WOUND HEALING

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Healing is the body's response to injury in an attempt to restore normal structure and function.

Wound healing is a complex biologic response that ultimately results in a mature scar.

We appreciate the importance of wound healing when we come to face all the unwanted outcomes of failure of the healing process.

Many patients suffer for a long time, a lot of money needs to be spent and we even lose patients as a result.

Wound healing is a mechanism whereby the body attempts

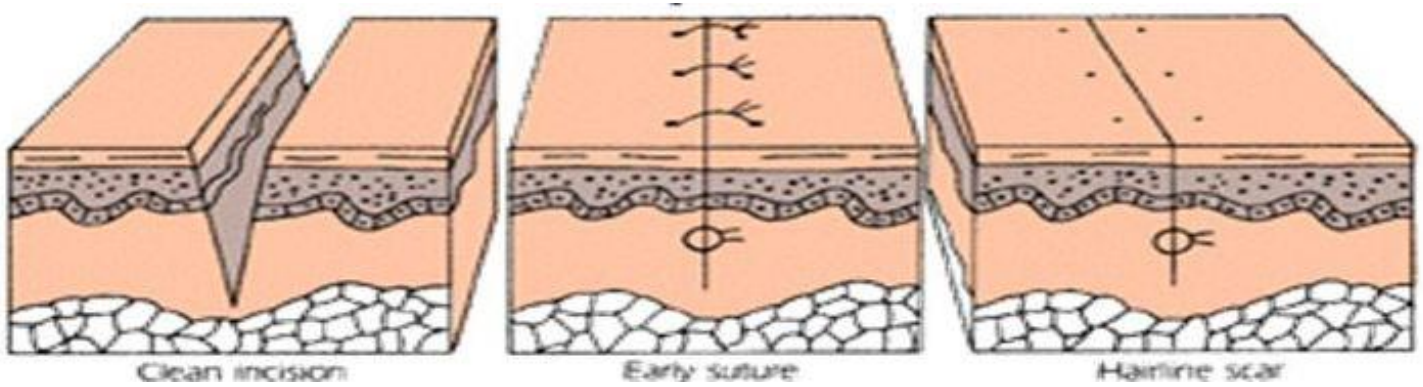
- To restore the integrity and function of the injured part
- To reform a barrier to fluid loss and infection
- To limit further entry of foreign organisms
- To re-establish normal blood and lymphatic patterns

Categories of Wound Healing

- Healing by **primary intention** or primary wound healing
- **Delayed primary healing**
- Healing by **secondary intention**

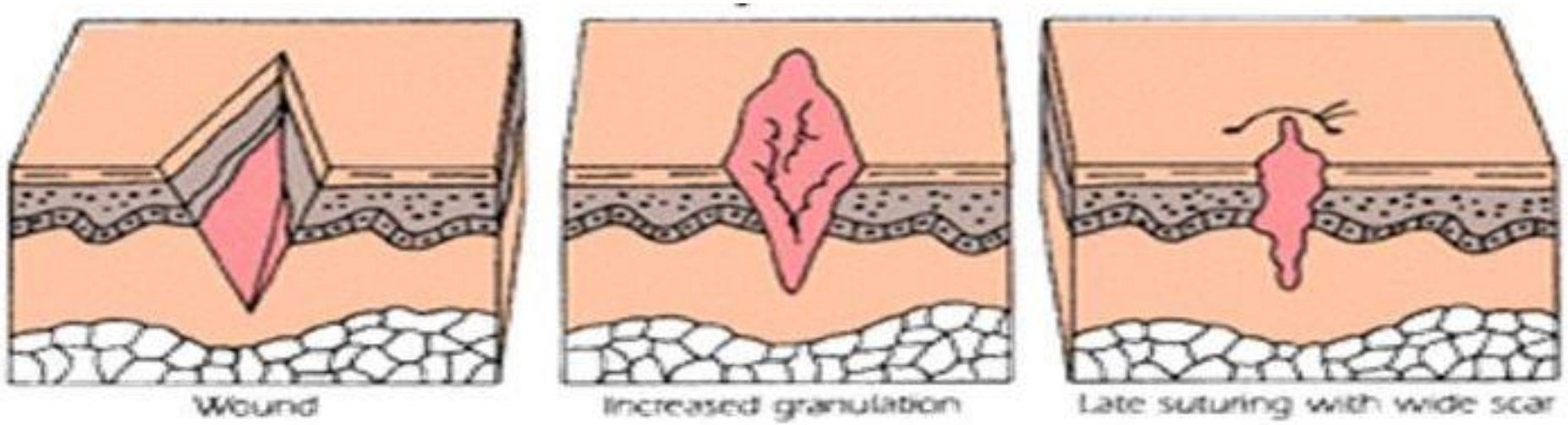
Categories of Wound Healing – Primary Intention

- Wounds are closed by reapproximation using suture or by some other mechanical means within hours of the creation of a full-thickness surgical wound.
- Clean wounds with opposed edges



