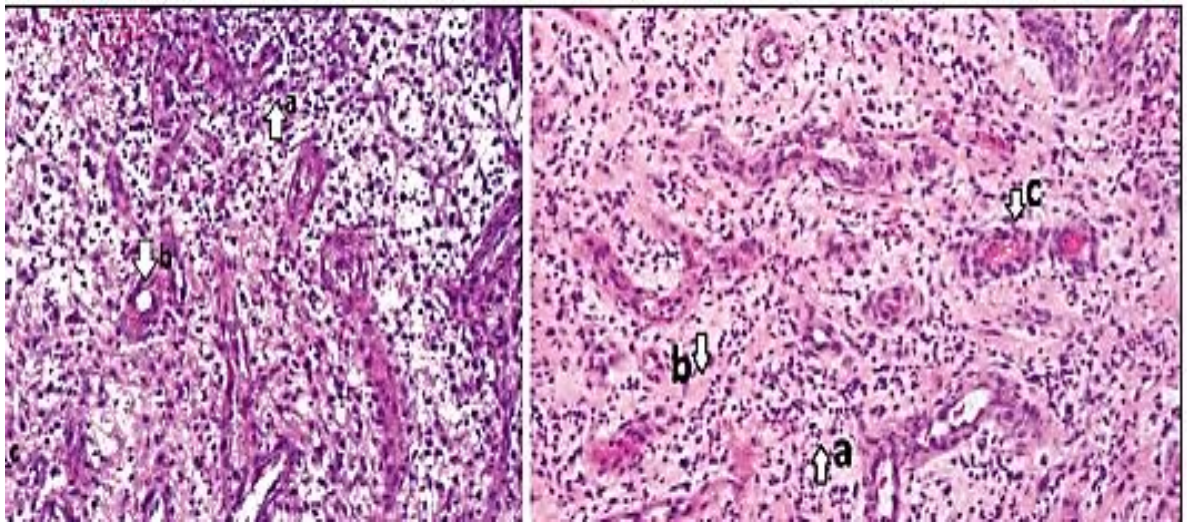
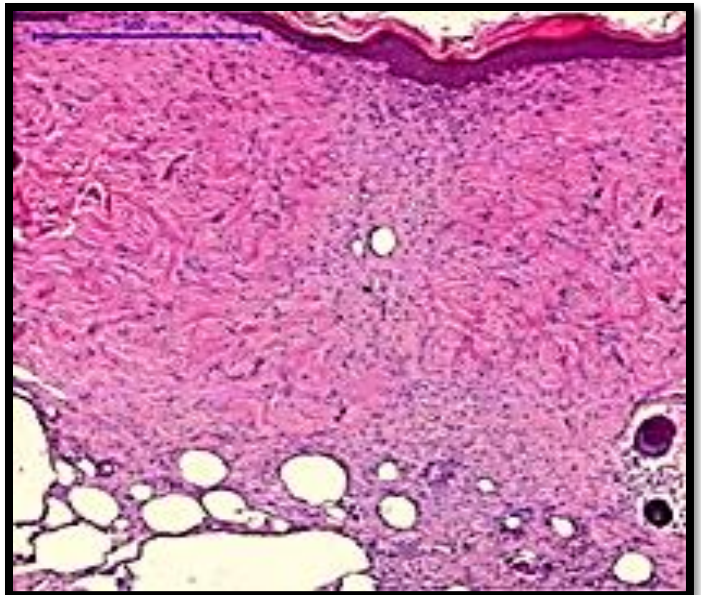
WOUND HEALING (REGENERATION AND REPAIR)

Lecture 8

2023-2024





Tissue repair (Healing)

- Injury to cells and tissues results in loss of cells and tissues.
- It sets in inflammation (restrict the tissue damage) and initiate replacement of lost tissue by living tissue derived from the parenchymal or connective tissue elements of the injured tissue.

Mechanism of tissue repair (healing):

1. Regeneration
2. Repair

- Regeneration occurs by proliferation of cells that survived in the injury and retain the capacity to proliferate.

Proliferative capacity of the tissue:

