

Pathology of Inflammation and Repair

LEC.4

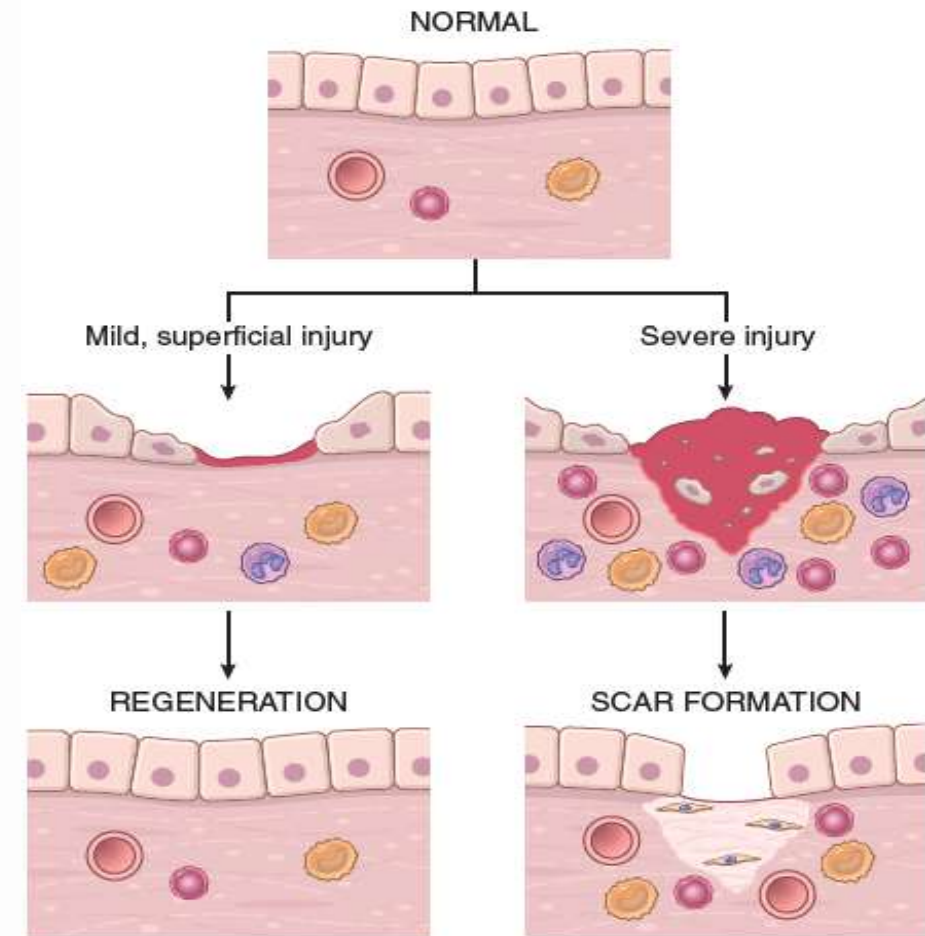
Dr. Raghad Hanoon

Objectives

- Recognize that tissue repair may occur through regeneration and/or scarring.
- Describe the steps of cutaneous wound healing by primary intension and secondary intension.
- List the factors that affect tissue repair and possible complications of tissue repair.

Tissue Repair

- Is the restoration of function and architecture of tissue after an injury.
- Repair begins very early in the process of inflammation and involves two processes:
 1. **Regeneration**; by parenchymal cells of the same type.
 2. **Replacement by connective tissue** (fibrosis & scarring).
- Both processes involve the **proliferation of various cells, and close interactions between cells and the extracellular matrix (ECM)**.
- Both regeneration and fibrosis are **controlled by soluble growth factors**.



Growth factors

- They are **polypeptides** circulating in the blood or produced locally by the cells.
- Mainly secreted by the **macrophage** that are activated by tissue injury.
- Most of growth factors have pleiotropic effect (stimulate cellular proliferation, cell migration, differentiation & tissue modeling).
- Some growth factors act on multiple cell types & others are cell selective.
- All growth factor activate signaling pathway that stimulate cell division.

➤ Examples of Growth factors:

- Epidermal growth factor (EGF), Platelets derived growth factor (PDGF), Fibroblast growth factor (FGF), Vascular endothelial growth factor (VEGF), Transforming growth factor (TGF- β), Cytokines (IL-1, TNF).

