REPAIR BY SCARRING

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OBJECTIVES

- Introduction / definition of wound healing.
- Overview of tissue repair.
- Various **steps** involved in the process of **repair by scarring**
- Describe the **various mediators** involved in the steps of scarring.

DEFINATION

- Wound healing refers to the body's replacement of destroyed tissue by living tissue.
- Can be achieved by 2 processes: tissue regeneration &scar formation.
- Dynamic balance between these 2 is different in different tissues.

HEALING

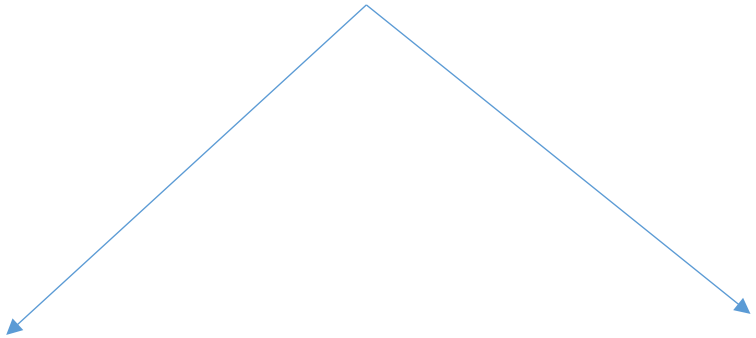
- **HEALING**….. Body response to injury in an attempt to restore normal structure and function

- Two processes in healing …… 1. REGENERATION

  2. Deposition of connective tissue…**SCAR**

INTRODUCTION

REPAIR



REGENERATION

(restores normal cells)