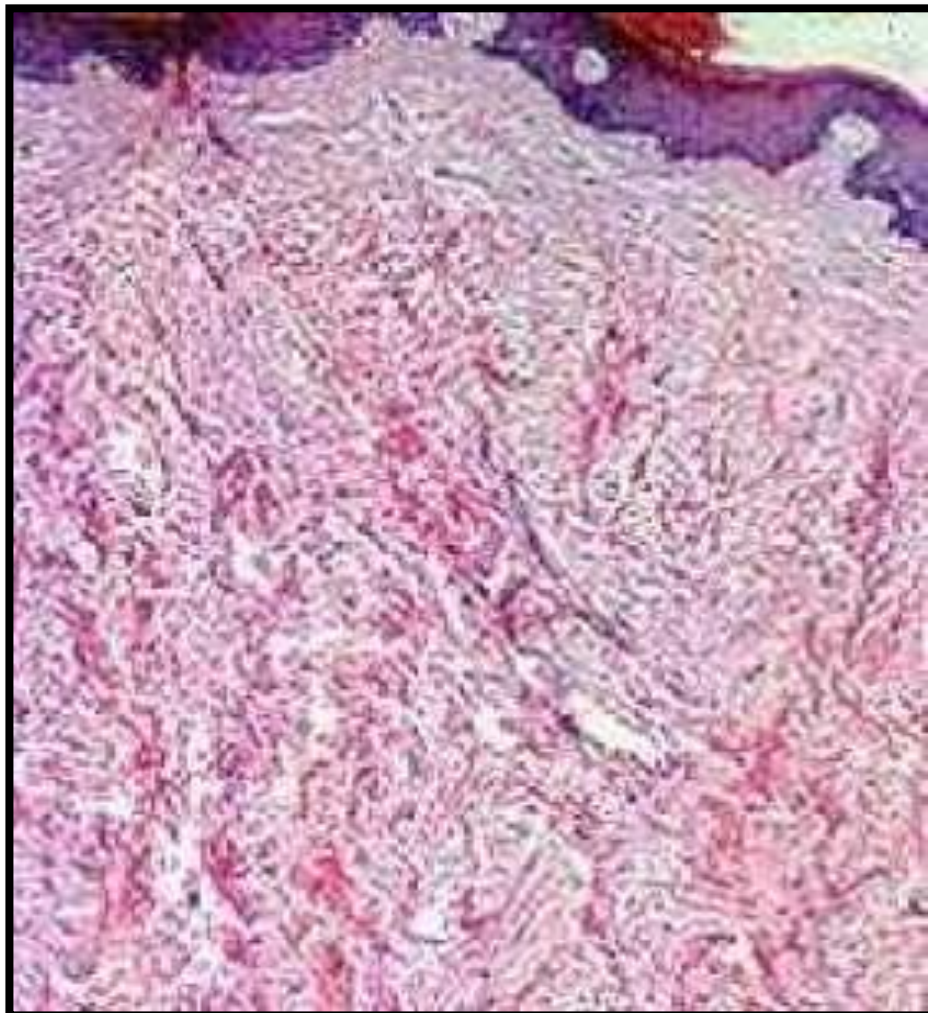
Depending on their relationship to the cell cycle, most mature tissues contain variable proportions of three types of cells:

- ✓ Continuously dividing cells (labile cells).
- ✓ Quiescent cells (stable cells) that occasionally go back to the cell cycle.
- ✓ Non-dividing cells (permanent cells).

Healing by repair, scar formation and fibrosis

- Healing may be either by regeneration or repair or combination of both.
- With mild and transient injury, there is regeneration.
- If the tissue injury or damage persists, inflammation becomes chronic, resulting in excessive deposition of connective tissue known as fibrosis (repair).

Healing
Skin Scar



Steps in healing by repair (scar formation)

1. ***Inflammation***
2. ***Angiogenesis***
3. ***Formation of Granulation Tissue***
4. ***Scar Formation***
5. ***Connective Tissue Remodeling***

Inflammation

- Whenever there is tissue injury, inflammatory reaction begins which tries to limit the damage and remove the injured tissue.
- At the same time, it also promotes the deposition of ECM components at the site of injury and stimulates angiogenesis.

Angiogenesis

Angiogenesis is the process of formation of new blood vessels from existing vessels. Steps in angiogenesis:

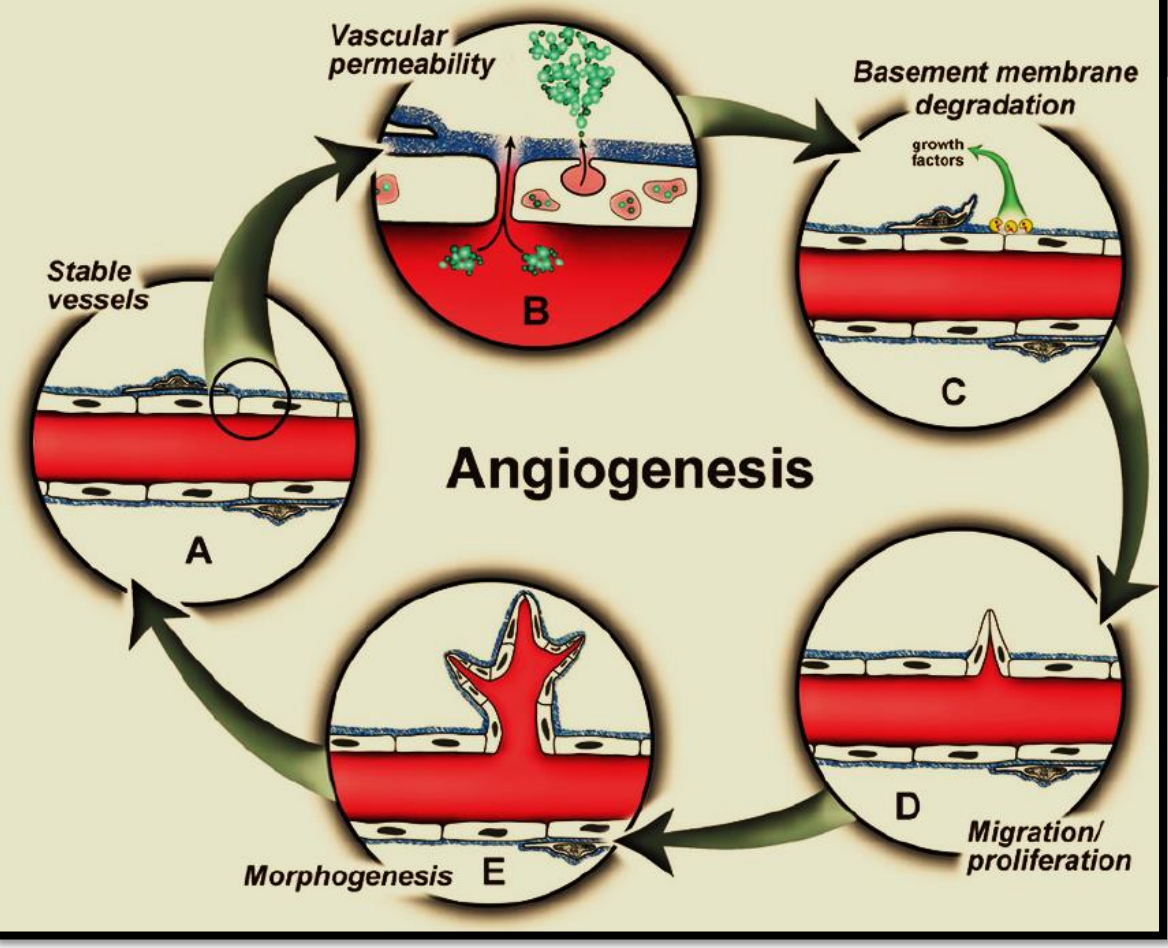
i. Vasodilatation in response to nitric oxide and increased permeability of the pre-existing vessel due to VEGF.