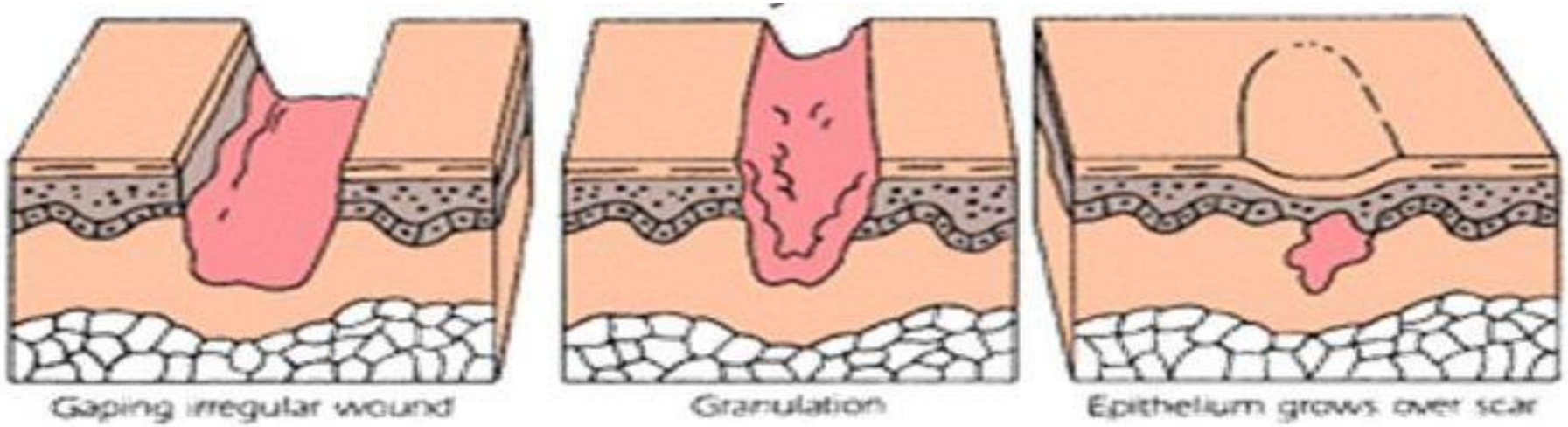
Categories of Wound Healing – Delayed Primary Healing

- To allow normal host defenses to debride the area, contaminated or poorly delineated wounds are left open and unopposed to prevent infection.
- By day 3 postinjury, local inflammatory cell recruitment into the wound has occurred to destroy contaminating bacteria. Furthermore, granulation tissue composed of inflammatory cells, extracellular matrix, and new capillaries begins to form.
- Following a delay of several days, the wound edges are surgically approximated.
- Collagen metabolism is undisturbed and tensile strength develops as if closure had been immediate.


Wound
Increased granulation
Late suturing with wide scar

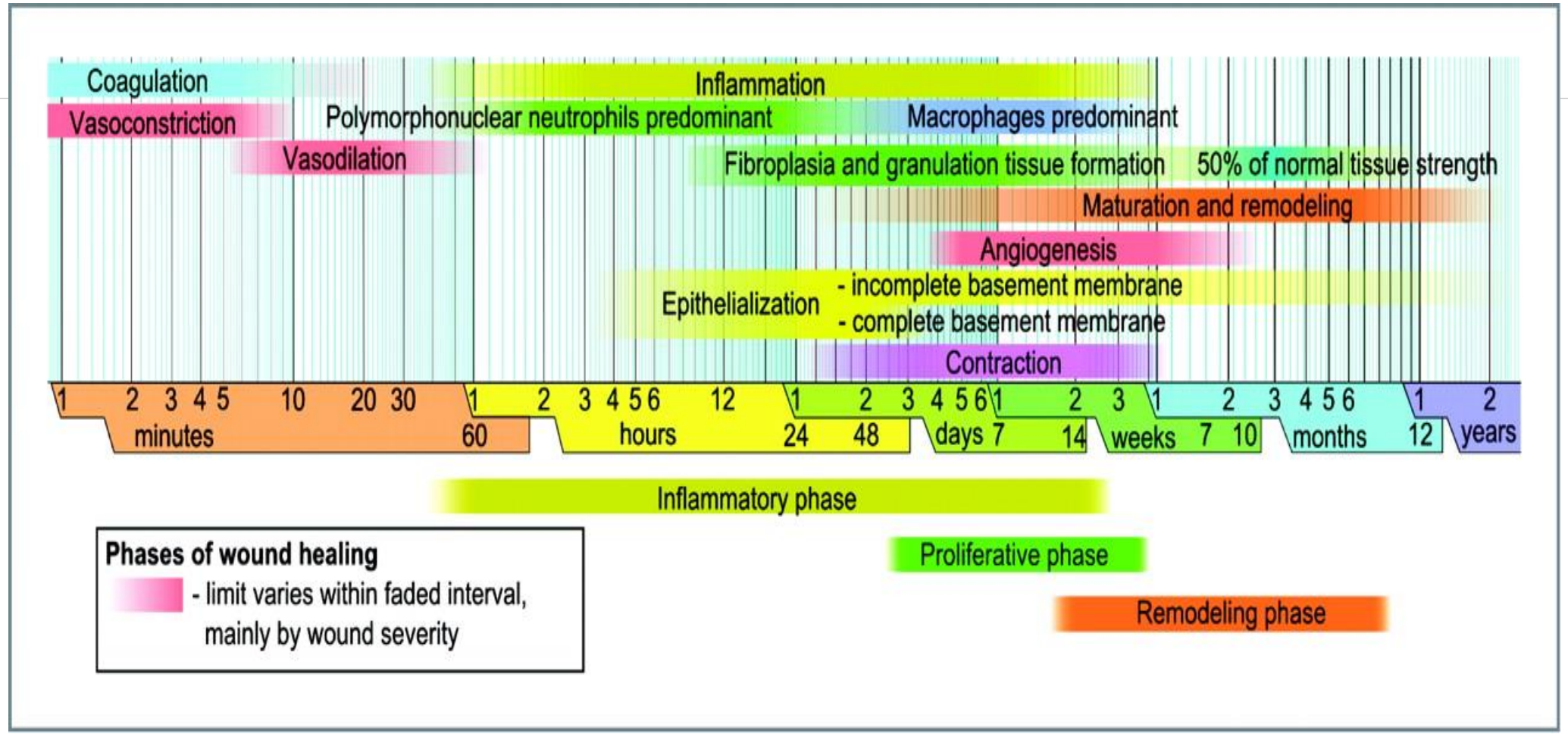
Categories of Wound Healing – Secondary Intention

- An open full-thickness wound is allowed to close by both wound contraction and epithelialization.
- It results in an inflammatory response that is more intense than with primary wound healing.
- A larger quantity of granulomatous tissue is produced because of the need for wound closure.
- Secondary healing results in pronounced contraction of wounds. Fibroblastic differentiation into myofibroblasts, which resemble contractile smooth muscle, is believed to contribute to wound contraction. These myofibroblasts are maximally present in the wound from the 10th-21st days.