Cells with capacity to proliferate

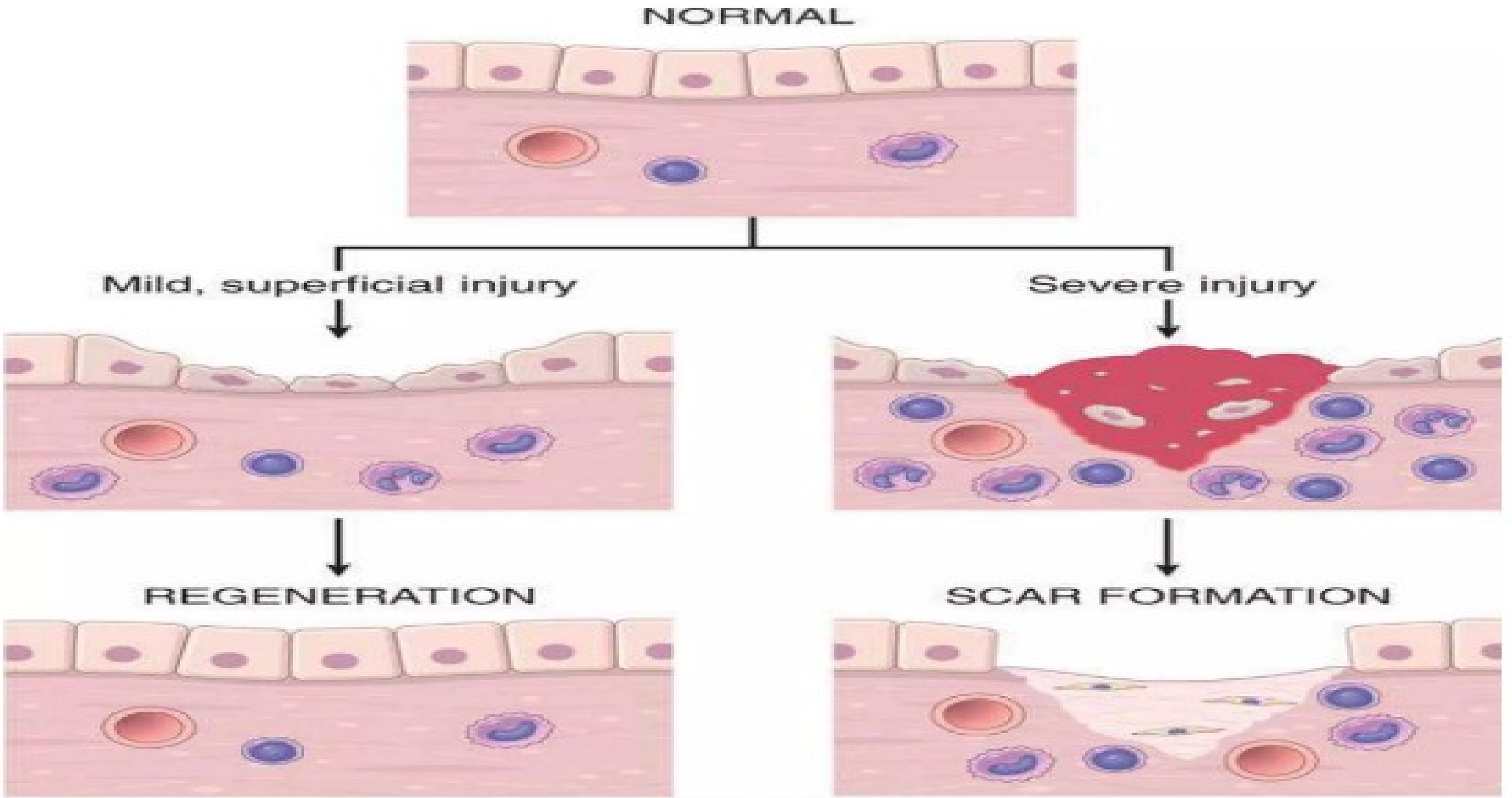
SCARRING

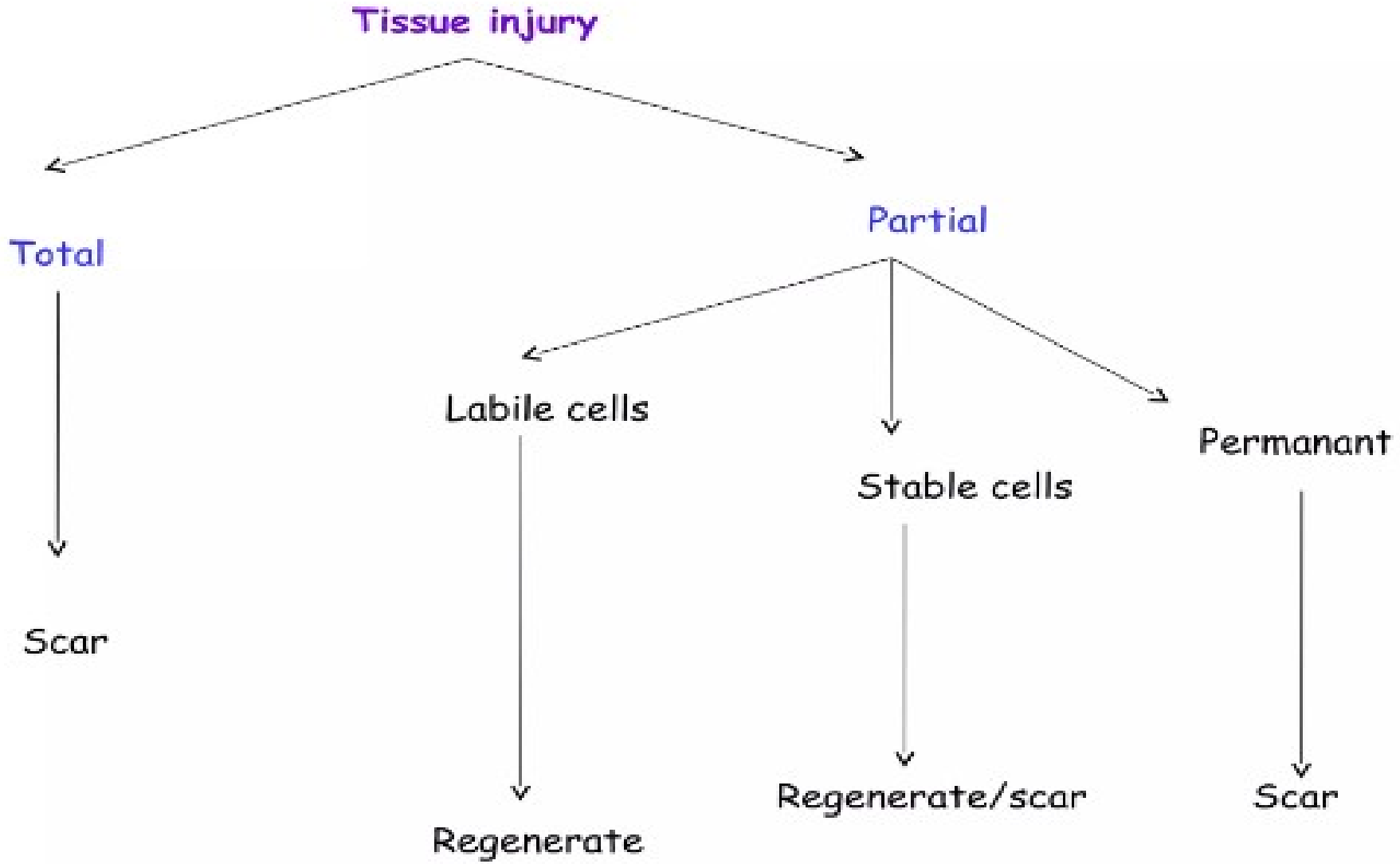
(connective (fibrous) tissue deposition)