iii. Migration and proliferation of endothelial cells toward the site of injury.

iv. Maturation of endothelial cells into capillary sprouts/tubes.

v. Formation of mature vessel: It involves recruitment of pericytes and smooth muscle cells to form the periendothelial layer.

Angiogenesis



Formation of Granulation Tissue

- The first 24-72 hours of the repair process begins with proliferation of fibroblasts and vascular endothelial cells.
- It forms a specialized type of tissue known as **granulation tissue**, which is a characteristic of tissue repair.

Scar Formation

- The leukocytes, edema, and angiogenesis disappear, accomplished by the increased accumulation of collagen.
- The granulation tissue scaffolding is converted into a pale, a vascular scar.

Components of scar:

- It is composed of spindle-shaped fibroblasts, dense collagen, fragments of elastic tissue, and other ECM components.
- By the end of the first month, the scar consists of a cellular connective tissue without inflammatory infiltrate.

Connective Tissue Remodeling

The processes of tissue repair are controlled and mediated by growth factors, which are low molecular weight polypeptides that initiate a series of intra-cellular events, resulting in cell proliferation.

- Remodeling of the connective tissue framework is an important feature.
- It is the long-lasting phase of tissue repair.
- Remodeling indicates that the balance between ECM synthesis (collagen deposition) and degradation has been restored.

Growth factors involved in healing (repair)

- Epidermal growth factor which stimulates regeneration of epithelial cells.
- Transforming growth factor α which also stimulates regeneration of epithelial cells.
- Platelet-derived growth factor which is chemotactic and mitogenic for fibroblast and smooth muscle cells.
- Tumor necrosis factor α which stimulates angiogenesis.

Cutaneous wound healing

1. **Healing by Primary Union or by First Intention**

2. **Healing by Secondary Union or by Second Intention**

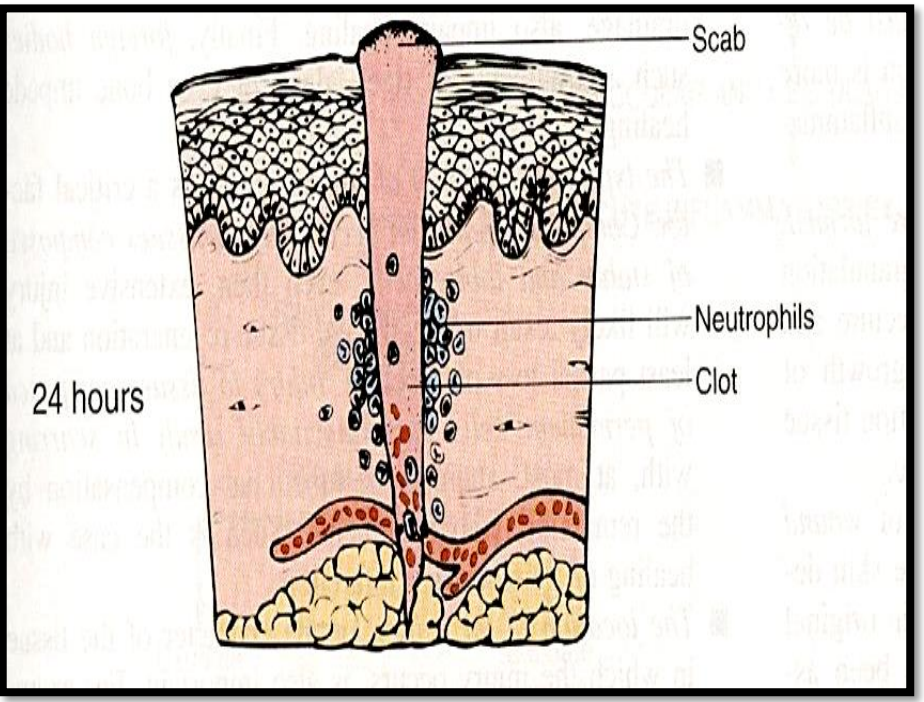
Stages in the Healing by First Intention: First Day