Gaping irregular wound
Granulation
Epithelium grows over scar

Phases of Wound Healing

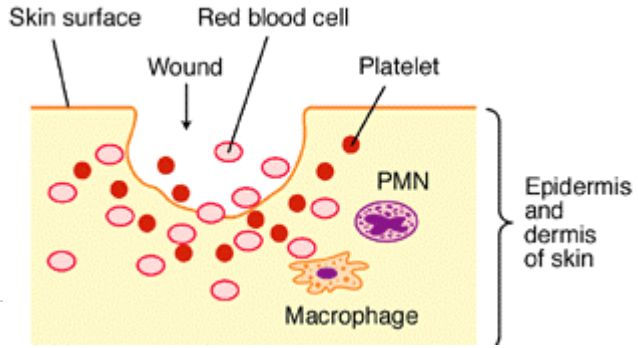
- Several phases define healing, namely, inflammation, proliferation, and remodelling.
- Although in the past these were considered distinct stages, a more accurate conceptualization of tissue repair recognizes that these are overlapping and present in some degree throughout most of the course of a healing wound.


Coagulation
Inflammation
Vasoconstriction
Polymorphonuclear neutrophils predominant
Macrophages predominant
Vasodilation
Fibroplasia and granulation tissue formation
50% of normal tissue strength
Maturation and remodeling
Angiogenesis
Epithelialization
- incomplete basement membrane
- complete basement membrane
Contraction
1 2 3 4 5 10 20 30 1 2 3 4 5 6 12 1 2 3 4 5 6 1 2 3 1 2 3 4 5 6 1 2
minutes 60 hours 24 48 days 7 14 weeks 7 10 months 12 years
Inflammatory phase
Phases of wound healing
- limit varies within faded interval, mainly by wound severity
Proliferative phase
Remodeling phase

Sequence of events in Wound Healing

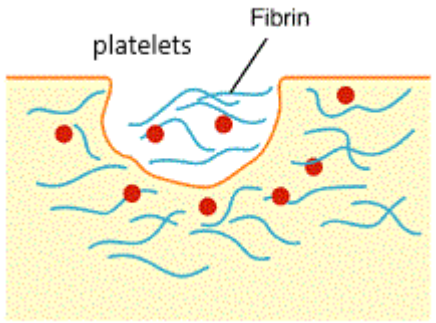
- Injury initiates a regulated sequence of events, including coagulation, inflammation, cell replication, angiogenesis, epithelialization, and matrix synthesis and turnover.
- Vascular injury leads to rapid constriction of affected vessels and activation of the coagulation cascade in order to limit blood loss.
- Inflammatory cells release vasoactive amines and other mediators, which contribute to vessel permeability and the leak of plasma and proteins into the wound and permit effector cells to enter the environment.

Hemostasis-Coagulation

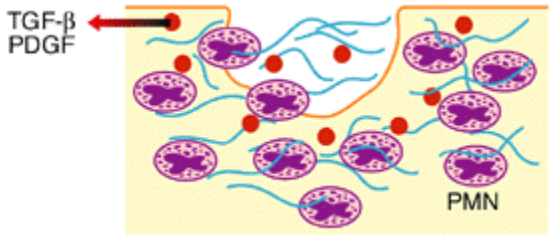


- The initial injury results in an outflow of blood and lymphatic fluid. This is also the process during which the initial reparative coagulum is created.
- Both the i**ntrinsic** and **extrinsic** clotting mechanisms are activated. The intrinsic mechanism is triggered by the platelets and the extrinsic mechanism by the injured tissues.
- Hemostasis, achieved by trapping platelets in the clot, eventually leads to coagulation. These **trapped platelets** are also essential for the normal inflammatory response by releasing **vasoactive amines**. These include serotonin, from dense bodies, and cytokines, including platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), epidermal growth factor (EGF), and platelet factor IV, from their α granules.
- The released **serotonin increases microvascular permeability**, while the **growth factors initiate the wound-healing cascade** by attracting and activating macrophages, fibroblasts, and endothelial cells, and by stimulating granulation tissue formation.

- **Fibrin** is the end product of both the intrinsic and extrinsic coagulation pathways**.** Derived from factor I, also known as fibrinogen, fibrin is essential to early wound healing because it provides the **matrix foundation** into which cells can migrate.
- In addition, fibrin can also serve as a reservoir for peptide growth factors. This infrastructure consists of fibronectin and traps platelets, bloodborne cells, and plasma proteins.
- Removal of the fibrin provisional matrix is known to impede wound repair.

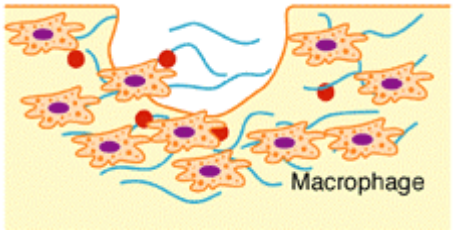


Inflammatory phase



- While the inflammatory phase commences during the hemostasis phase, the early component of the inflammatory phase is predominated by the influx of the polymorphonuclear leukocytes (PMNs) and the later component predominated by monocytes/macrophages.
- Within the first 6-8 hours, PMNs engorge the wound. TGF-β facilitates PMN migration from surrounding blood vessels, where they extrude themselves from these vessels. These cells cleanse the wound, clearing it of debris. The PMNs attain their maximal numbers in 24-48 hours and commence their departure by hour 72. Other chemotactic agents are released, including fibroblast growth factor (FGF), TGF-β and TGF-α, PDGF, and plasma-activated complements C3a and C5a (anaphylactic toxins). They are sequestered by macrophages or interred within the scab or eschar.

