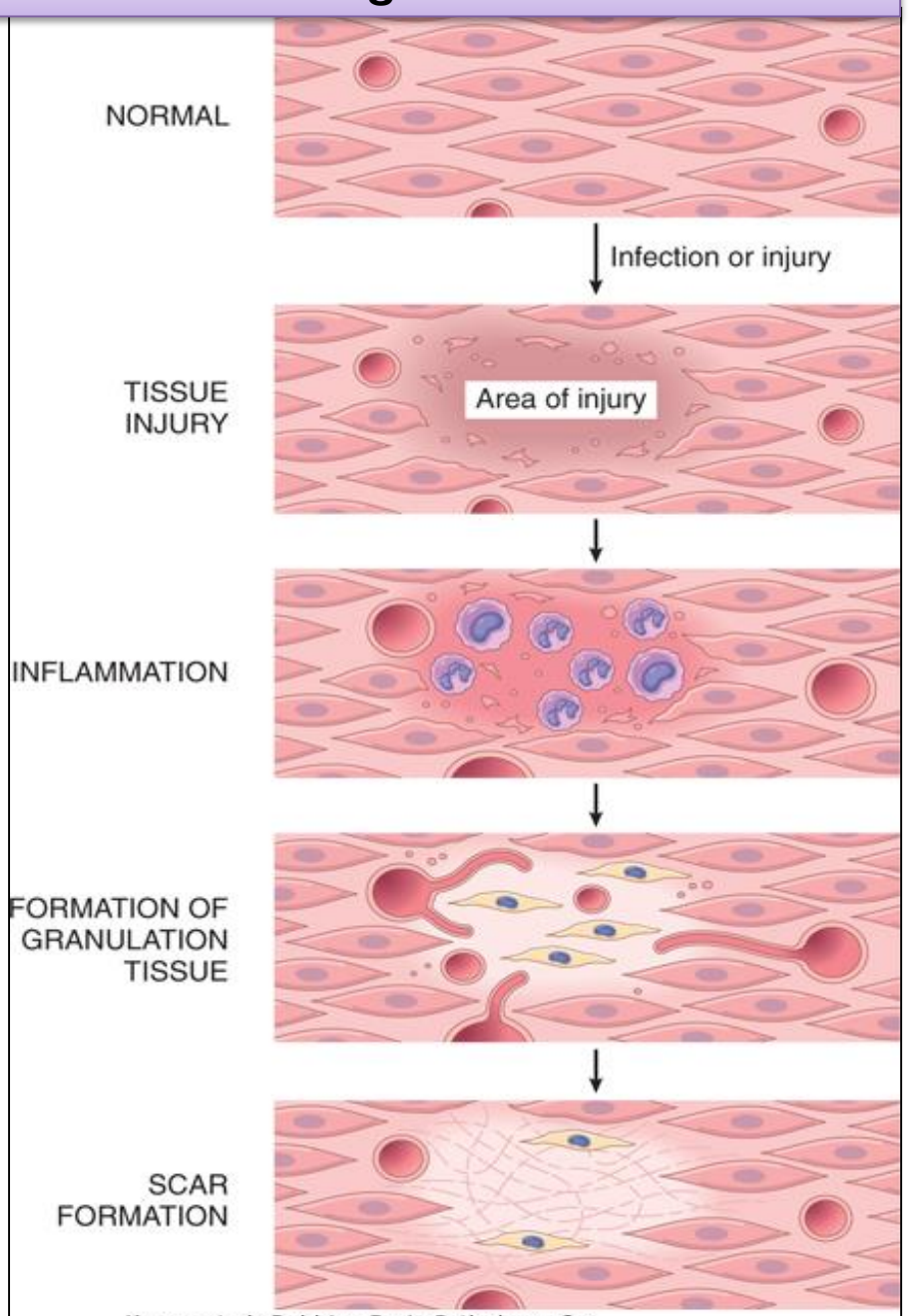
Mechanism of repair

- 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

3. Know the mechanism of repair and formation of granulation tissue.



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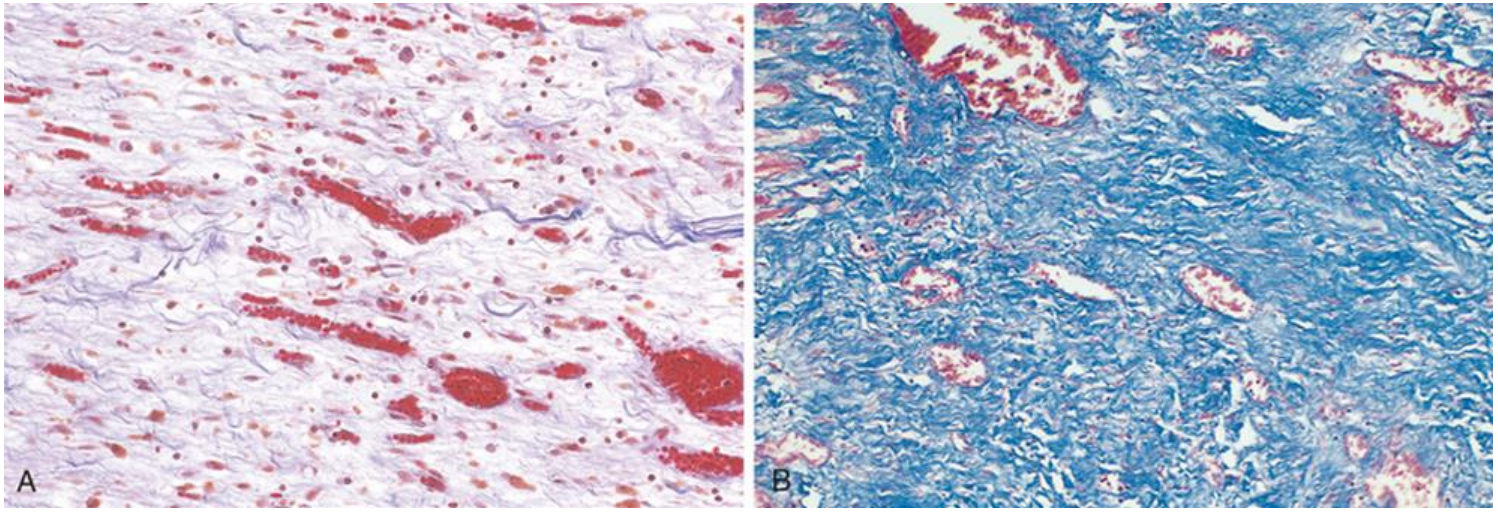