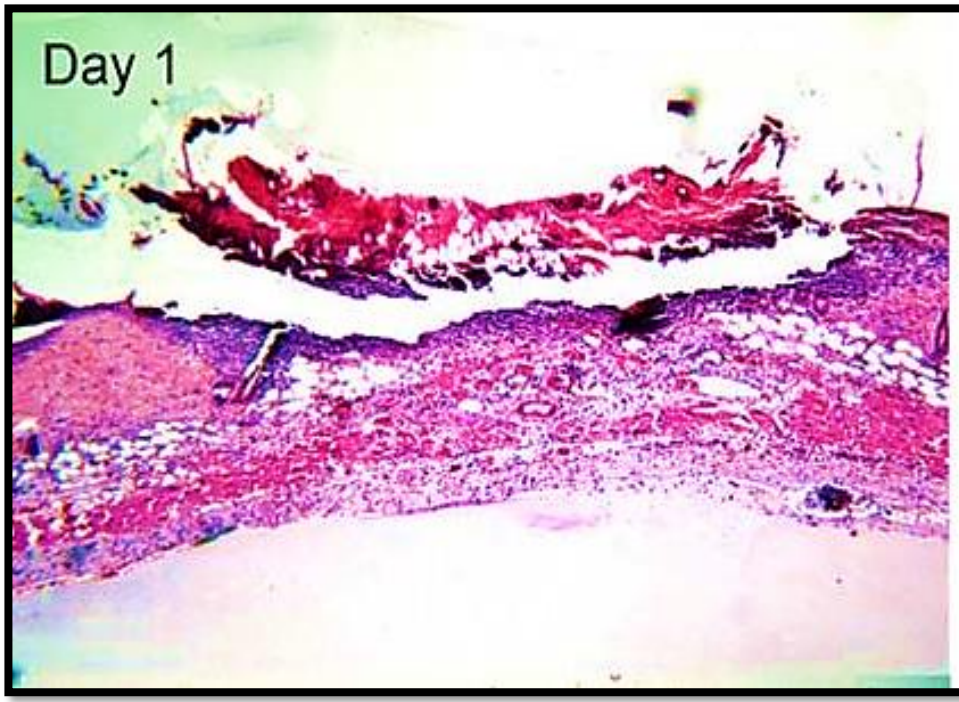
Formation of blood clot: It is formed in the space between sutured margins.

- Blood clot contains not only trapped red cells but also fibrin, fibronectin, and complement components. Clot stops bleeding and acts as a scaffold for migrating and proliferating cells.
- Dehydration at the external surface of the clot leads to formation of a scab over the wound.

First Day; Epithelial changes:

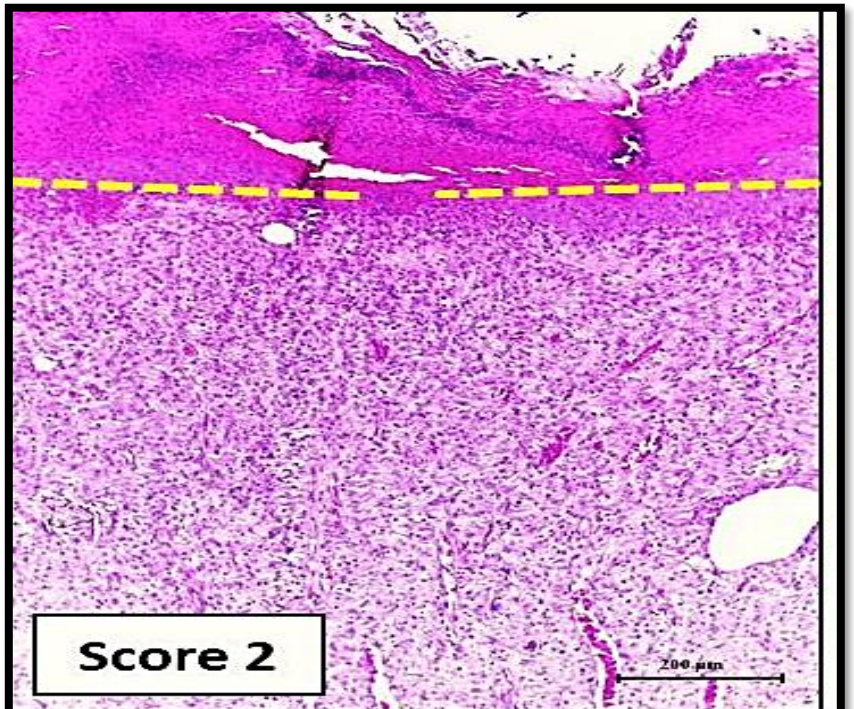
- Within 24 hours of wound, neutrophils appear at the margins of the incision. They release proteolytic enzymes which clean out debris
- At the cut edges of the wound, the basal cells of the epidermis begin to show mitotic activity (re-epithelization).

