

# INFLAMMATION

## L31- HEALING AND REPAIR

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### Complete Restitution

- Loss of labile population eg. skin abrasion
- Cells at margin proliferate to cover defect
- Spread as a thin sheet till defect covered
- When form confluent layer - **contact inhibition**
- Epidermis then rebuild from base upwards
- Ability of adnexal glands to regenerate - **used in plastic surgery**

### Wound Healing is a Multi-Step Process

1. Inflammatory Phase (Reaction)
  - Hemostasis
  - Phagocytosis
2. Proliferative Phase (Regeneration)
3. Maturation Phase (Remodeling)

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#### 1. Inflammatory Phase – Hemostasis

- Hemostasis aims at the cessation of bleeding.
- It results from vasoconstriction of the larger blood vessels in the affected area, retraction of injured blood vessels, deposition of the extracellular matrix protein fibrin and formation of a blood clot.
- The blood clot includes blood platelets surrounded by a provisional matrix of fibrin fibers and **ECM** proteins **vitronectin**, plasma **fibronectin** and **thrombospondin**, providing the framework for repair.
- The **clot** also serves as a reservoir for **growth factors** and cytokines, released from degranulating **platelets**.

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- A **scab** forms at the surface to inhibit contamination by microorganisms.
- The blood supply increases causing redness and edema.
- **Neutrophils** invade the wound during 6-24 hours
- After ~24 hours, neutrophils are replaced by **macrophages**.
- Macrophages engulf microorganisms and debris by phagocytosis.
- Macrophages secrete **angiogenesis factors**, which stimulate formation of epithelial buds at the termini of injured blood vessels.

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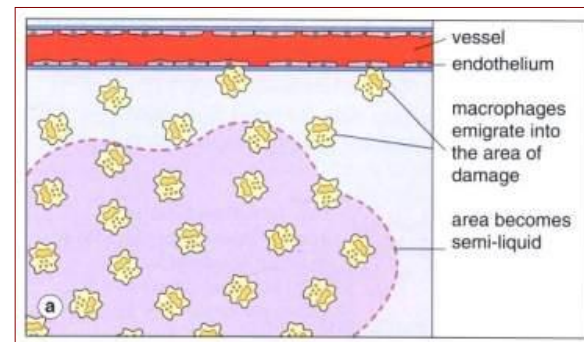
## 2. Proliferative Phase – Re-Vascularization

- The wound is invaded by numerous capillaries, resulting in a granular tissue appearance = **granulation tissue**.
- **FGF** and **VEGF**, released by damaged endothelial cells, macrophages and keratinocytes (VEGF) promote **angiogenesis**.
- Endothelial cells express a new **integrin subset** ( $\alpha v\beta 3$ ) to migrate at tips of sprouting capillaries.
- **Fibroblast recruitment** (**PF4, PDGF, LTB<sub>4</sub>, TGF-beta**)
- **Angiogenesis** (**FGF $\alpha$  and  $\beta$ , TGF- $\alpha$ , TNF- $\alpha$** )

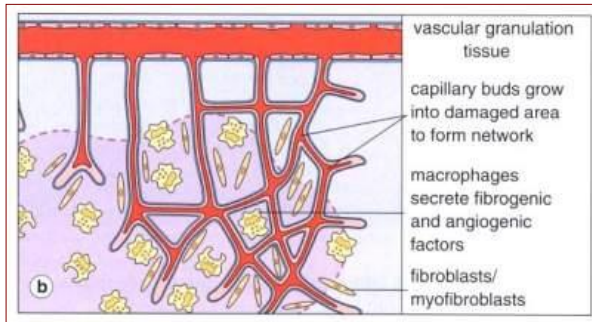
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## Angiogenesis

- ❑ Proteolysis of ECM
- ❑ Migration and chemotaxis
- ❑ Proliferation
- ❑ Lumen formation , maturation and inhibition of growth
- ❑ Increased permeability through gaps and transcytosis



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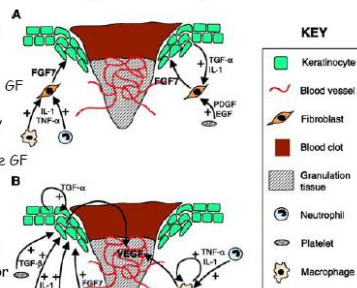
- Under the scab, epithelial cells migrate into the wound from the edges.
- If wound closure does not occur this way, the denuded area is covered with dried plasma protein and dead cells.
- If the wound is not re-epithelialized, it becomes covered with thick, gray, fibrous tissue that is eventually converted into scar tissue.

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### Growth Factors Regulate Regeneration

Important growth factors in wound healing:

**VEGF** - vascular endothelial GF  
**EGF** - epidermal GF  
**FGFs** - fibroblast GF family  
**NGF** - nerve GF  
**KGF** - (FGF7) - keratinocyte GF  
**TGF $\alpha$**  - transforming GF  $\alpha$   
**TGF $\beta$**  - transforming GF  $\beta$   
**Activins** (TGF $\beta$  family)  
**HGF** - hepatocyte GF / SF  
**PDGF** - platelet-derived GF  
**TNF** - tumor necrosis factor  
**IGF** - insulin-like GF  
**CTGF** - connective tissue GF  
**ILs** - interleukin family  
**GM-CSF** - granulocyte-macrophage colony stimulating factor



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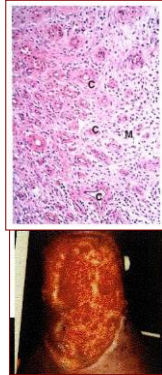
### 3. Maturation – Granulation Tissue Contraction

- Begins about day 21 and may last 1-2 years
- Fibroblasts continue to synthesize collagen, which gets organized into a more orderly structure
- Wound is remodeled and contracted

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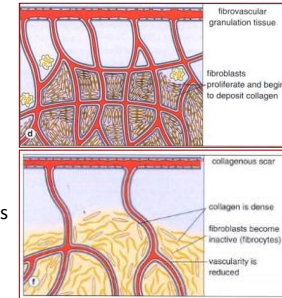
## GRANULATION TISSUE

- The term granulation tissue derives from its pink, soft, granular appearance on the surface of wounds.
- Proliferation of new small blood vessels and fibroblasts are its characteristic histological features.
- Proud flesh - excess



## Repair by - fibrosis

- 1. **Angiogenesis**
- 2. Migration and proliferation of fibroblasts
- 3. Deposition of Extra Cellular Matrix
- 4. Maturation and reorganization
- Granulation bed contracts as it matures
- **myofibroblasts** act as contractile cells



## Skin wounds are classically described to heal by either primary or secondary intention

- **Healing by first intention:** wounds with clean opposing edges (surgical incision)
- **Healing by second intention:** wounds with separated edges (trauma that requires abundance of granulation tissue for wound closure)
  - Granulation tissue consists of newly formed blood vessels, macrophages, fibroblasts and loose ECM framework
  - As collagen accumulation increases, the granulation tissue scaffolding is converted into a mature scar composed of mature spindle-shaped fibroblasts, dense collagen and elastic fibers.
  - The mature scar does not contain vessels