3. Know the mechanism of repair and formation of granulation tissue.

Repair by connective tissue (granulation tissue)

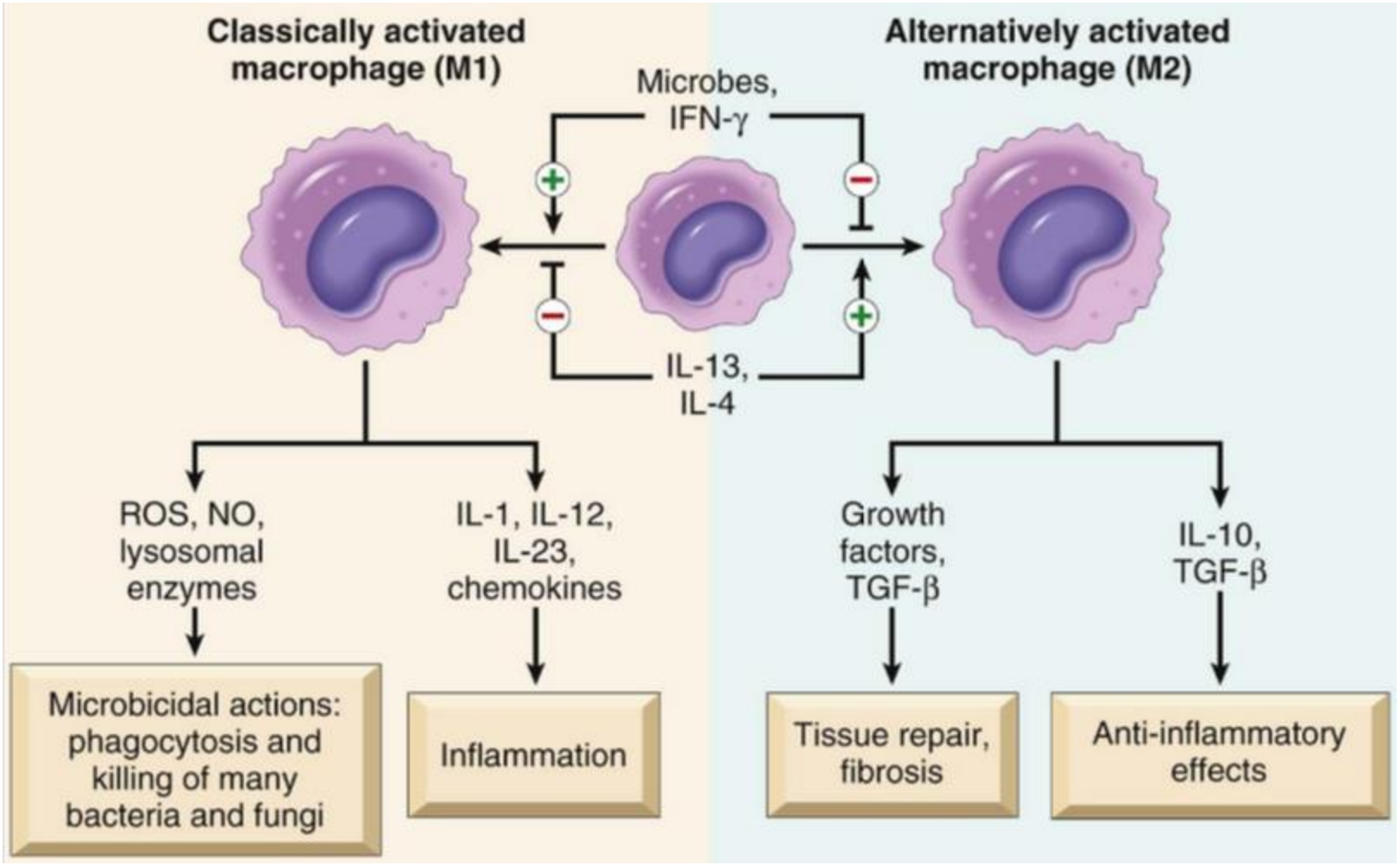
- It consists of:
  1. fibroblasts surrounded by abundant extracellular matrix
  2. newly formed blood vessels
  3. scattered macrophages and some other inflammatory cells.