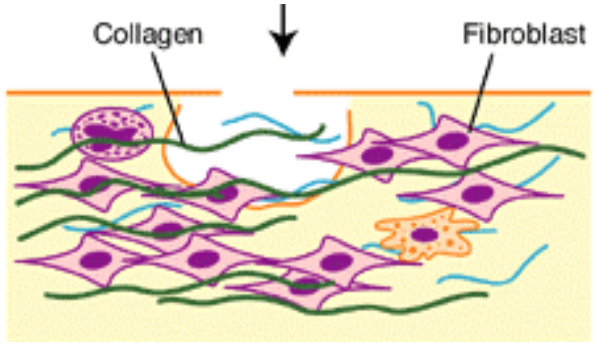
Inflammatory phase- cont.



- As the process continues, monocytes also exude from the vessels. These are termed macrophages once they leave the vessel.
- The macrophages continue the cleansing process and manufacture various growth factors during days 3-4.
- The macrophages orchestrate the multiplication of endothelial cells with the sprouting of new blood vessels and the duplication of smooth muscle cells.
- Many factors influencing the wound healing process are secreted by macrophages. These include TGFs, cytokines and interleukin (IL)–1, tumor necrosis factor (TNF), and PDGF.
- Limited numbers of lymphocytes arrive later, but their significance is unknown.

Proliferation

- This phase consists of different subphases.
  - fibroplasia
  - matrix deposition
  - angiogenesis
  - re-epithelialization
- These subphases do not happen in discrete time frames but constitute an overall and ongoing process.



Proliferation
Fibroplasia

- In days 5-7, fibroblasts have migrated into the wound, laying down new collagen of the subtypes I and III. Early in normal wound healing, type III collagen predominates but is later replaced by type I collagen.

Proliferation

Matrix deposition

- The wound is suffused with GAGs and fibronectin produced by fibroblasts. These GAGs include heparan sulfate, hyaluronic acid, chondroitin sulfate, and keratan sulfate. Proteoglycans are GAGs that are bonded covalently to a protein core and contribute to matrix deposition along with collagen.

Proliferation
Angiogenesis

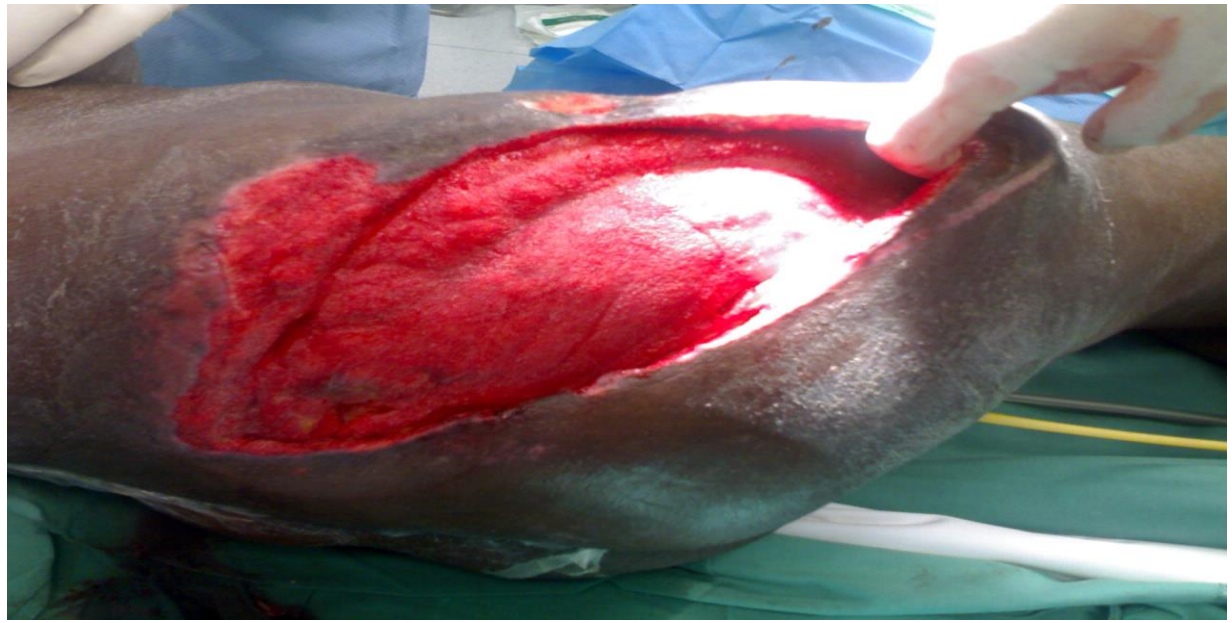
- Angiogenesis, stimulated by TNF- α is marked by endothelial cell migration and capillary formation.
- The migration of capillaries into the wound bed is critical for proper wound healing (delivery of nutrients).

Proliferation
Epithelialization

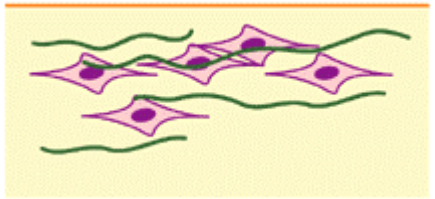
- Epithelialization occurs early in wound repair.
- If the basement membrane remains intact, the epithelial cells migrate upward in the normal pattern. The epithelial progenitor cells remain intact below the wound (in skin appendages), and the normal layers of epidermis are restored in 2 to 3 days.
- If the basement membrane has been destroyed, then epithelial cells located on the skin edge begin proliferating and sending out projections to re-establish a protective barrier.

Granulation tissue:

- It is a fragile structure composed of an extracellular matrix of fibrin, fibronectin, glycosaminoglycans,proliferating endothelial cells, new capillaries, and fibroblasts mixed with inflammatory macrophages and lymphocytes.