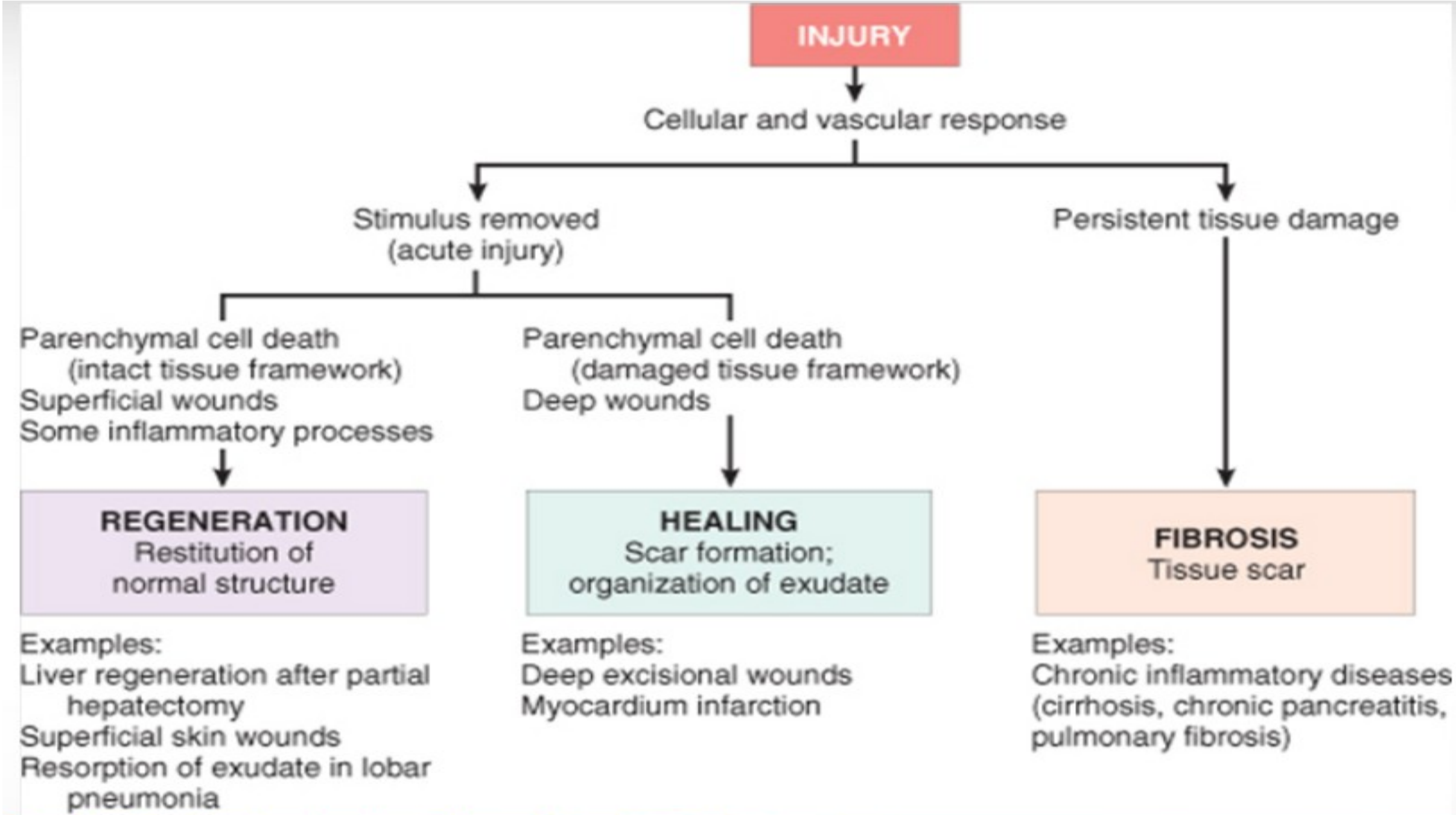
Cells with no capacity to proliferate

If severely damage cells.. Even if tissue has proliferative capacity

Tissue donot return to normal architecture. .**SCAR**


NORMAL
Mild, superficial injury
Severe injury
REGENERATION
SCAR FORMATION


Tissue injury
Total
Scar
Partial
Labile cells
Regenerate
Stable cells
Regenerate/scar
Permanant
Scar