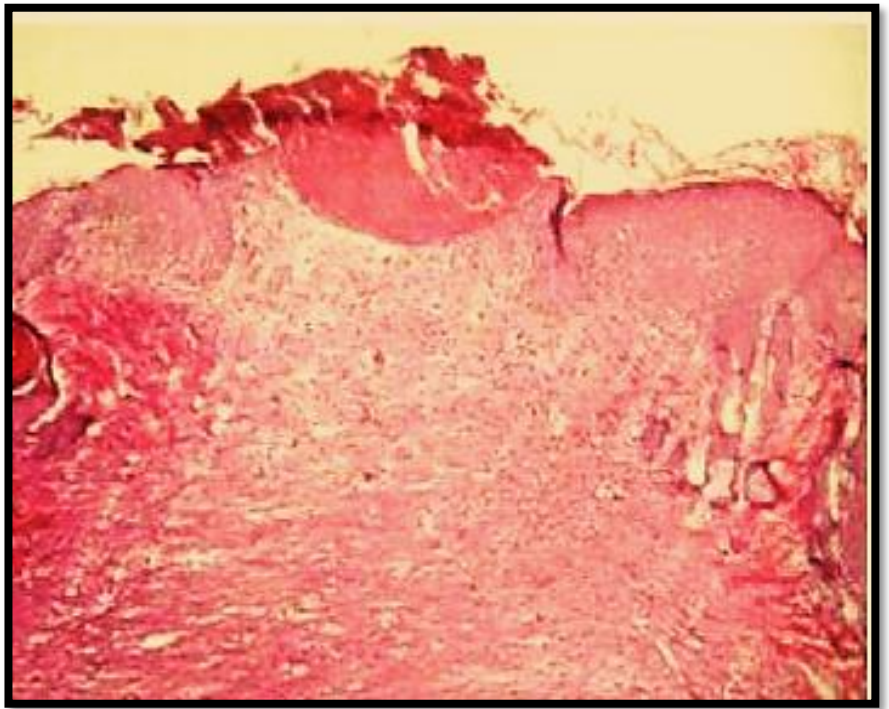




Two days:

- Neutrophils are replaced by macrophages.
- The epithelial cells fuse in the midline below the surface scab and epithelial continuity is re-established in the form of a thin continuous surface layer (re-epithelization).