What is the role of macrophages in wound healing?

- Cleanup of debris, fibrin, and other foreign material at the site of repair.
- Macrophages recruit other cells: fibroblasts and angioblasts
- Stimulation of matrix production , interleukins that stimulate fibroblasts and angioblasts to produce the extracellular matrix.
- Remodeling of the scar. They secrete collagenases

3. Know the mechanism of repair and formation of granulation tissue.

Role of macrophages in wound healing



3. Know the mechanism of repair and formation of granulation tissue.

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
- This lead to:
  1. *increased synthesis of collagen and fibronectin*
  2. *decreased degradation of extracellular matrix (ECM) by metalloproteinases*
-

3. Know the mechanism of repair and formation of granulation tissue.

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.*

3. Know the mechanism of repair and formation of granulation tissue.

Granulation tissue morphology

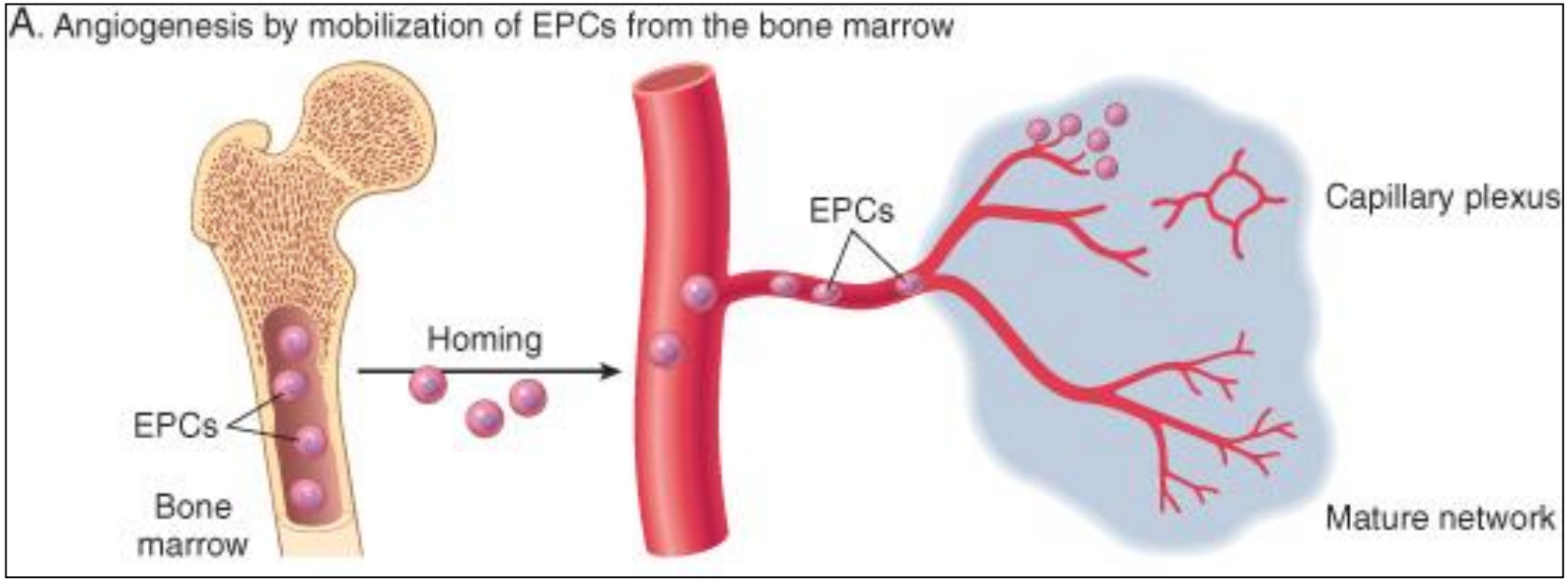
As early as 24 hr. after injury, fibroblasts and vascular endothelial cells begin proliferating to form (by 3-5 days) granulation tissue - pink soft granular appearance on the surface of the wound.

New granulation tissue is often edematous.