1. Cell and Tissue Regeneration

- The process by which some tissue are able to replace the damage component and return to normal state.
- Regeneration occur by proliferation of cells that **survive the injury & have ability to generate the mature cells** of that tissue.
- Cell proliferation is stimulated by growth factors & interactions of cells with the extracellular matrix.
- The regenerated cells are either **mature differentiated cells or tissue stem cell**.

- According to regenerative capacity of cells, we have **three types of cells** in our body:
 1. **Labile (continuously dividing) tissues:** Cells of these tissues are continuously being lost and replaced by maturation from tissue stem cells and proliferation of mature cells e.g., **hematopoietic cells, surface epithelial cells e.g. skin epidermis, mucosal lining of gastrointestinal tract.** These tissues can readily regenerate after injury as long as the stem cells are preserved.
 2. **Stable tissues:** Cells of these tissues are quiescent (in the G0 stage of the cell cycle) with minimal proliferative activity in the normal state, but can divide in response to injury or loss of tissue mass e.g. **parenchyma of most solid organs e.g. liver, kidney; also endothelial cells, fibroblasts, smooth muscle cells.** Generally limited capacity to regenerate after injury except for liver.
 3. **Permanent tissues:** Cells of these tissues are generally terminally differentiated and non- proliferative e.g. **majority of neurons, cardiomyocytes and skeletal muscles.** Repair is therefore typically dominated by scar formation.

Mechanisms of tissue regeneration

- **In labile tissues**, such as the epithelia of the intestinal tract and skin, injured cells are rapidly replaced by **proliferation of residual cells and differentiation of tissue stem cells** provided the **underlying basement membrane is intact**.
- **The residual epithelial cells produce the growth factors** involved in these processes. The newly generated cells migrate to fill the defect created by the injury and tissue integrity is restored.
- Tissue regeneration can occur in parenchymal organs with **stable cell** populations, but this process is **usually limited**, **except in the liver**.
- **Pancreas, adrenal, thyroid, and lung have some regenerative capacity.**
- **Surgical removal of a kidney** elicits in the remaining kidney a compensatory response that consists of both **hypertrophy and hyperplasia** of proximal duct cells.
- Mechanisms underlying this response are not understood, but likely involve local production of growth factors and interactions of cells with the ECM.
- **Extraordinary capacity of the liver to regenerate** has made it a valuable model for studying this process.

Liver Regeneration

- The human liver has a remarkable capacity to regenerate, as demonstrated by its growth after partial hepatectomy.
- Liver regeneration occurs by **two major mechanisms**, one of which may be dominant depending on the nature of the injury:

1. Proliferation of remaining hepatocytes:

- In humans, resection of up to 90% of the liver can be corrected by proliferation of the residual hepatocytes. This process is driven by cytokines such as **IL-6** produced by Kupffer cells, and by growth factors such as **hepatocyte growth factor (HGF)** produced by many cell types.

2. Repopulation from progenitor cells (stem cells):

- Occurs when the proliferative capacity of hepatocytes is impaired such as after chronic liver injury or inflammation, **Progenitor cells may reside in canals of Hering**. The exact mechanism is still being investigated.

2. Repair by scarring (Fibrosis)

- If repair cannot be accomplished by regeneration alone, there is replacement of the injured cells with **connective tissue**, leading to the formation of scar.

➤ Scarring occur in the following situation:

1. Tissue injury is **sever or chronic** with damage to **parenchymal cell & epithelia** as well as the **connective tissue frame work**.
2. **Non dividing** cells are injured.
 - Scar formation is a response that **patch** rather than restore the tissue.
 - Scarring in lung, liver, kidney & other parenchymal organ refers to as **fibrosis**

Steps in Scar Formation

- Repair by connective tissue deposition consists of sequential processes that **follow tissue injury** and the **inflammatory response**.

1. Angiogenesis;

- **Is the formation of new blood vessels, which supply nutrients and oxygen needed to support the repair process.**
- Several factors induce angiogenesis, but the most important are **VEGF**, which acts through VEGFR-2 to mobilize endothelial cell precursors from the bone marrow and to induce proliferation and motility of these cells at the sites of angiogenesis.