INJURY
Cellular and vascular response
Stimulus removed
(acute injury)
Persistent tissue damage
Parenchymal cell death
(intact tissue framework)
Superficial wounds
Some inflammatory processes
Parenchymal cell death
(damaged tissue framework)
Deep wounds
REGENERATION
Restitution of
normal structure
HEALING
Scar formation;
organization of exudate
FIBROSIS
Tissue scar
Examples:
Liver regeneration after partial hepatectomy
Superficial skin wounds
Resorption of exudate in lobar pneumonia
Examples:
Deep excisional wounds
Myocardium infarction
Examples:
Chronic inflammatory diseases (cirrhosis, chronic pancreatitis, pulmonary fibrosis)

INTRODUCTION

- During healing, a complex cascade of cellular events occur to achieve resurfacing, reconstitution and restoration of tensile strength of injured tissue.
- Wound healing occurs in 3 phases

1. Inflammatory phase
2. Proliferative phase
3. Remodeling phase

WOUND HEALING

TWO WAYS :

1. **HEALING BY FIRST INTENTION**……. PRIMARY UNION

2. **HEALING BY SECOND INTENTION**…… SECONDARY UNION

1. HEALING BY FIRST INTENTION…… PRIMARY UNION

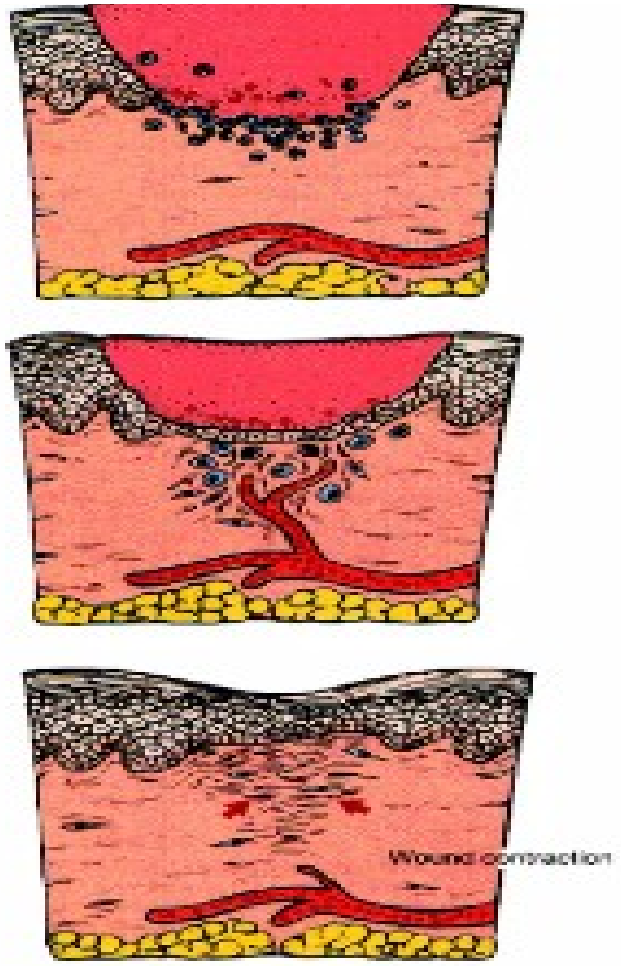
- Occurs in **clean incised wounds** with good apposition of edges ……. Surgical , clean wound with no infection or foreign bodies.
- Only **slight disruption of epithelial BM continuity** .
- **Death of only few epithelial and connective tissue cells**.
- **Result**……epithelial regeneration predominates over fibrosis.

2. HEALING BY SECOND INTENTIONS …. SECONDARY UNION

- Occurs in **open wounds** …..
- When there is **significant loss of tissue , necrosis** .
- **Large wounds with irregular margins**.
- Regeneration of parenchymal cells cannot completely reconstitute the original architecture.
- Growth of abundant **GRANULATION TISSUE** … from the margin of wound to complete the repair.
- **GRANULATION TISSUE CONSISTS** : **ECM fibroblasts, Macrophages, Neutrophils** and **Blood vessels.**

