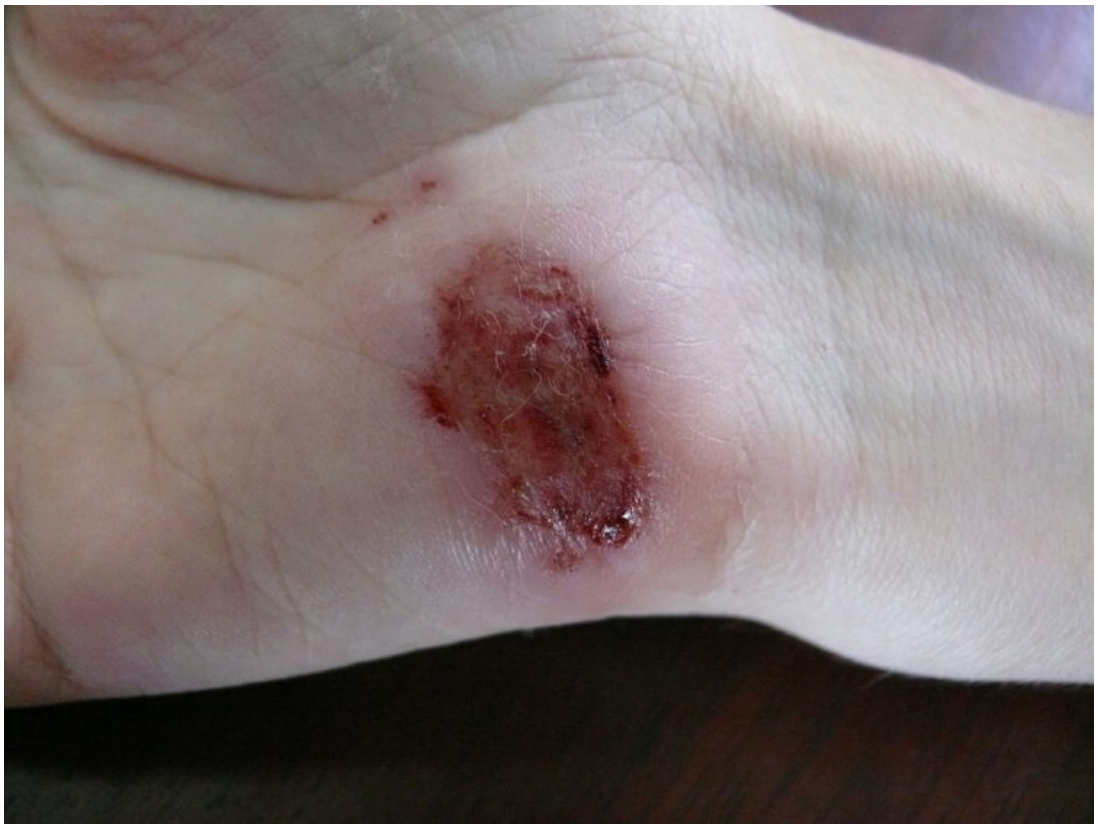
# Stages of Wound Repair and Types of Wound Healing

See online here

**A wound is the loss of the normal integrity of the skin and underlying soft tissue leading to a devitalized structure. Wounds can result from a skin injury, such as in the case of surgery, puncture wounds and abrasions or can be secondary to skin necrosis as a result of ischemia or pressure. People with diabetes mellitus, peripheral ischemia, venous stasis, infection and bad nutritional status are vulnerable to wounds due easy skin disruption and difficult healing processes that may lead to chronic ulcers. The process of wound healing occurs to protect the underlying structures from infection or blood loss. Wound healing occurs through several physiological stages in healthy individuals that include hemostasis, inflammation, epithelialization (granulation) or proliferation and finally fibroplasia or remodeling.**



## Definition of Wound Healing

It is a complex process involving the regeneration of damaged and lost cells and tissues.

# Pathophysiology and Stages of Wound Repair

## Hemostasis

This is the immediate stage following an injury.

Hemostasis starts with **vasoconstriction** of a blood vessel and a **platelet plug** that activates more platelets. Vasoconstriction limits blood loss. The intrinsic and extrinsic **clotting cascade** is activated by platelets and damaged tissues to form a **fibrin mesh** consisting of platelets, WBCs and RBCs.

Activated platelets release **growth factors, chemokines, and cytokines,** including platelet-derived growth factor and transforming growth factor beta, to help with **cellular proliferation and granulation**. Cytokines released attract the inflammatory cells and initiate the next stage of healing.

## Inflammation

Inflammation comes next in order to clear dead cells, bacteria, and cellular debris with **phagocytes** and **inflammatory cells**. Growth factors are released from these cells to facilitate migration and proliferation of cells to allow **tissue regeneration**.

Fibrin and thrombin increase the vascular permeability and help in the migration of inflammatory cells to the site of injury, thus intravascular cells responsible for healing are released in extravascular space.

**Neutrophils** migrate from circulation and into the intercellular space within hours, guided by a complement system and cytokines. These help to cleanse the wound of pathogens and debris. **Monocytes** leave the circulation to become macrophages, which are responsible for more wound cleaning from dead cells and debris within the first few days after injury. These are the most important cells in healing. Macrophages phagocytize the debris and pathogens. They release many factors responsible for the proliferation of fibroblasts, muscle cells and attract endothelial cells to the site of injury for the formation of vessels.

**Cytokines, tumor necrosis factor (TNF), interlukin-1 and PDGF** are all secreted by macrophages to facilitate growth of fibroblasts, myofibroblasts, smooth muscles cells, epithelial cells and endothelial cells. This stage lasts for a few days after injury with neutrophils acting in 3 days and macrophages in the first week.