2. Formation of granulation tissue;

- Migration and proliferation of fibroblasts and deposition of loose connective tissue, together with the vessels and interspersed leukocytes, form granulation tissue.
- The term granulation tissue derives from its **pink, soft, granular gross appearance**.
- Its **histologic appearance** is characterized by proliferation of **fibroblasts** and new **thin-walled, delicate capillaries** (angiogenesis), in a loose extracellular matrix (**edematous stroma**), often with admixed inflammatory cells, mainly **macrophages**.
- Granulation tissue progressively invades the site of injury; the amount of granulation tissue that is formed depends on the size of the tissue deficit created by the wound and the intensity of inflammation.

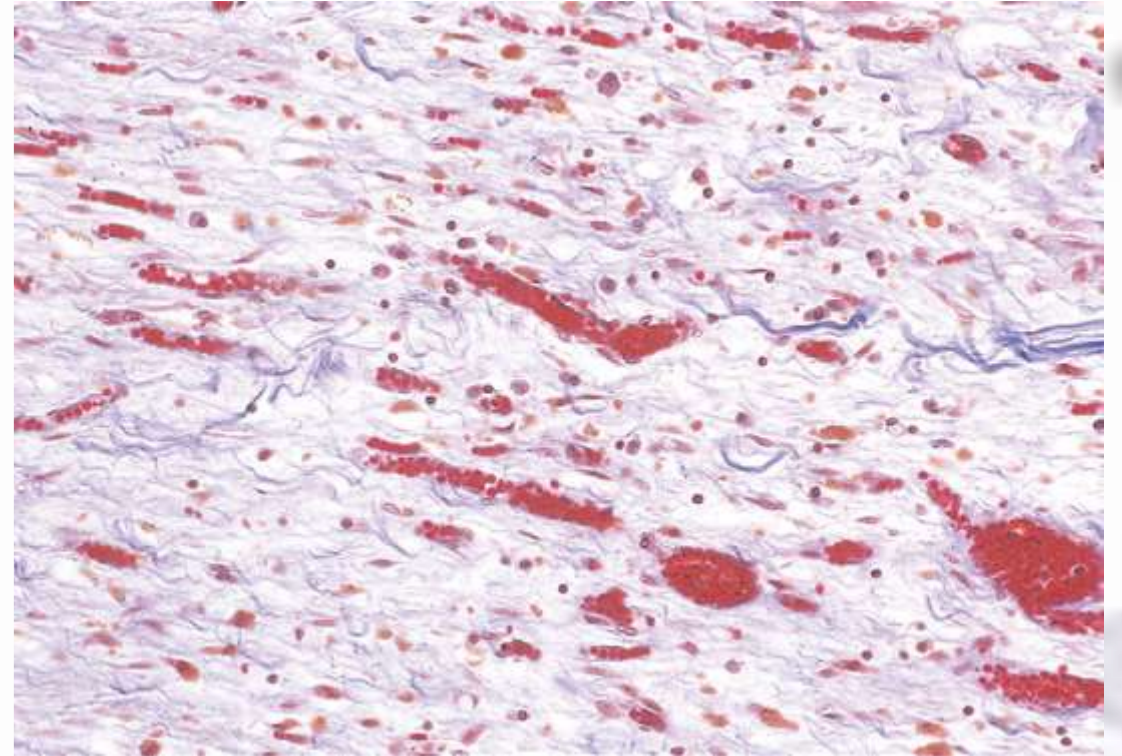
3. Remodeling of connective tissue;

- **Maturation and reorganization of the connective tissue** (remodeling) produce the stable fibrous scar.

Granulation tissue



Gross: Pink, soft, granular.



Mic.: Small blood vessels, fibroblasts, edematous stroma & macrophages.