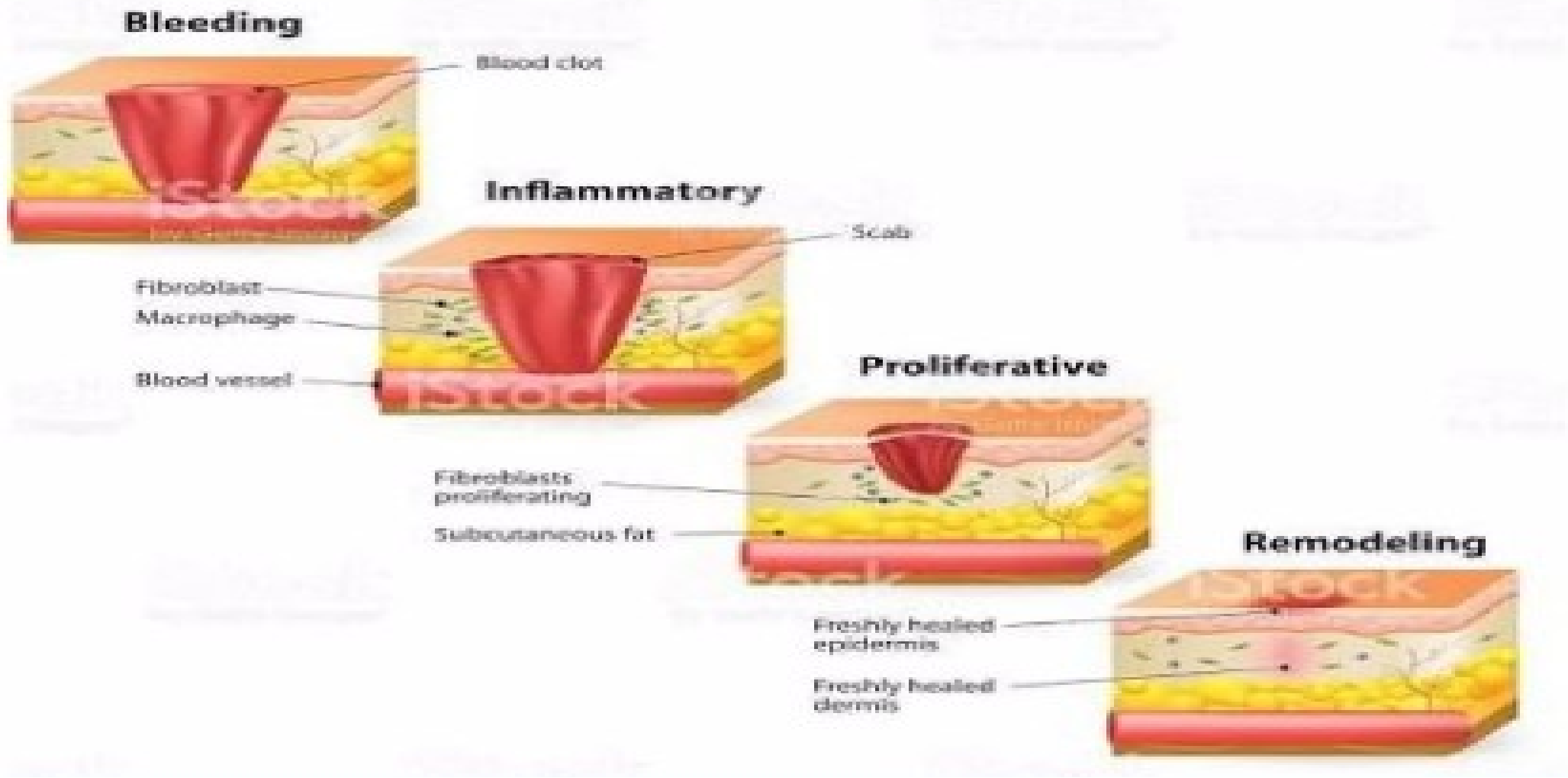
SECONDARY UNION DIFFERS FROM PRIMARY UNION

1. inflammatory reaction is more intense
2. larger amounts of granulation tissue formation
3. larger scar
4. ***wound contraction
   - Myofibroblasts: modified fibroblasts with feature of SMC
   - defect significantly decreases in size as wound heals.



Feature	Primary union	Secondary union
Cleanliness of wound	Clean	Unclean
Infection	Generally uninfected	May be infected
Inflammation	Mild	More intense
Granulation tissue	Scanty	Much larger amount
Wound contraction	Not present	Present
Outcome	Neat linear scar	Contracted irregular wound
Complications	Infrequent. Epidermal inclusion cyst formation	More frequent The most important is suppuration

STAGES OF WOUND HEALING



SCARRING

Repair occurs by the deposition of connective (fibrous) tissue

Although the fibrous scar is not normal, it provides enough structural stability that the injured tissue is usually able to function

Repair occurs by scar formation when:

- Tissue injury is severe or chronic
- There is damage to parenchymal cells as well as the connective tissue
- Nondividing cells are injured

CONDITIONS LEADING TO SCAR FORMATION

Scar formation occurs when

1)Damage to permanent cells

2)Severe destruction of connective tissue frame work

3)With extensive cell injury

4)In chronic inflammation

SCARRING

A **scar** is a mass of collagen that is the end result of repair by organization and fibrosis

Repair by scar formation occurs :

(1) When resolution fails to occur in an **acute inflammatory process**.