- histologically : granulation tissue is composed of :
  - proliferation of new small blood vessels and
  - proliferation of fibroblasts
  - macrophags

3. Know the mechanism of repair and formation of granulation tissue.

Angiogenesis



Angiogenesis from Endothelial Precursor Cells

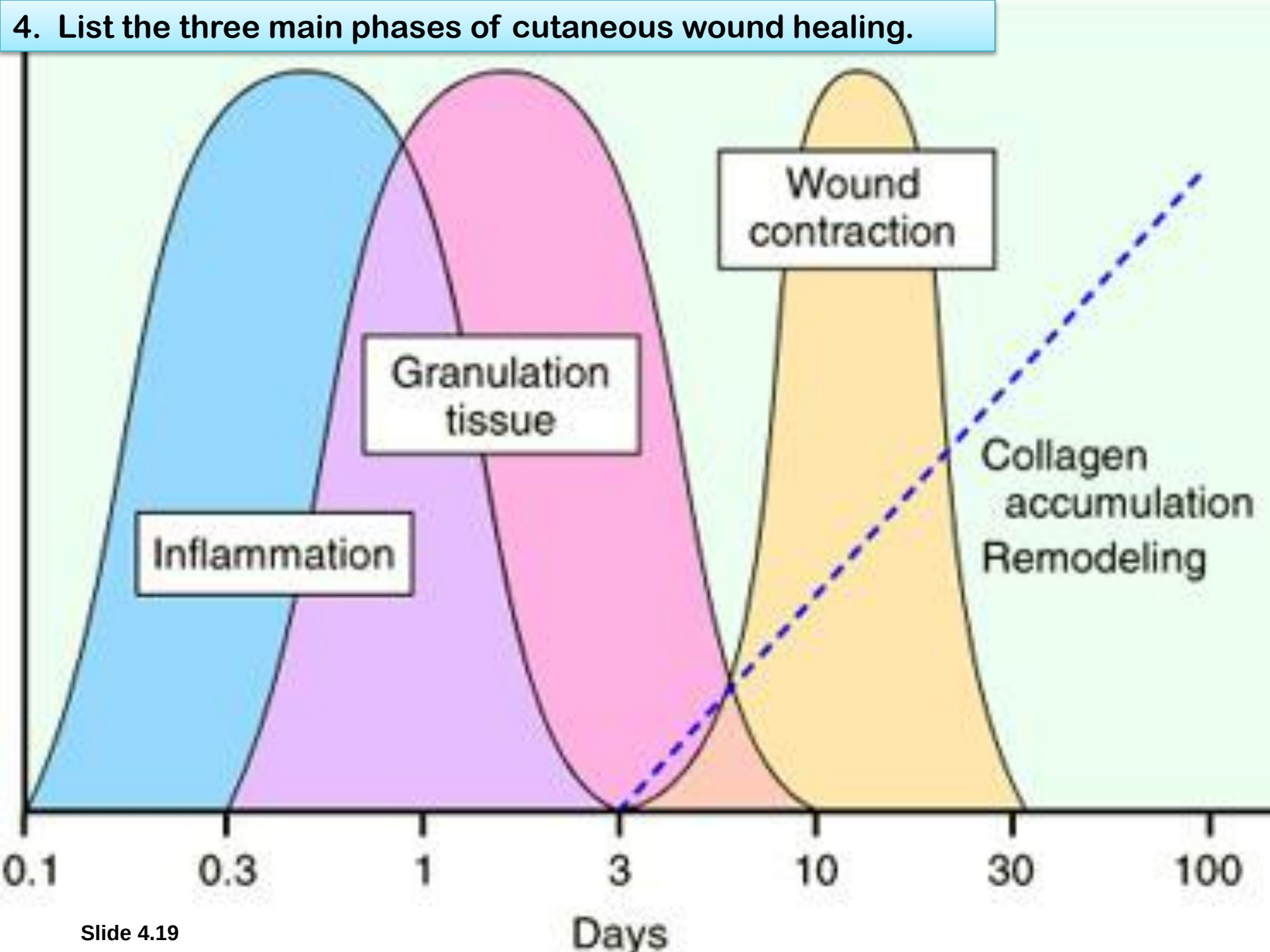
4. List the three main phases of cutaneous wound healing.

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).