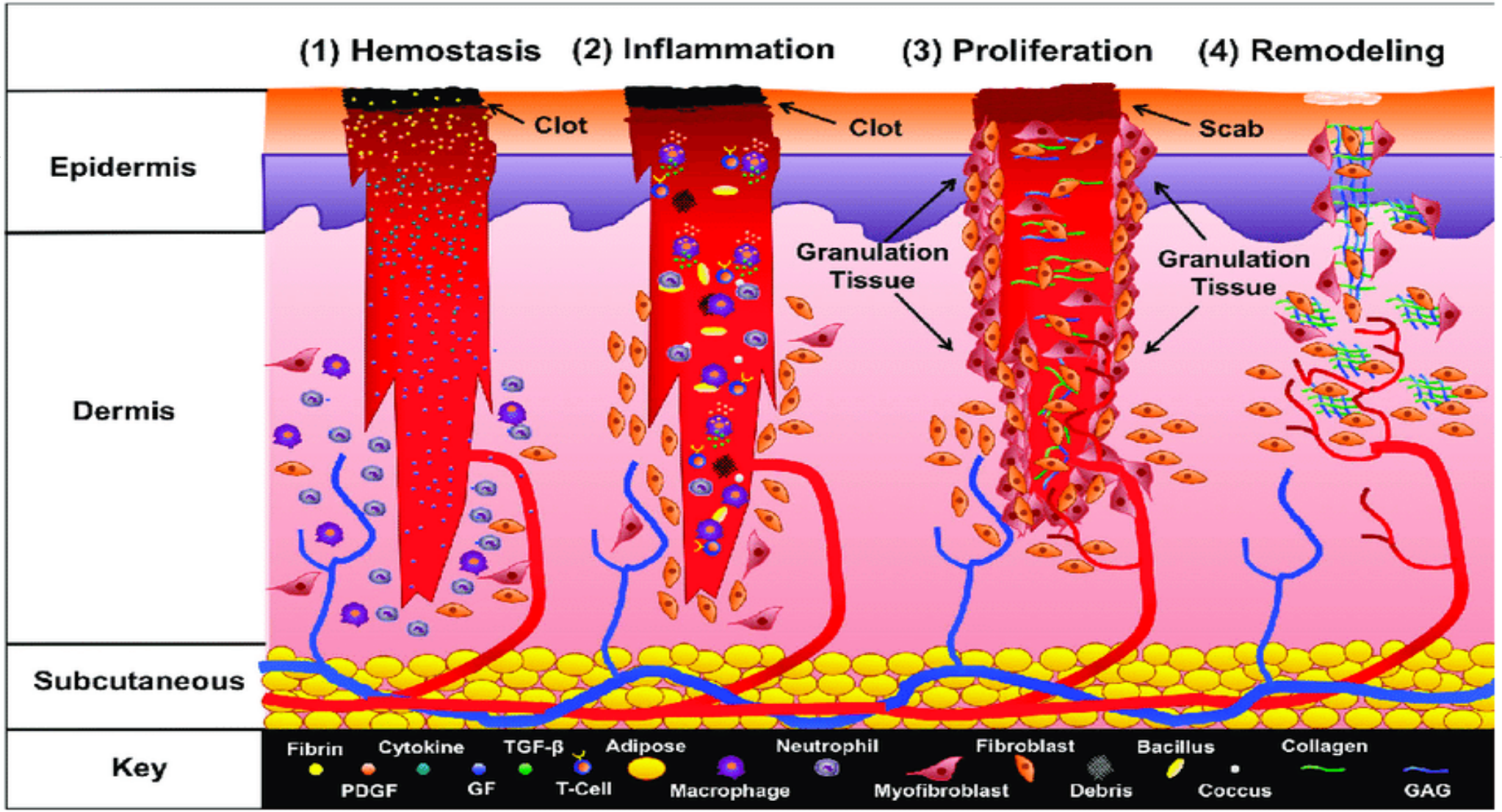
Remodeling



- Clinically, the maturation and remodeling phase is perhaps the most important. The main feature of this phase is the deposition of collagen in an organized and well-mannered network.
- The collagen that is initially laid down is thinner than collagen in uninjured skin and is orientated parallel to the skin. Over time, the initial collagen threads are reabsorbed and deposited thicker and organized along the stress lines. These changes are also accompanied by a wound with an increased tensile strength.
- As the wound matures, type I collagen replaces type III collagen.

Remodeling- cont.

- Contraction of the wound is an ongoing process resulting in part from the proliferation of the specialized fibroblasts termed **myofibroblasts**, which resemble contractile smooth muscle cells.
- Wound contraction occurs to a greater extent with secondary healing than with primary healing.
- Maximal tensile strength of the wound is achieved by the 12th week, and the ultimate resultant scar has only 80% of the tensile strength of the original skin that it has replaced.
- The process takes more than 6 months up to 2 years (!scar revision)


(1) Hemostasis
(2) Inflammation
(3) Proliferation
(4) Remodeling
Epidermis
Dermis
Subcutaneous
Key
Clot
Clot
Scab
Granulation Tissue
Granulation Tissue
Fibrin
Cytokine
TGF-β
Adipose
Neutrophil
Fibroblast
Bacillus
Collagen
PDGF
GF
T-Cell
Macrophage
Myofibroblast
Debris
Coccus
GAG

Factors affecting wound healing

- **Local factors:**
  - i. Infection – increased collagen breakdown and decreased epithelialization.
  - ii. Presence of necrotic tissue and foreign body
  - iii. Poor blood supply – inhibits collagen production, encourages infection
  - iv. Venous or lymph stasis - edema
  - v. Tissue tension
  - vi. Hematoma
  - vii. Large defect or poor apposition
  - viii. Recurrent trauma
  - ix. X-ray irradiated area - ischemic due to vascular fibrosis, less collagen production
  - x. Site of wound, eg.wound over the joints and back has poor healing
  - xi. Underlying diseases like osteomyelitis and malignancy

Factors affecting wound healing

- **Systemic factors:**
  - i. Age, obesity, smoking
  - ii. Malnutrition, zinc, copper
  - iii. Vitamin deficiency (vit C, vit A)
  - iv. Anemia
  - v. Malignancy
  - vi. Jaundice
  - vii. Diabetes – micro- macroangiopathy
  - viii. Hypothyroidism
  - ix. HIV and immunosupressive diseases
  - x. Steroids and cytotoxic drugs - Inhibit the inflammatory phase & collagen synthesis

Fetal wound healing

- Skin (but not all fetal tissue) heals by regeneration without scarring. This is limited to the first two trimesters.
- Many aspects of fetal tissue and the fetal environment may contribute to scarless healing.
  1. The fetal environment (amniotic fluid) is sterile.
  2. Amniotic fluid contains growth factors and extracellular matrix molecules.
  3. The inflammatory phase is minimal, and macrophages may or may not be the main organizing cells in the healing process in the fetus.
  4. The growth factor and cytokine milieu is different in the fetus, although the significance of any particular difference is unclear.