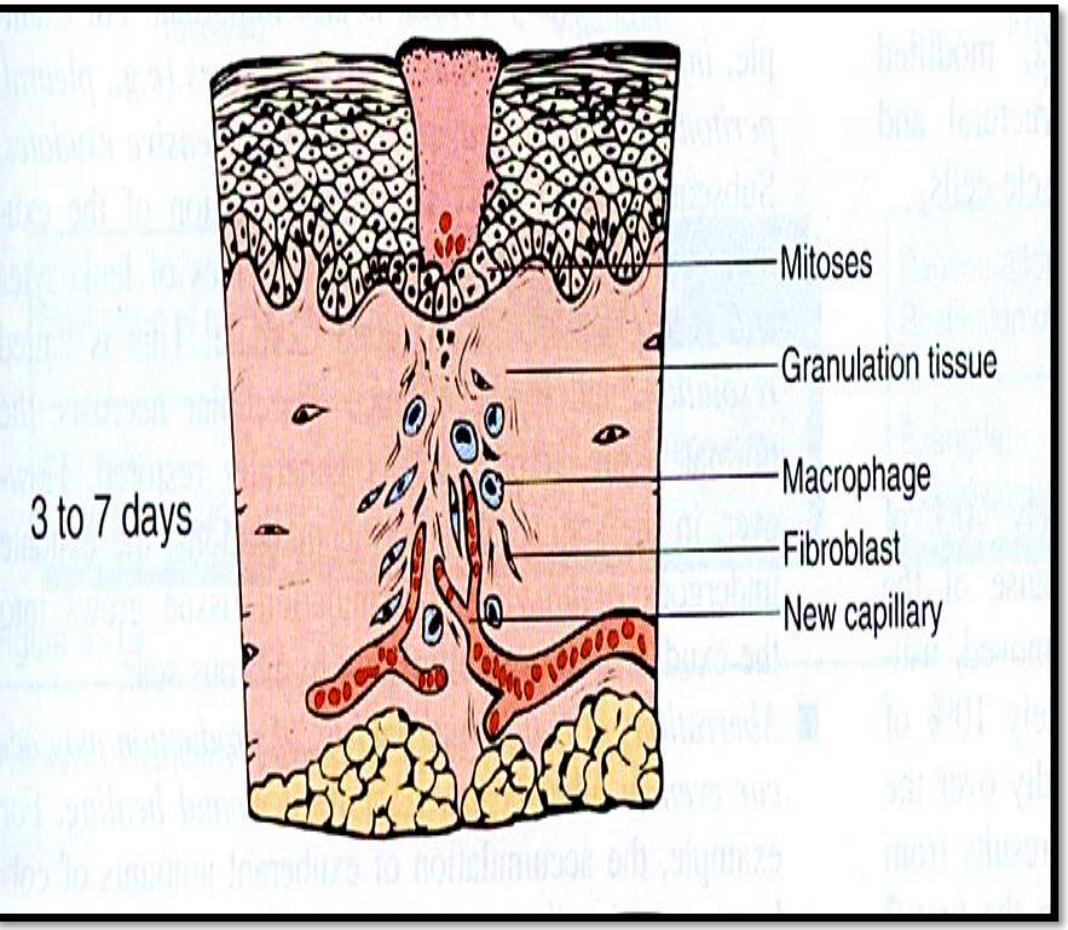


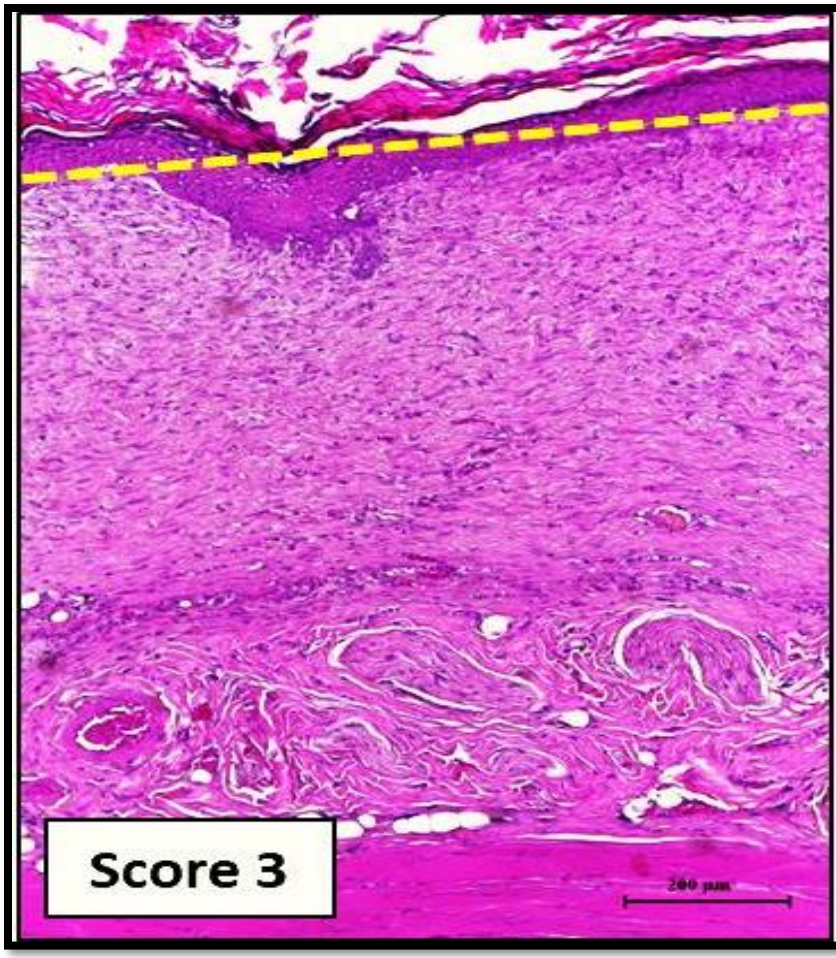


Three-Seven days:

- Granulation tissue begins to invade incision space and fills the wound area by 5-7 days.
- Collagen is progressively laid down.
- Surface epidermis achieves its normal thickness and differentiation.
- Acute inflammatory response begins to subside.