## Granulation stage

Granulation tissues consist mainly of **new blood vessels, connective tissue, and collagen**. Collagen in the wound is mainly of type III which converts to type I collagen.

**Fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF) promote angiogenesis and cellular proliferation**.

**Angiogenesis** is the formation of new vasculature with migration and proliferation of endothelial cells to form new capillaries along with basement membrane surrounded by myofibroblasts. Fibroblasts divide and promote contraction of the wound edges to facilitate **epithelialization** from the periphery to the center. This stage can last for a few weeks.

| | |
|---|---|
| **Day 1** | • Fibrin clot (hematoma)<br>• Neutrophils infiltrate |
| **Day 2** | • Squamous cells seal off wound<br>• Macrophages emigrate into wound |
| **Day 3** | • Granulation tissue begins to form<br>• Initial deposition type III collagen<br>• Macrophages replace neutrophils |
| **Days 4-6** | • Peak granulation tissue formation<br>• Fibronectin key glycoprotein |
| **Week 2** | Tensile strength ~10% |
| **Month 1** | • Remodeling of wound (collagenase/lysyl oxidase)<br>• Tensile strength ~80% in 3 months |

## Remodeling

Remodeling is defined as constant changes in the wound starting from after 3 weeks, and may continue up to several years. Remodeling follows along with apoptosis of excess cells and **degradation and alignment** of collagen fibers with skin tension lines. This phase can last for years after injury.

# Factors Affecting Wound Healing

There are several factors which could delay wound healing and lead to **chronic ulcer or scar formation**. These factors include systemic factors and local factors in the wound. **Systemic factors** are diabetes mellitus, vascular and connective tissue diseases, age, nutritional deficiency, smoking and alcohol consumption.

**Local causes** that impair wound healing include presence of foreign bodies within the wound, infection, edema and moisture.

# Types of Wound Healing

There are 3 different types of wound healing: primary closure, delayed primary closure and secondary closure. However, the healing mechanisms of all three are similar to each other.
**Primary closure** or intention occurs with paper cut wounds and surgical incisions where there is a small defect with little risk of complications and infection. All the stages of healing follow smoothly without interruption.

**Secondary closure** occurs when there is a gap or tissue defect in large wounds that prevents the edges from closing by means of primary intention e.g. lacerations, burns, and ulcers. Granulation tissue with new blood vessels and collagen is needed to close the defect or skin loss leading to **scar formation**. Granulation and proliferation take longer time in this type of healing. This type of wound healing poses the **risk of infection** and it needs longer time to close.

**Delayed primary closure** or tertiary intention occurs mainly in wounds that need to be left open to ensure that there was no contamination with organisms, after which the wound is surgically closed. The wound is watched while open for a few days and then closed surgically to heal through primary and secondary intention. Examples of such wounds are dog bites, wounds that have foreign bodies and wounds healing by tissue grafting.

## Complications of Wound Healing

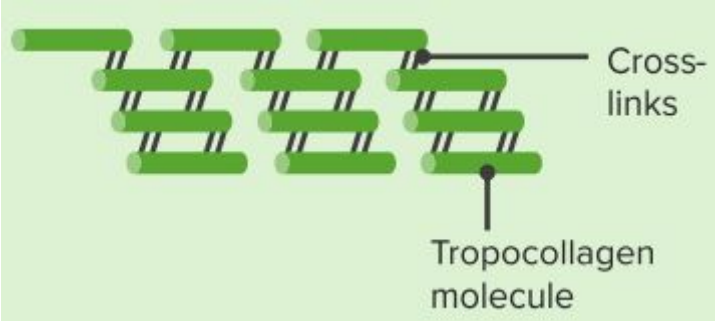
Wound healing can result in **hypertrophic scar or keloid** that is raised above the skin due to the proliferation of fibroblasts. Keloid is different in that it extends beyond the borders of the wound site with irregular dense collagen fibers and is usually painful. Keloids are not common in people of white origin dark-skinned people are at higher risk of developing keloids. Hypertrophic scar stays within the limits of borders of the wound and they regress spontaneously. These are seen immediately after injury while keloids may be seen years after injury.

**Hypotrophic or atrophic scars** occur as a depression in the wound site due to scanty collagen such as in the case of acne and some viral infections. Rapid healing of the wound will affect scar size. The more rapid the healing process is, the lesser the size of the scar will be.

**Long-term complications include hypo- or hyperpigmentation**, **calcification and incisional hernia**.

Other complications include excess contracture as in burns, joint contractures and wound dehiscence due to defective granulation.

## Impaired Healing




"Impaired Healing. Vitamin C deficiency" Image created by Lecturio

**Infection –** Staphylococcus aureus

**Diabetes –** Infection, blood flow

**Poor nutrition –** Infection, protein

**Vitamin C deficiency –** Cross-links (areas of hydroxylation)

**Metal deficiency –** Zinc (collagenase), copper (lysyl oxidase)

**Glucocorticoids –** Collagen synthesis; scar in bacterial meningitis/wounds

## References

**Inflammation and wound healing: the role of the macrophage** via nih.gov

**Inflammation** via wikipedia.org

Charles N. Serhan, Peter A. Ward, Derek W. Gilroy. 2010: **Fundamentals of Inflammation.**

**Inflammation in Wound Repair: Molecular and Cellular Mechanisms**. Journal of Investigative Dermatology or via nih.gov

woundeducators.com

**Woundhealing and repair** via medscape.com

**Wound healing** via wikipedia.org

**Wound healing and risk factors for non-healing** via uptodate.com



Notes