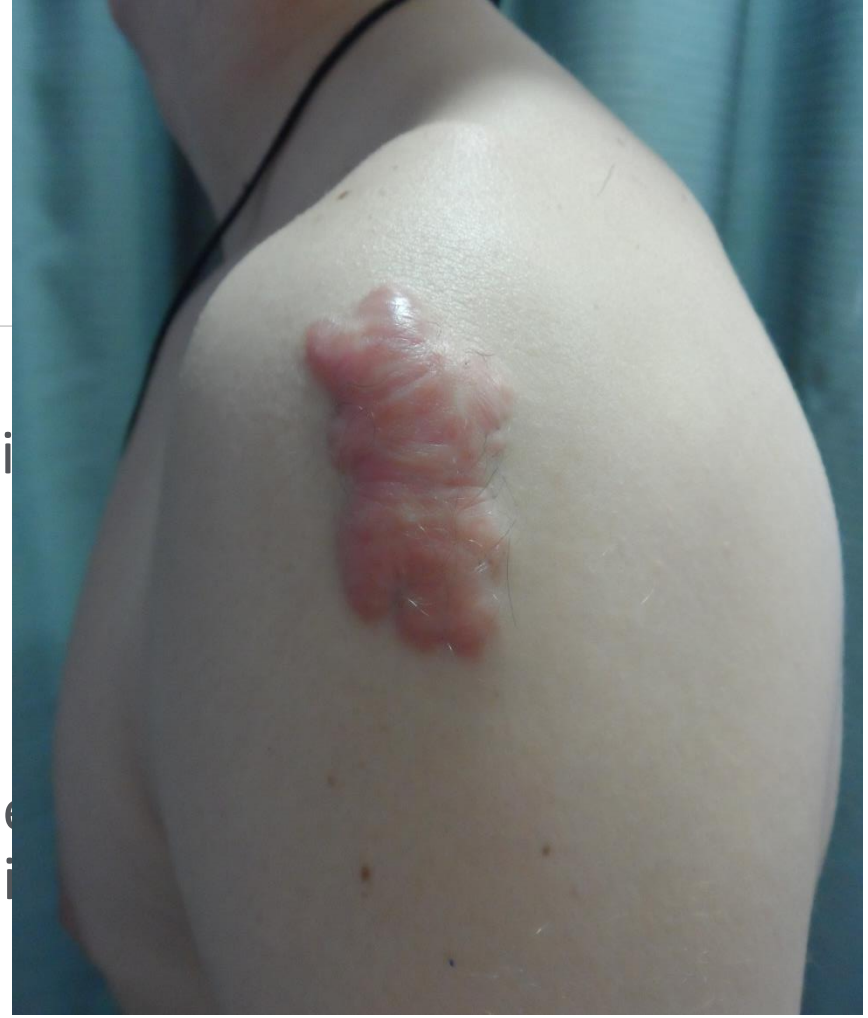
Complications

- **Deficient scar formation**:
  - Wound dehiscence
- **Excessive formation of the repair components**:
  - Aberrations of growth: hypertrophic scar & keloid
  - Excessive amount of granulation tissue formation
- **Infection**
- **Contractures**

Excessive Wound Healing

- Keloids - Excessive scar formation: Defined by scar ti
  the boundaries of the incision or wound.

- Hypertrophic scars - Excessive scar formation: Define
  does not extend beyond the boundaries of the incisi



Excessive Wound Healing
Keloids

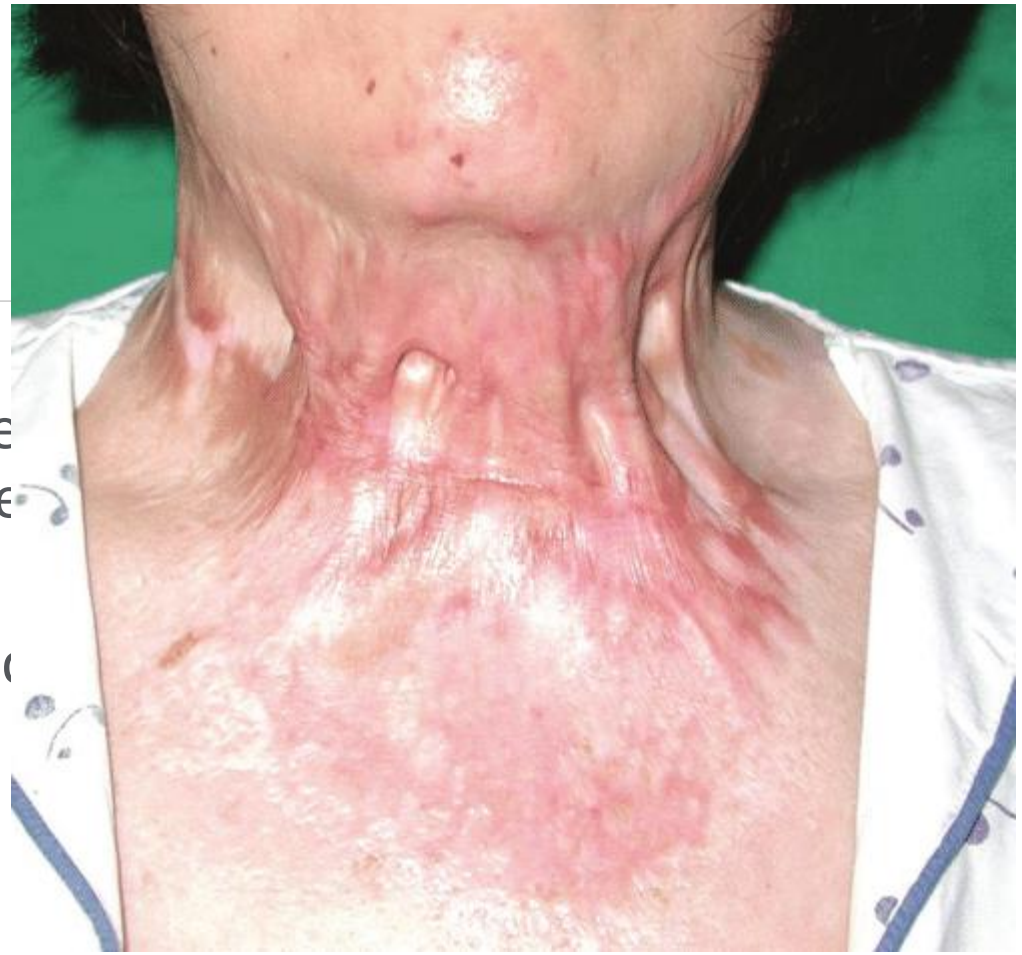
- Not completely understood, but growth factors certainly play a role. Keloids contain elevated levels of TGF-β.
- More common in patients of African ancestry.
- Common in ear lobes and areas of tension.
- Keloids may develop months to a year after injury, and do not resolve spontaneously.
- Excess collagen, and increased vascularity compared with normal scar tissue. Collagen production is many times that seen in normal scar tissue, and there is a higher proportion of type III collagen.
- Excision alone is rarely successful.
- Corticosteroid injection may cause some reduction in keloid size.
- Recurrence is common.