4. List the three main phases of cutaneous wound healing.

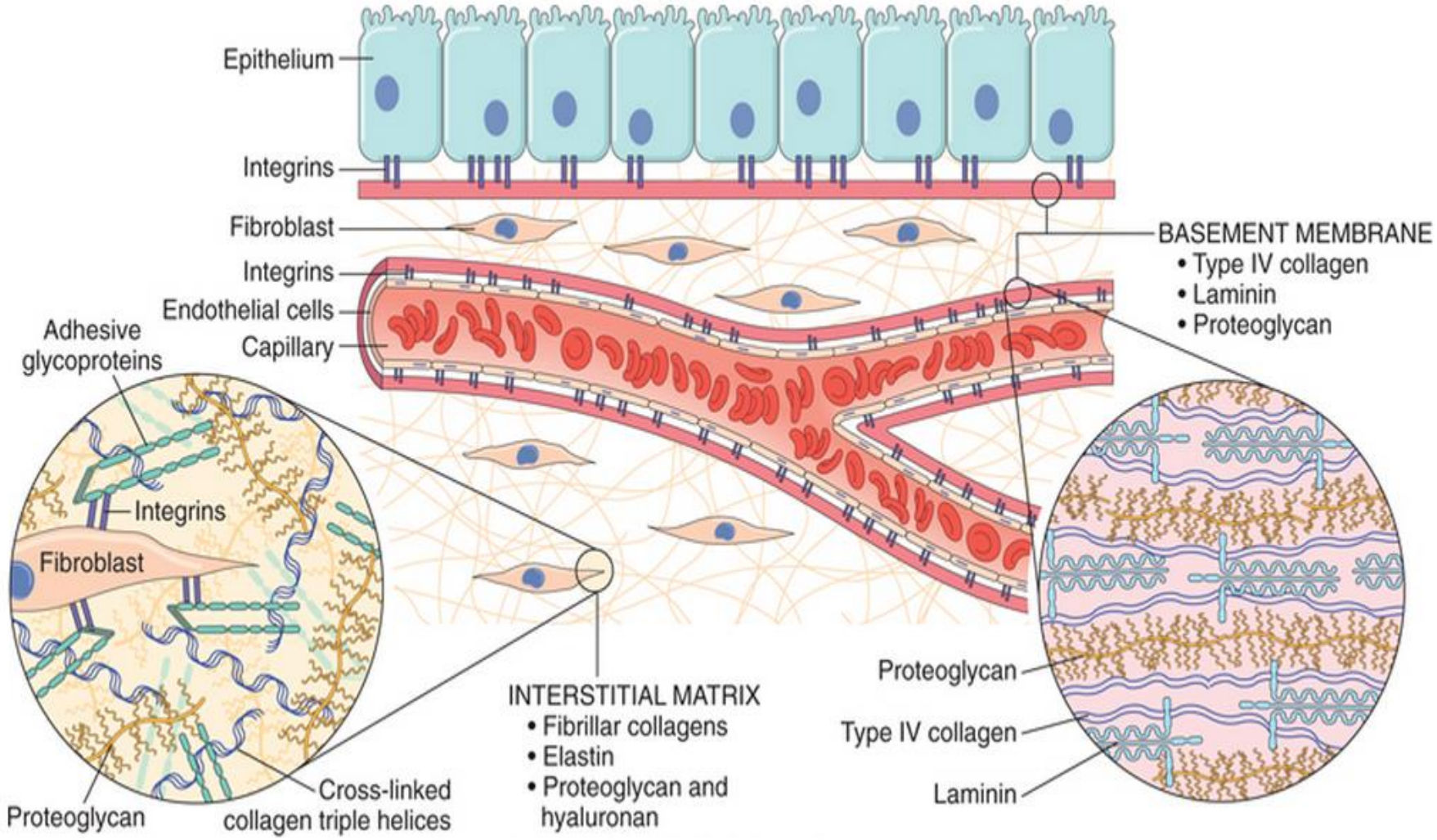


4. List the three main phases of cutaneous wound healing.

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.*

4. List the three main phases of cutaneous wound healing.



Cutaneous Wound healing

1. Primary union
(healing by 1st intention)

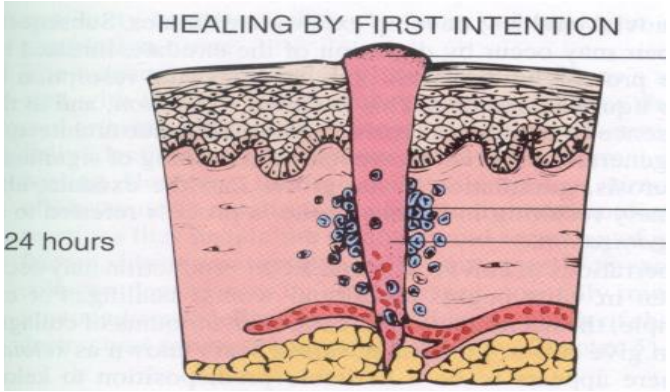
- clean surgical incision
- no significant bacterial contamination
- minimal loss of tissue
- clot, scab formation

2. Secondary union
(healing by 2nd intention)

- more extensive loss of cells and tissue:
  - -infarction
  - -inflammatory ulceration
  - -abscess formation
- surface wound with large defect
- large tissue defect that must be filled

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 and fibroblasts, blanching
End of 1st month: scar (cellular connective tissue, intact epidermis, lost appendages).