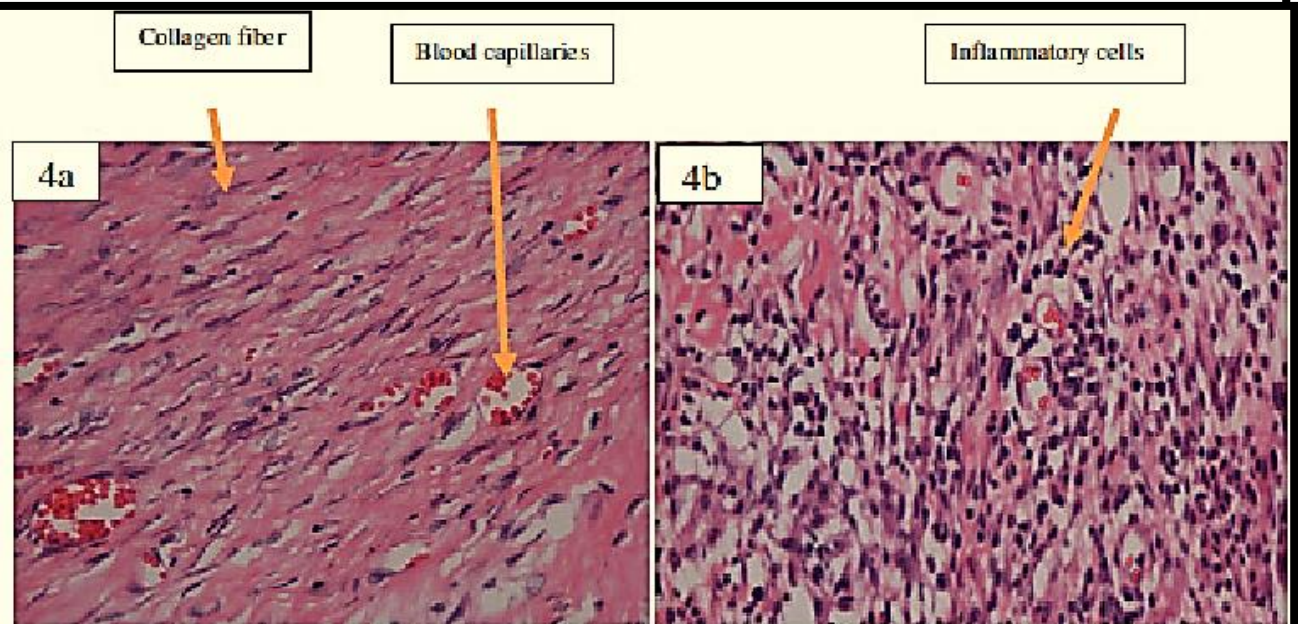
Healing of wound by 1st Intention

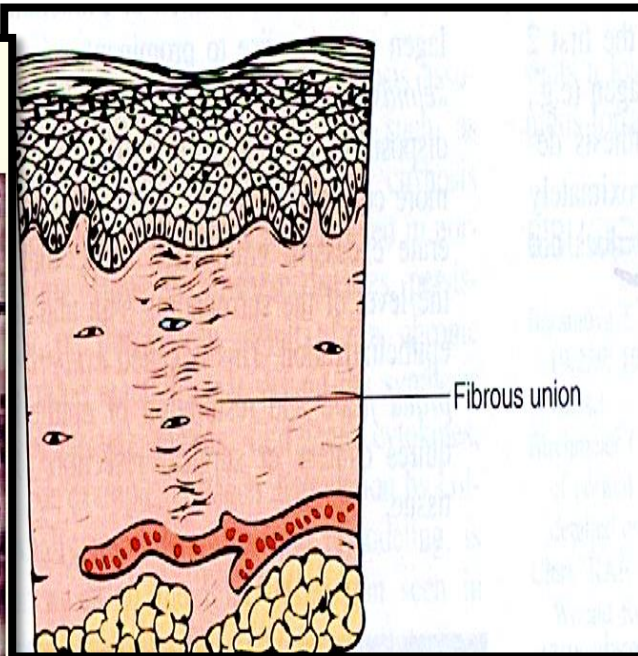




Ten to fourteen days:

- Increased accumulation of collagen and regression of vascular channels.
- The granulation tissue scaffolding is converted into pale, a vascular scar.
- Wound normally gains about 10% strength of normal skin.





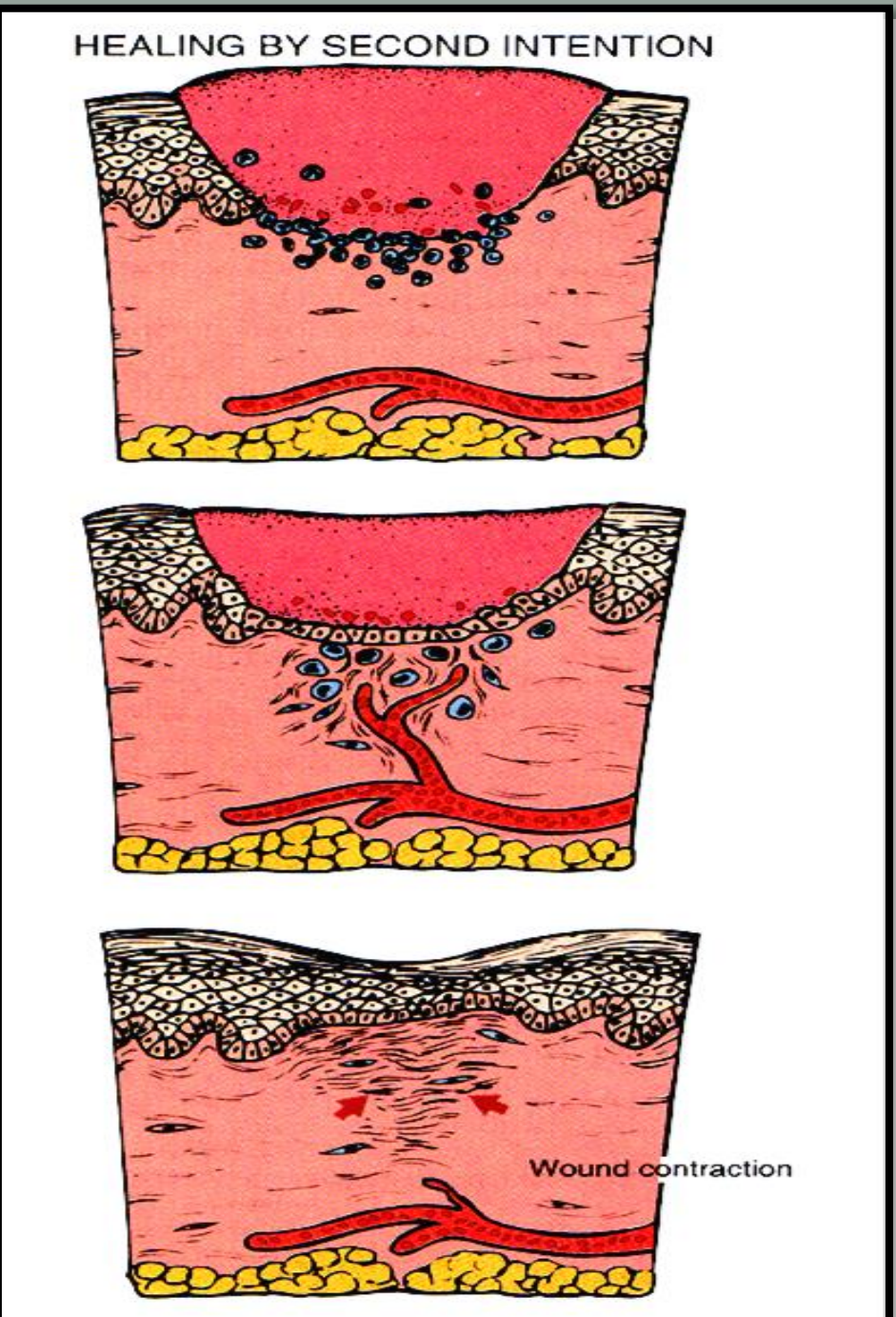
Weeks to months:

- The scar appears as a cellular connective tissue covered by intact epidermis and without inflammatory infiltrate.
- Collagen deposition along the line of stress and wound gradually achieves maximal 80% of tensile strength of normal skin.
- The resulting scar is commonly raised above the surface due to underlying proliferative process and is a pale red in color due to increased vascularity.
- Elastic fibers are formed much later than collagen.
- Sensory nerves may grow into the scar in about 3 weeks but specialized nerve endings such as the Pacinian corpuscles do not reform.