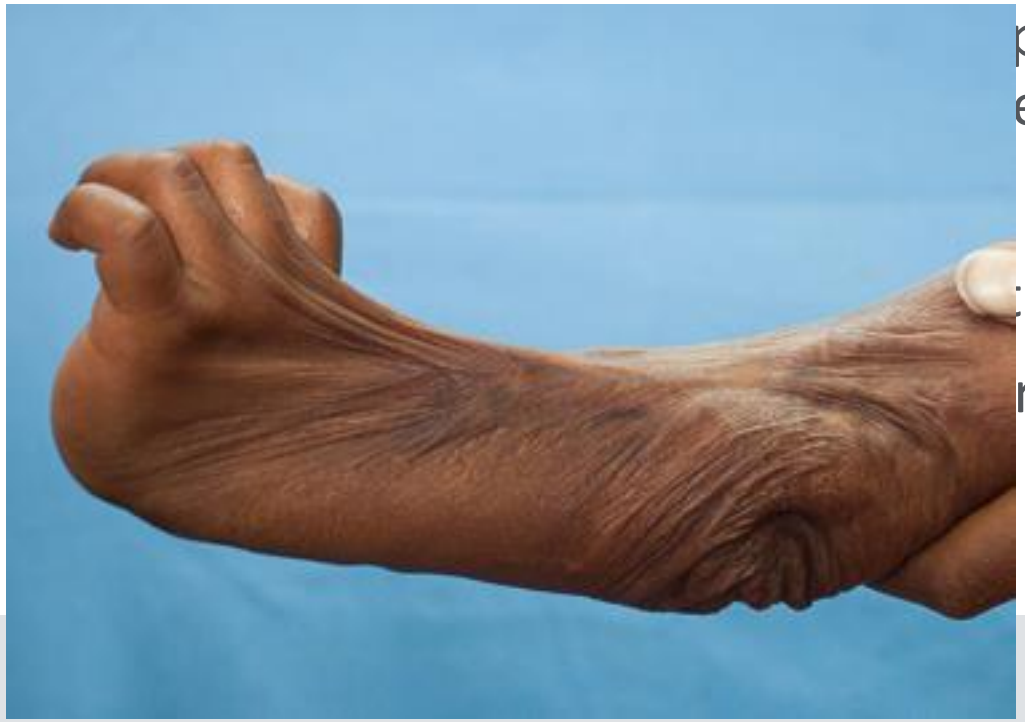
Excessive Wound Healing
Hypertrophic scars

- Prolonged or increased inflammatory phase of healing. Increased wound tension.
- More common in patients of African ancestry.
- Tendency decreases with age, as the inflammatory phase of healing decreases.
- More common in areas of tension, such as the presternal area.
- Develop within weeks of wounding (during the inflammatory phase), and there is usually some degree of improvement with time.
- Increased collagen with collagen nodules, hypervascularity. Collagen production is increased compared with normal scar tissue, but less than in keloids.
- Corticosteroid injection, silicone sheeting, and pressure are often successful in reducing the degree of scar hypertrophy. Multiple treatments with corticosteroids may be required, and silicone sheeting and pressure garments must be applied for at least 6 months before improvement is seen.
- Surgical excision and reclosure may be successful if nonsurgical modalities are not working, and if the wound can be closed without tension.

Excessive Wound Healing Contractures

- A scar contracture is the result of contractile
  occurring in a scar that has already been re-e
  healed.