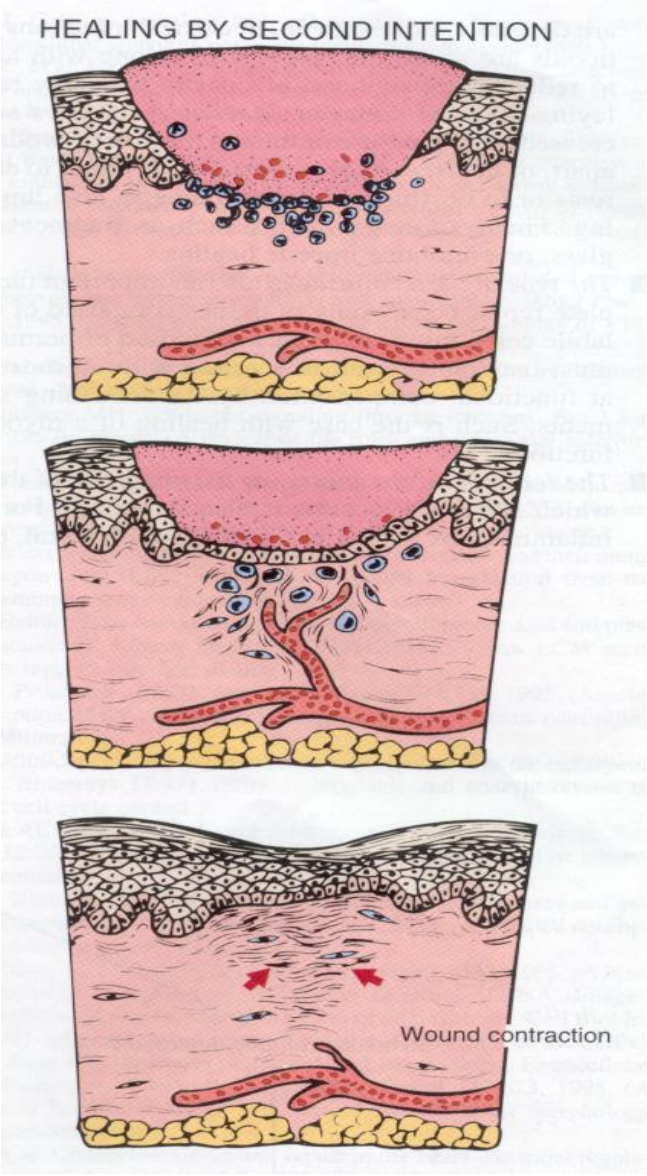
Primary union (healing by first intention)

- 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.

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

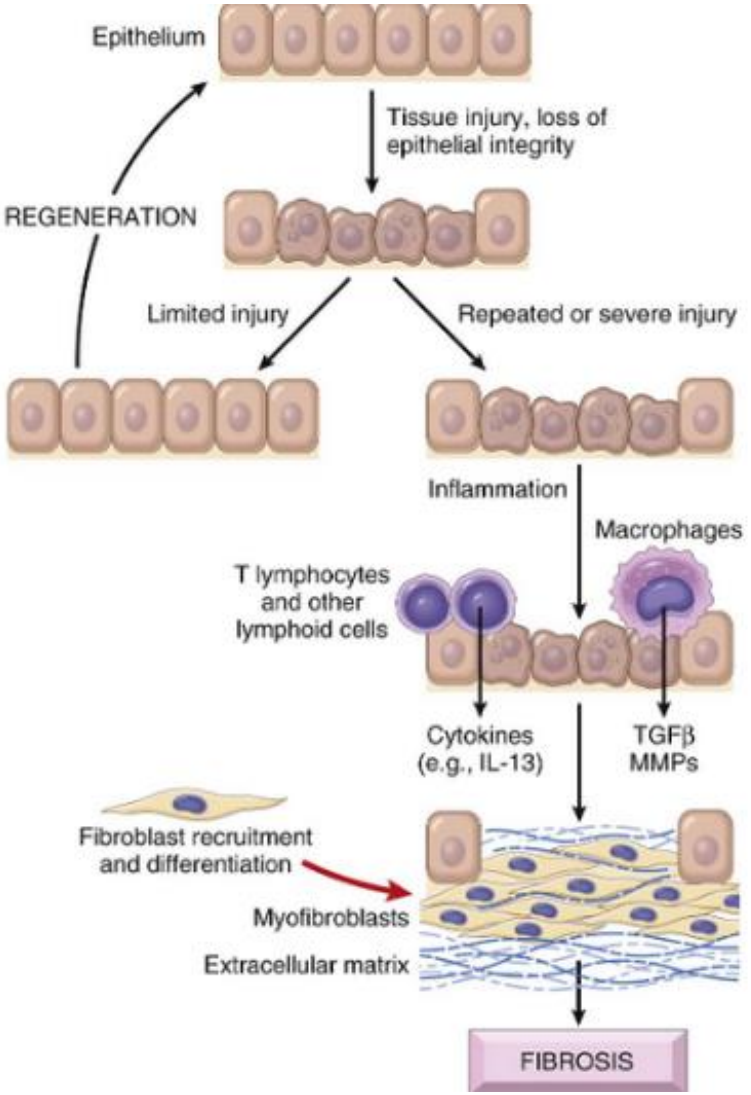


Difference between primary intention and secondary intention

- 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%), ?myofibroblasts

Mechanisms of fibrosis

- Persistent tissue injury leads to chronic inflammation and loss of tissue architecture.
- Cytokines produced by macrophages and other leukocytes stimulate the migration and proliferation of fibroblasts and myofibroblasts and the deposition of collagen and other extracellular matrix proteins.
- The net result is replacement of normal tissue by fibrosis.