Examples on tissue repair and fibrosis:

1. Healing of Skin Wounds
2. Fibrosis in injured parenchymal organ

1. Healing of Skin Wounds

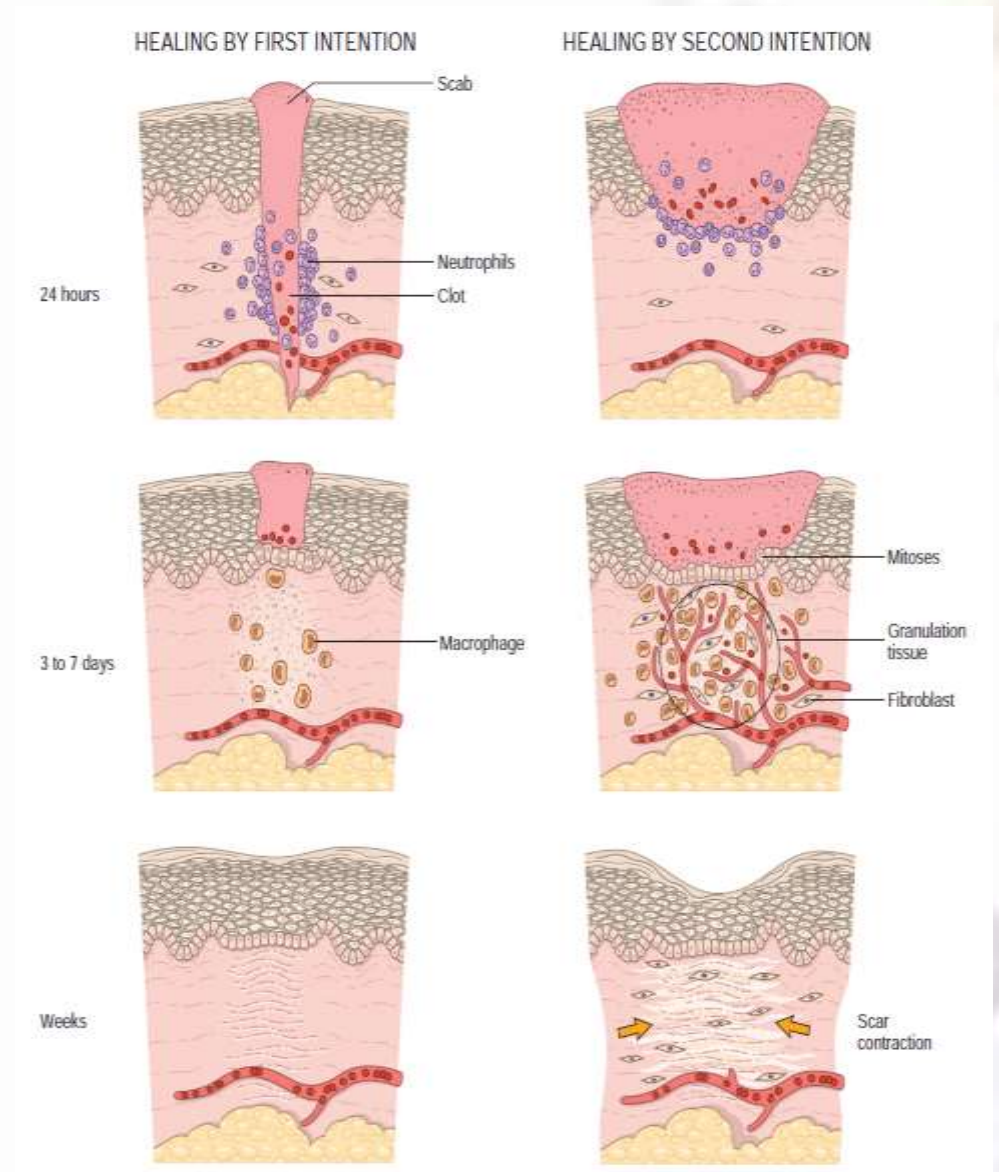
- Based on the **nature and size of the wound**, the healing of skin wounds is said to occur by first or second intention

➤ Healing by first intention (primary union):

- This is the healing of a **clean, uninfected wound with limited tissue loss** e.g. surgical incision.
- Here the epithelial proliferation predominates over fibrosis.
- **Wounding rapidly activates coagulation pathway, forming a blood clot on the wound surface**
- **Within 24 hours: neutrophils** reach the incision margin and migrate toward the fibrin clot; basal layer of epidermis showing mitosis.
- **Within 24–48 hours:** epithelial cells migrate and proliferate from both edges, forming a **thin continuous layer that closes the wound**.
- **Day 3:** neutrophils are largely replaced by macrophages; **granulation tissue** invades the incision, clearing debris and promoting angiogenesis and ECM deposition.
- **Day 5:** neovascularization peaks and **granulation tissue** fills the space; vessels are leaky, causing edema; fibroblasts migrate and lay down collagen.
- **Second week: Continuous** collagen accumulation and fibroblast proliferation and **decrease** leucocytes infiltration, edema & vascularity.
- **End of month 1: the scar** is cellular connective tissue with few inflammatory cells, covered by near-normal epidermis; tensile strength gradually increases.