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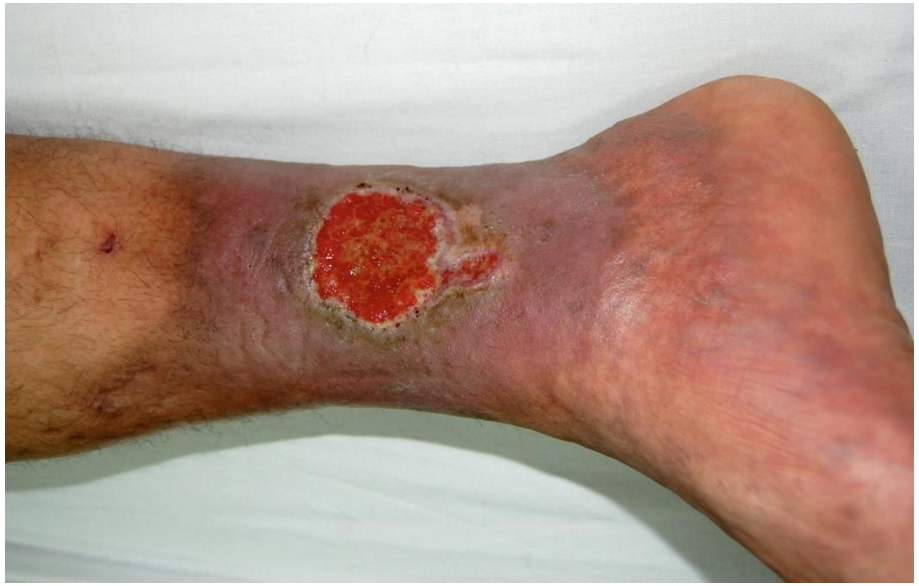
Chronic wounds

- A chronic wound is one that has failed to progress through the phases of healing in an orderly and timely fashion and has **shown no significant progress toward healing** after 3 months.
- Factors contributing to the chronicity of the wound may include:
  - Pressure, trauma and/or lower extremity wounds
  - Increased bacterial load
  - Excessive proteases: Degraded growth factors, matrix metalloproteinases (MMPs), degraded cell surface structures
  - Senescent/Aberrant cells
  - Inappropriate treatment

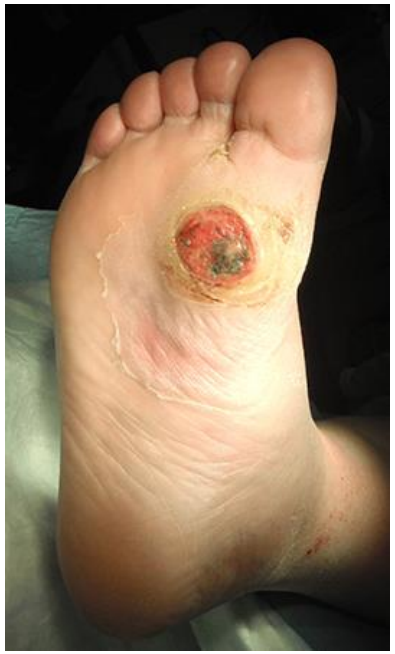
Ulcers
Venous – Diabetic -Pressure

- **Venous ulcers** - lower extremities of elderly patients caused by problems with blood circulation due to dysfunctional blood valves.



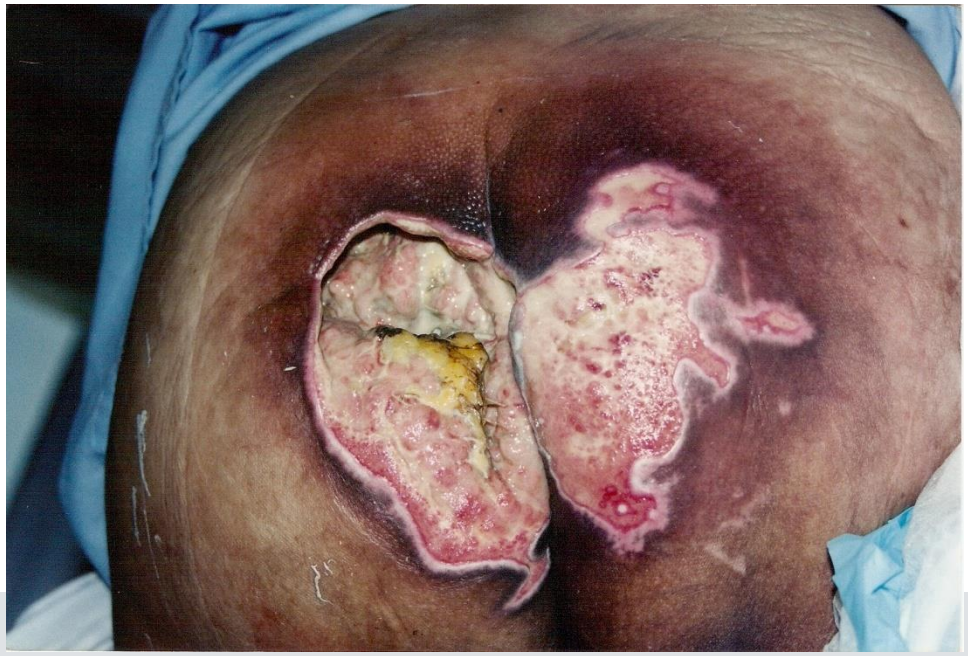
Ulcers

- **Diabetic ulcers** – micro-macroangiopathy, peripheral neuropathy



Ulcers

- **Pressure ulcers** - bedridden or limited mobility. The constant pressure on the tissue over powers the pressure of the capillaries, affecting blood flow. Areas at the greatest risk for pressure ulcers are the sacrum, greater trochanter, scapula and heels.



Wound Care

- Optimize systemic parameters (nutritional status, control diabetes)
- Debride nonviable tissue, remove foreign bodies
- Reduce wound bioburden
- Optimize blood flow (warmth, hydration, revascularisation)
- Reduce edema – elevation, compression, negative pressure therapy
- Appropriate dressings
- Use pharmacologic therapy – (antibiotics, GF)
- Close wounds with grafts/flaps as indicated

Moist Wound Healing

Moist wound healing is the practice of keeping a wound in an optimally moist environment in order to promote faster healing.

- Wound Healing Takes Less Time (3-5 x less)
- Keratinocyte Cells Function More Easily
- Autolytic Debridement is Facilitated
- Decreases Incidence of Wound Infection
- Preserves Growth Factors in Wound Fluid
- Stimulates Collagen Synthesis
- Reduces Pain
- Reduces Scarring

Dressings

- Absorption characteristics: low –hydrogels, moderate - hydrocolloids, high – alginates
- Hydrogels rehydrate wounds
- Hydrocolloids promote wound debridement by autolysis.
- Antimicrobial dressings: silver

Thank You!

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