Delayed wound healing

What is the most common cause of delayed wound healing?

- Infection

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

- Foreign bodies in the wound
- Mechanical factors

Suture help healing of wound

- 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

- Excess corticosteroid

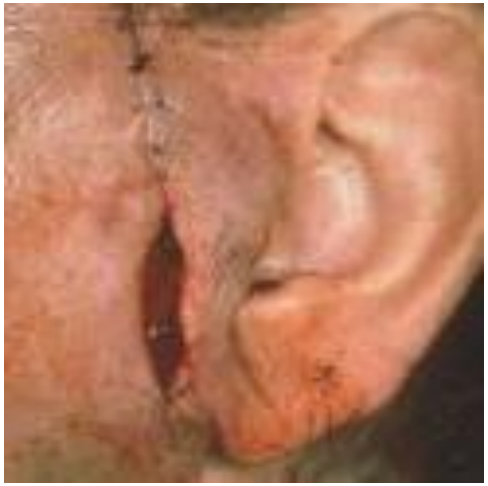
Excess corticosteroid

- 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

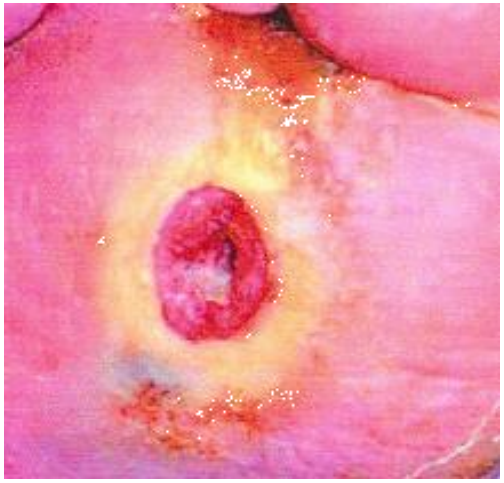
COMPLICATIONS IN CUTANEOUS WOUND HEALING

- 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*
  - (3) *formation of contractures.*