➤ Healing by second intention (secondary union):

- Occur in wound with excess tissue loss e.g. infarction, ulceration.
- **Differ from first intention:**
 1. The fibrin clot is larger, and there is more exudate and necrotic debris in the wounded area.
 2. More inflammation because of more tissue loss.
 3. More granulation tissue formation.
 4. **Wound contraction** that narrows the gap between dermal edges and reducing surface area. It occurs by myofibroblasts. Within 6 weeks, large skin defects may shrink to 5–10% of their original size.



Steps in wound healing by first intention (left) and second intention (right). In the latter, note the large amount of granulation tissue and wound contraction.

Factors affect the wound healing

- Tissue repair may be impaired by a variety of factors that reduce the quality or adequacy of the reparative process. Factors that interfere with healing may be extrinsic (e.g. infection) or intrinsic to the injured tissue, and systemic or local;
- **Infection:** Clinically one of the **most important causes of delayed healing**. Prolongs inflammation and likely increases local tissue injury.
- **Diabetes:** Metabolic disease-causing impaired tissue healing for various reasons (**macro and microangiopathy, prone to infections**).
- **Nutritional status:** **Protein deficiency and vitamin C deficiency** inhibit collagen synthesis and retard healing.
- **Glucocorticoids (steroids):** Anti-inflammatory effects may cause scar weakness due to **inhibition of TGF- β** , although may be useful in certain circumstances e.g. to reduce scarring.

- **Mechanical factors:** e.g. Increased local pressure, torsion, causing **wound dehiscence**.
- **Poor vascular perfusion:** e.g. due to peripheral vascular disease, arteriosclerosis, diabetes, obstructed venous drainage in varicose veins.
- **Foreign bodies:** perpetuates chronic inflammation.
- **Type and extent of tissue injury:** Injury to permanent tissues will always result in scarring.
- **Location of injury:** in tissue spaces e.g. serous cavities, inflammation results in extensive exudates, which can either undergo resolution (via proteolytic digestion and resorption) or organization (when granulation tissue grows into the exudate and fibrous scarring occurs).

Complications of wound healing

- Complications in wound healing can arise from abnormalities in any of the basic components of the repair process.
- These complications can be grouped into three general categories:
 1. Defects in Healing
 2. Excessive Scarring
 3. Formation of contractures

1. Defects in Healing

- Inadequate formation of granulation tissue or assembly of a scar can lead to two types of complications: wound dehiscence and ulceration.

➤ Dehiscence or rupture of a wound;