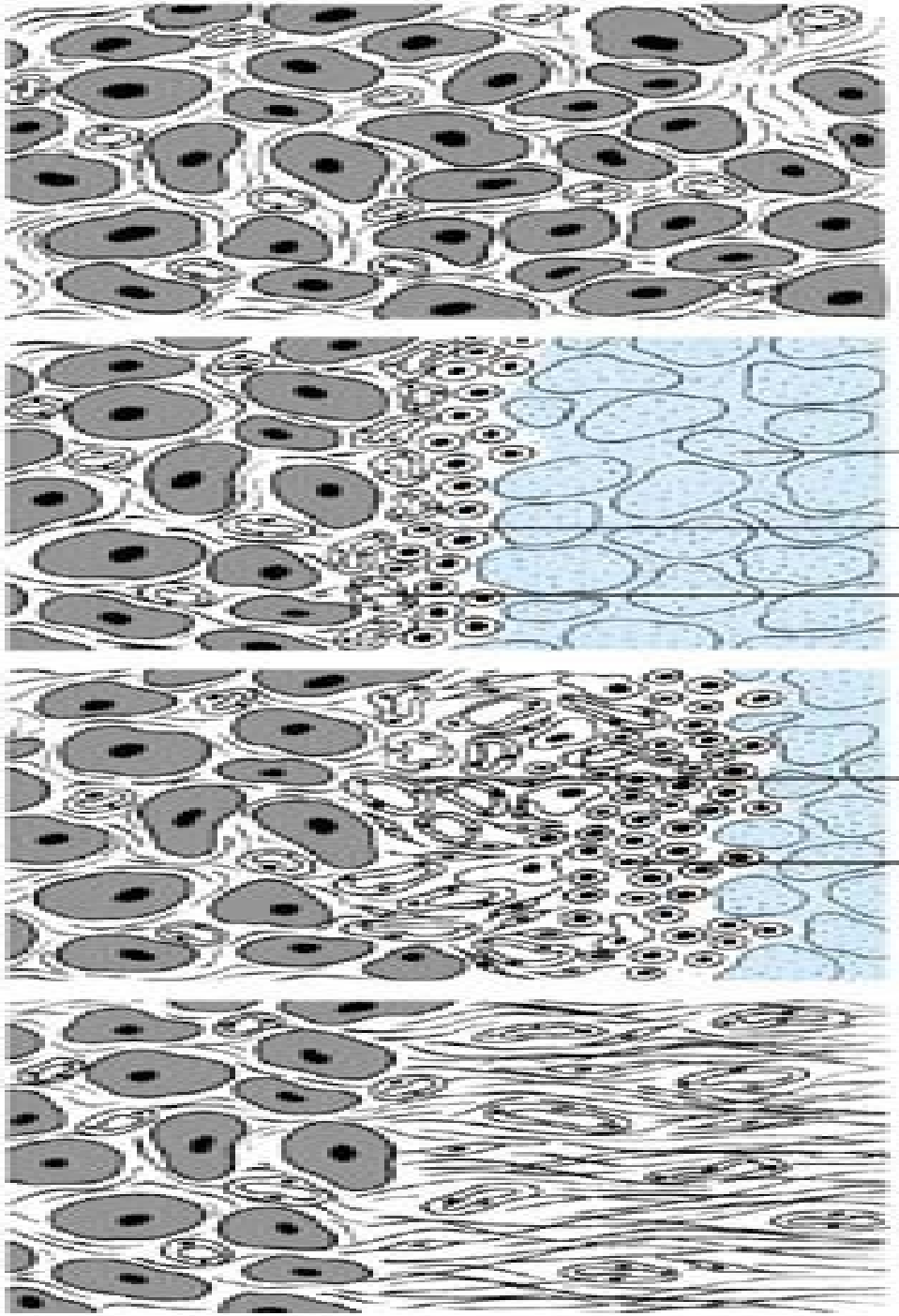
(2) When there is **ongoing tissue necrosis in chronic inflammation**

and

(3) When **parenchymal cell necrosis cannot be repaired by regeneration**.

STEPS IN SCAR FORMATION

- Inflammation
- Angiogenesis (new vessel formation)
- Migration and proliferation of fibroblasts
- Scar formation (synthesis of collagen)
- Connective tissue remodeling



A
Normal myocardium

B
Injury

Necrosis of myocardium, capillaries, and interstitial tissue

Neutrophils entering necrotic area

Dilatation of capillaries at edge of necrotic area

C
Preparation

Granulation tissue

Liquefaction and phagocytosis of debris

D
Collagenization and scar formation

ANGIOGENESIS……MECHANISM

- Is a **fundamental process** , affects the wound healing, regeneration, and vascularization of ischemic tissue …..**Physiologic process**
- **Also Pathological process….** Tumor development and metastasis and chronic inflammation.
- **ANGIOGENESIS……..** means new vessel formation from the adjacent pre-existing vessels + also by recruitment Endothelial progenitor cells **(EPCs)** from the bone marrow.