Healing by Secondary Union or by Second Intention

Features of Healing by Secondary Intention:

- Larger wounds show more exudate and necrotic tissue with severe inflammatory reaction. The clot or scab formed at the surface of wound is large.
- Full re-epithelialization of the wound surface is slow because of the larger gap.
- The larger defect requires more amount of (abundant) granulation tissue with extensive deposition of collagen and substantial scar formation.
- Wound is an important feature in healing by secondary union.



Healing by **Second Intention**

(Larger injury, abscess, infarction)

Process is similar but Results in much larger Scar and then CONTRACTION

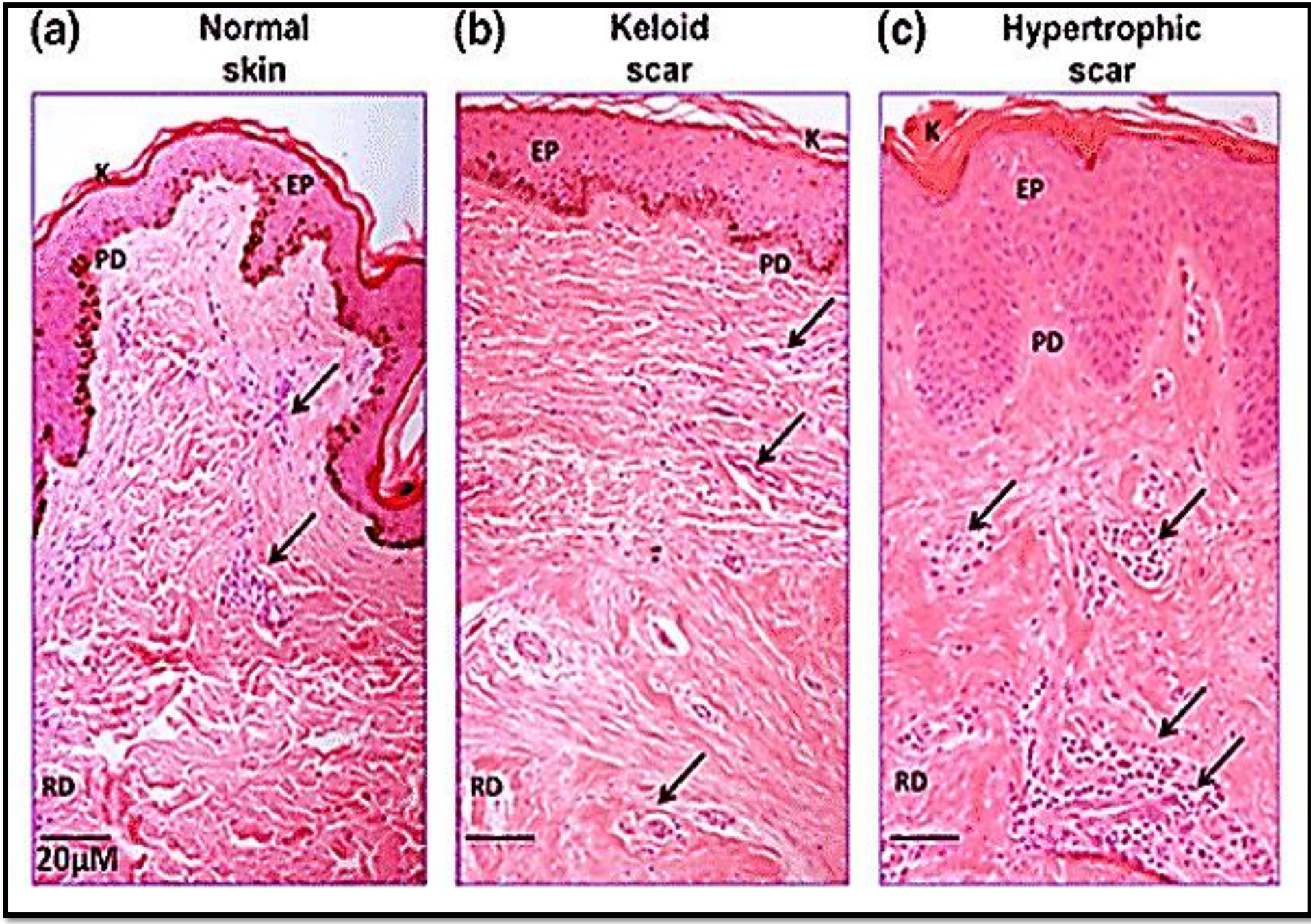
Factors that influence wound healing

Local Factors

5. Location of injury: Wound over the skin covering bone with little intervening tissue prevents wound contraction (e.g. skin over the anterior tibia).

6. Blood supply:

- Wounds in areas with good blood supply, such as the face, heal faster than those with poor blood supply, such as the foot.
- Varicose veins of the legs decrease the venous drainage and can cause non-healing ulceration.


(a)
Normal skin
K
EP
PD
RD
20μM
(b)
Keloid scar
EP
K
PD
RD
(c)
Hypertrophic scar
K
EP
PD
RD