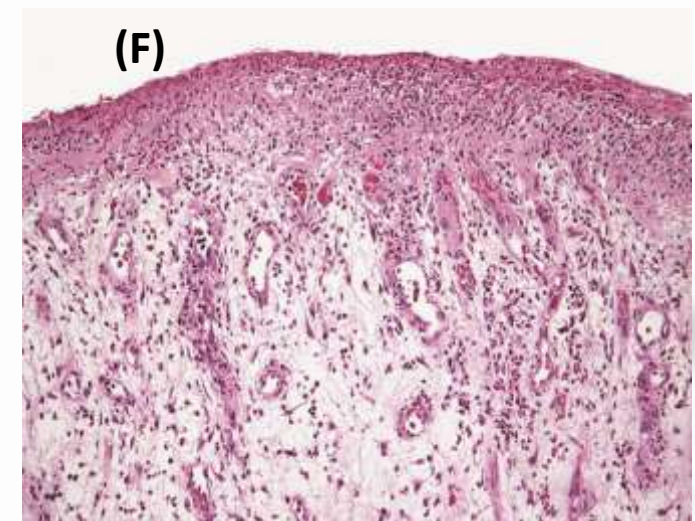
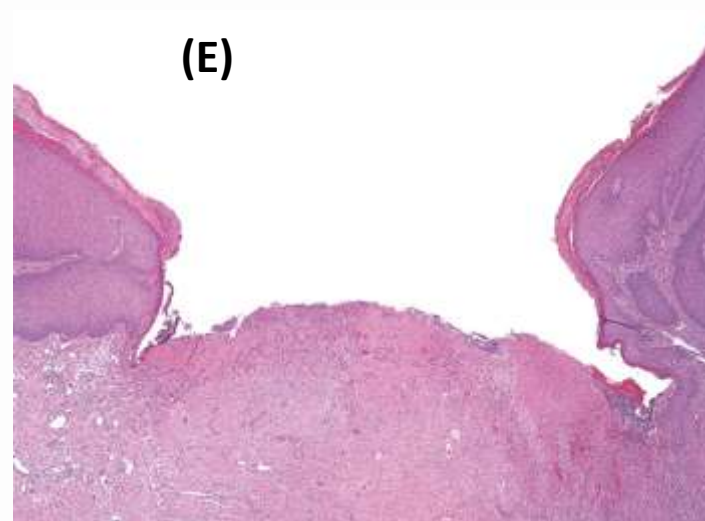
- Is most common after **abdominal surgery** and is due to **increased abdominal pressure** such as vomiting or coughing, can generate mechanical stress on the abdominal wound.



Dehiscence or rupture of a wound

➤ **Ulceration:** is due to inadequate vascularization

- **Venous leg ulcers** (due to venous congestion causing poor oxygenation of local tissues)
- **Arterial ulcers** (in patients with peripheral vascular disease),
- **Diabetic ulcers.**
- **Pressure sores** (due to prolonged mechanical tissue compression and local ischemia).

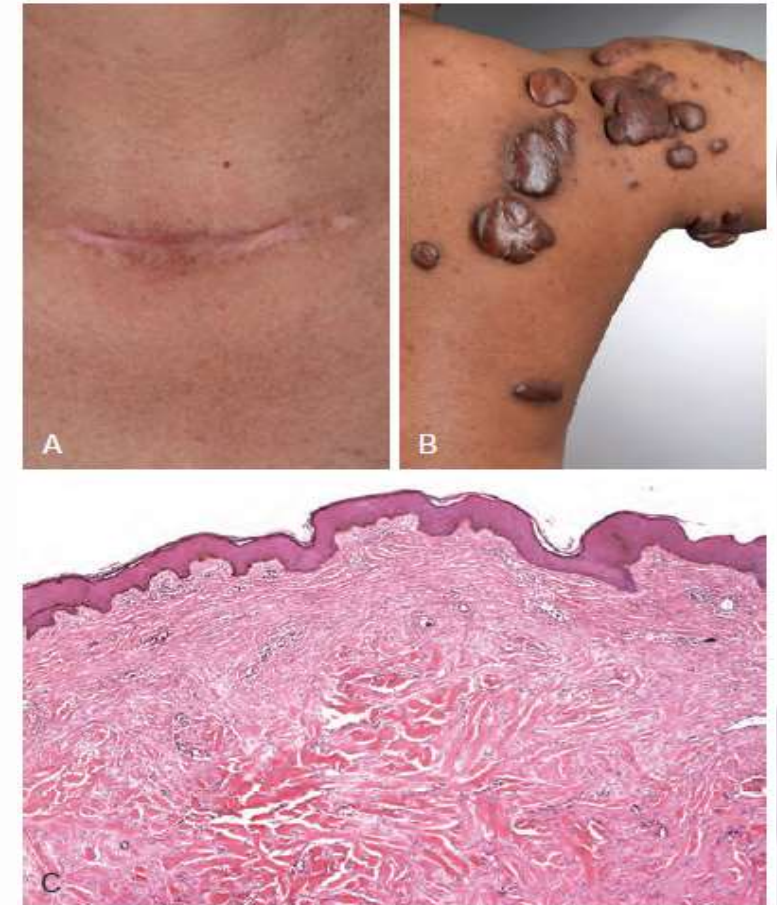


Chronic wounds illustrating defects in wound healing. (A–D) External appearance of skin ulcers.