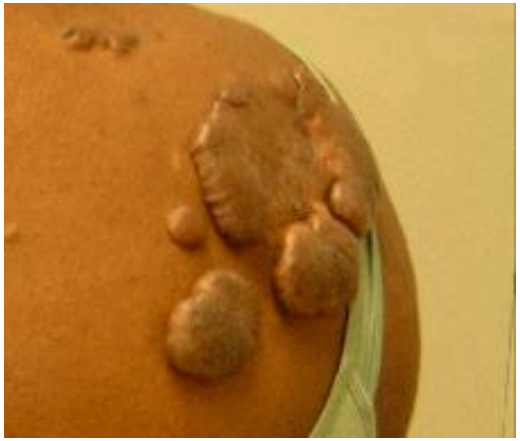
6. Complications of wound healing



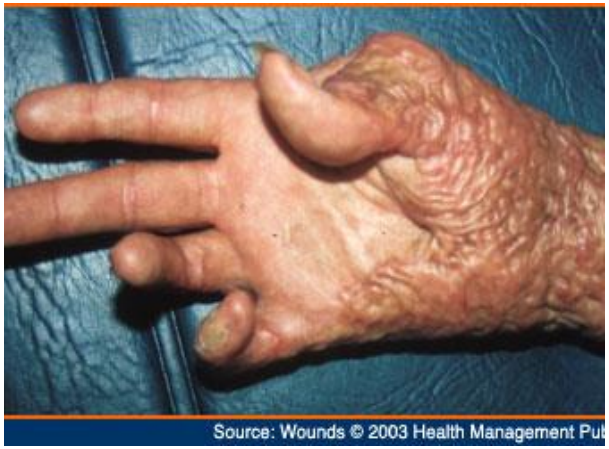
Wound dehiscence



Wound ulceration



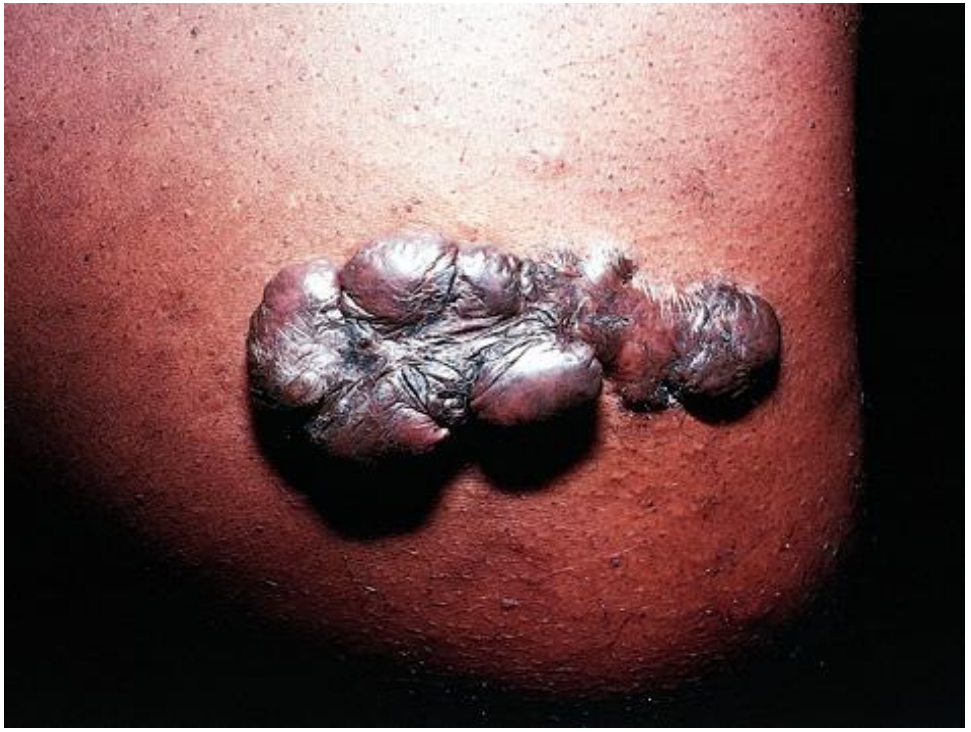
Keloid



Contracture

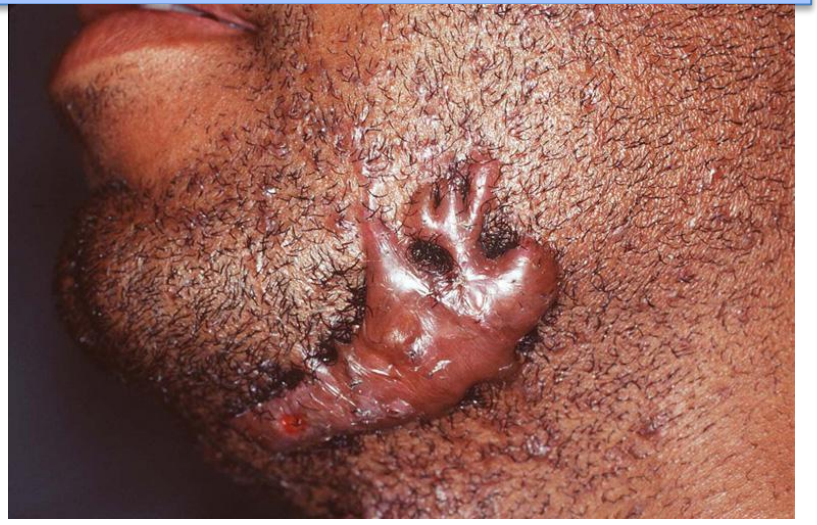
What is a keloid?

- Keloids are excessive scars composed of irregularly deposite hyalinized collagen bands. They may appear as bulging masses.

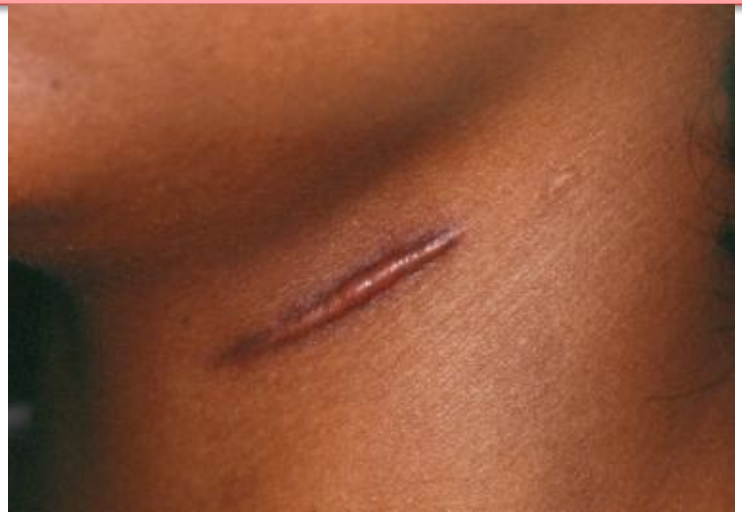


What is the difference between keloid and hypertrophic scar?

- Keloids are the 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 are characterized by erythematous, pruritic, raised fibrous lesions that typically do not expand beyond the boundaries of the initial injury and may undergo partial spontaneous resolution. Hypertrophic scars are common after thermal injuries.



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.