(A) Venous leg ulcer; **(B)** arterial ulcer, with more extensive tissue necrosis; **(C)** diabetic ulcer; **and (D)** pressure sore. **(E–F)** Histologic appearance of a diabetic ulcer. **(E)** ulcer crater; **(F)** chronic inflammation and granulation tissue.

2. Excessive scarring

- Excessive formation of the components of the repair process can give rise to **hypertrophic scars and keloids**.
- **Hypertrophic scars**; **raised scar** that **regresses over months**, generally after thermal or traumatic injuries involving the deep dermis.
- **Keloids**; when the scar tissue **grows beyond the boundaries of the original wound** and **does not regress**; seems to be an individual predisposition and for unknown reasons, it is somewhat **more common in African Americans**.
- **Proud flesh**; excessive granulation tissue that protrudes above the level of the surrounding skin and blocks re-epithelization, must be removed by cautery or surgical excision to allow re-epithelialization.



Clinical examples of **excessive scarring and collagen deposition**. (A) Hypertrophic scar. (B) Keloid. (C) Microscopic appearance of a keloid. **Note the thick connective tissue deposition in the dermis.**

3. Formation of contractures

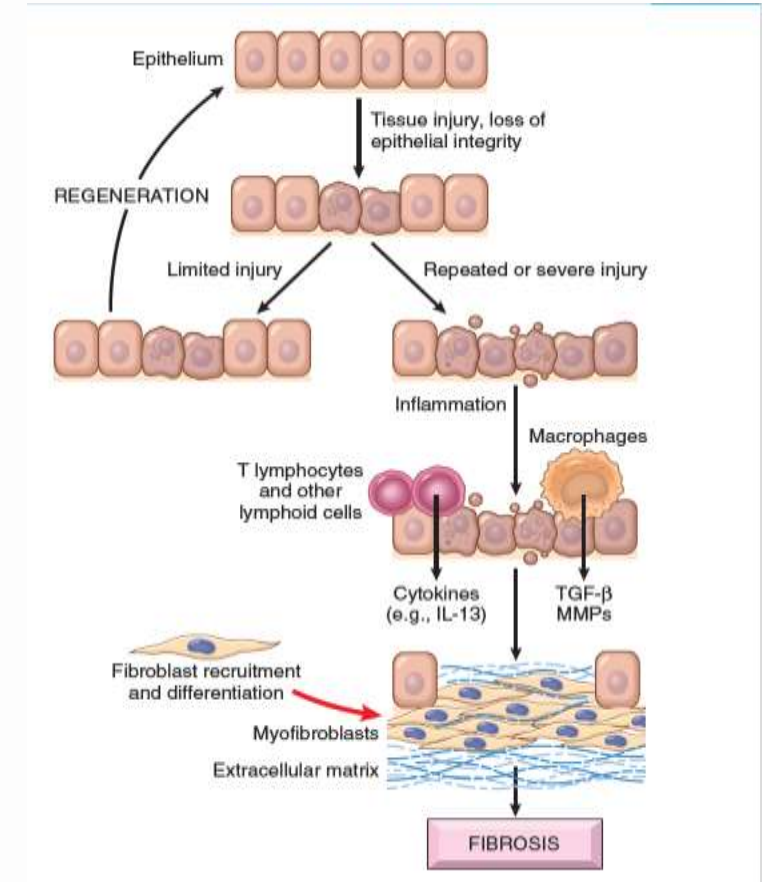
- **Contraction in the size of a wound** is an important part of the normal healing process especially in large wound that heal by secondary intention, usually done with myofibroblast.
- **An exaggeration of wound size contraction gives rise to **contracture** and results in deformities of the wound and the surrounding tissues.**
- Contractures are particularly prone to develop **on the palms, the soles and the anterior aspect of the thorax.**
- Contractures are commonly seen **after serious burns** and can compromise the movement of joints.



Wound contracture. Severe contracture of a wound after deep burn injury.

Fibrosis in parenchymal organ

- Abnormal deposition of collagen in internal organ in chronic disease such as **chronic infection or immunologic reactions** & may be responsible for substantial **organ dysfunction & even organ failure**.
- The major cytokines involved in fibrosis is **TGF- β** .
- **Examples:** liver cirrhosis, constrictive pericarditis, end stage kidney disease.



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.

THANK YOU