ANGIOGENESIS……MECHANISM

1. FROM PRE-EXISTING VESSELS :

- There is **vasodilatation** and **increased permeability** of the existing vessels.
- **Degradation of ECM**.
- **Migration of Endothelial cells.**

ANGIOGENESIS……MECHANISM

1. FROM PRE-EXISTING VESSELS

- **VASODILATATION** ……in response to Nitric Oxide, and VEGF- induced increased permeability of the pre- exiting vessels.
- **PROTEOLYTIC DEGRADATION OF BM.. .** of the parent vessel Matrix metalloproteinases (MMPs)
- **DISRUPTION OF CELL- TO – CELL CONTACT…** between Endothelial cells by **Plasminogen activator**

ANGIOGENESIS……MECHANISM

1. FROM PRE-EXISTING VESSELS

- **MIGRATION OF ENDOTHELIAL CELLS**……toward angiogenic stimuli.
- **PROLIFERATION OF ENDOTHELIAL CELLS** …..just behind the leading front of migrating cells.
- **MATURATION OF ENDOTHELIAL CELLS**……includes inhibition of growth and remodeling into capillary tubes.
- **RECRUITMENT OF PERI-ENDOTHELIAL CELLS** (PERICYTES and VASCULAR SMOOTH MUSCLE CELLS …….to form mature vessel.

ANGIOGENESIS……MECHANISM

2. ANGIOGENESIS FROM ENDOTHELIAL PRECURSOR CELLS (EPCs):

- **EPCs…..** recruited from bone marrow into tissues to initiate Angiogenesis.
- Express some markers of haemopoietic stem cells and VEGFR-2 and vascular endothelial- cadherin (VE-Cadherin) .

GROWTH FACTORS AND RECEPTORS INVOLVED IN ANGIOGENESIS

1. VEGF (Vascular Endothelial GF) especially VEGF-A …….most important growth factor undergoing Physiological Angiogenesis …. proliferating endometrium.

- As well as Angiogenesis occurring in Chronic Inflammation, wound healing, tumors and Diabetic Retinopathy.
- **VEGF ……SECRETED BY MESENCHYMAL and STROMAL CELLS…** Stimulates both migration and proliferation of endothelial cells
- **VEGFR-2 ……A Tyrosine Kinase receptor** ……most important in angiogenesis , expressed by endothelial cells and their precursors and also by tumor and other cells type

GROWTH FACTORS AND RECEPTORS INVOLVED IN ANGIOGENESIS

2.FIBROBLAST GROWTH FACTORS (FGFs) mainly FGF-2 :

- Promotes endothelial cell proliferation.
- Promotes migration of macrophages and fibroblasts to damage areas .
- Stimulates Epithelial cell migration to cover Epidermal wounds.

3. ANGIOPOIETINS 1 and 2 (Ang-1 and Ang-2) promotes

- Structural maturation of new vessels

GROWTH FACTORS AND RECEPTORS INVOLVED IN ANGIOGENESIS

- **PLATELET DERIVED GROWTH FACTORS (PDGFs)** and **TGF-β ……**

  Participate in wound stabilization

- **PDGFs……** recruits smooth muscle cells

- **TGF-β……** endothelial proliferation and migration and enhances

  production of ECM proteins

GROWTH FACTORS AND RECEPTORS INVOLVED IN ANGIOGENESIS

NOTCH SIGNALLING....regulates spouting and branching of new vessels....

So, the new vessels have proper spacing to effectively supply the healing tissue with blood

ECM PROTEINS.... Participate in vessels sprouting in Angiogenesis

ENZYMES IN ECM..... MMPs (matrix metalloproteinases) degrade ECM to allow remodeling and extension of vascular tube.

VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF)

Proteins	Family members: VEGF (VEGF-A), VEGF-B, VEGF-C, VEGF-D Dimeric glycoprotein with multiple isoforms Targeted mutations in VEGF result in defective vasculogenesis and angiogenesis.
Production	Expressed at low levels in a variety of adult tissues and at higher levels in a few sites, such as podocytes in the glomerulus and cardiac myocytes
Inducing agents	Hypoxia TGF-β PDGF TGF-α
Receptors	VEGFR-1 VEGFR-2 VEGFR-3 (lymphatic endothelial cells) Targeted mutations in the receptors result in lack of vasculogenesis
Functions	Promotes angiogenesis Increases vascular permeability Stimulates endothelial cell migration Stimulates endothelial cell proliferation VEGF-C selectively induces hyperplasia of lymphatic vasculature Up-regulates endothelial expression of plasminogen activator, plasminogen activator inhibitor 1, and collagenase

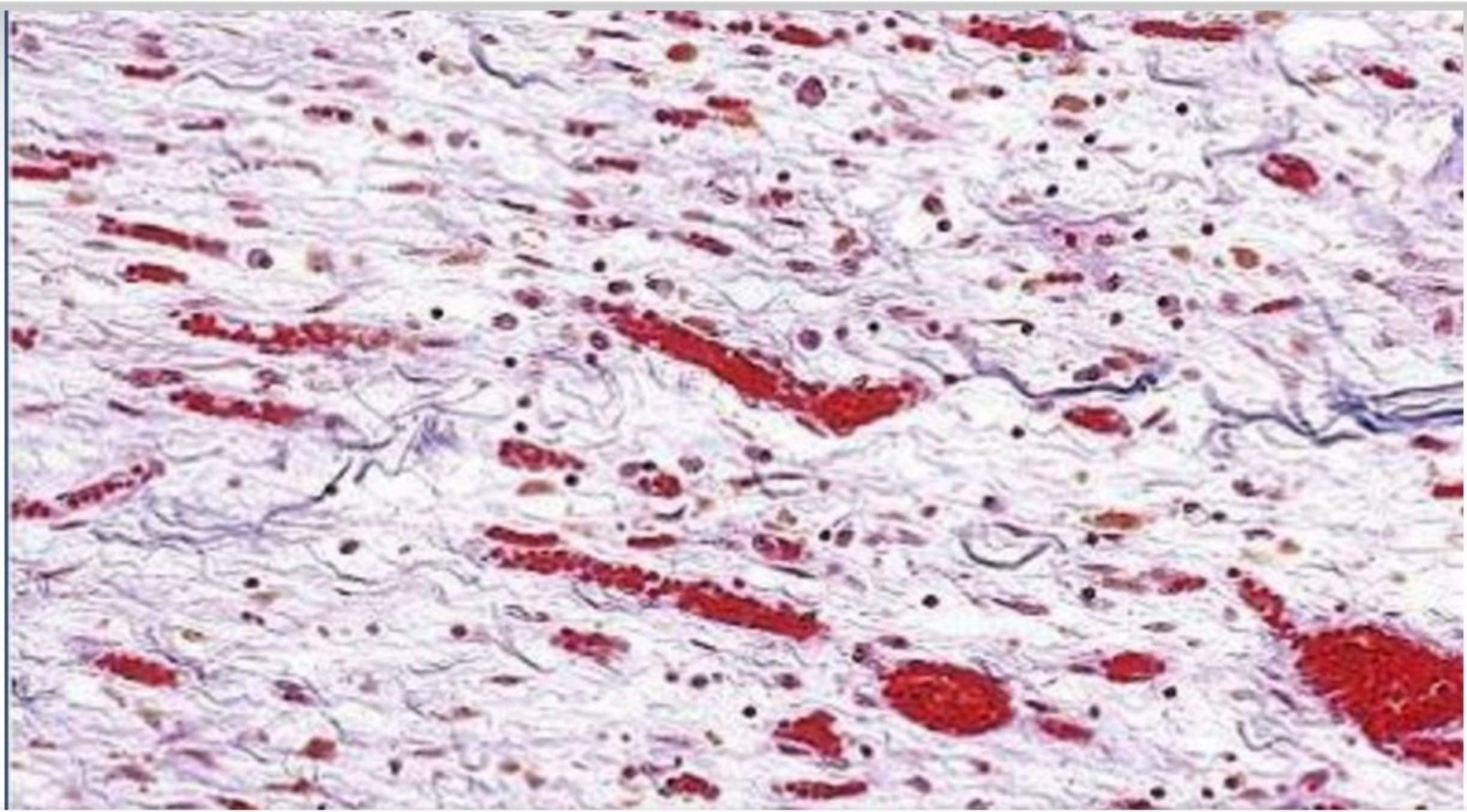
GRANULATION TISSUE

The red, granular tissue filling the nonhealing wounds

Granulation tissue occurs in all wounds during healing but that it may occur in chronic inflammation as well

It consists of

- Fibroblasts
- Surrounded by abundant ECM
- Newly formed blood vessels
- Scattered macrophages, and some other inflammatory cells



SCAR

The granulation tissue evolves into a scar composed of:

- Inactive, spindle-shaped fibroblasts
- Dense collagen
- Fragments of elastic tissue
- Other ECM components

As the scar matures, it become pale, largely avascular tissue

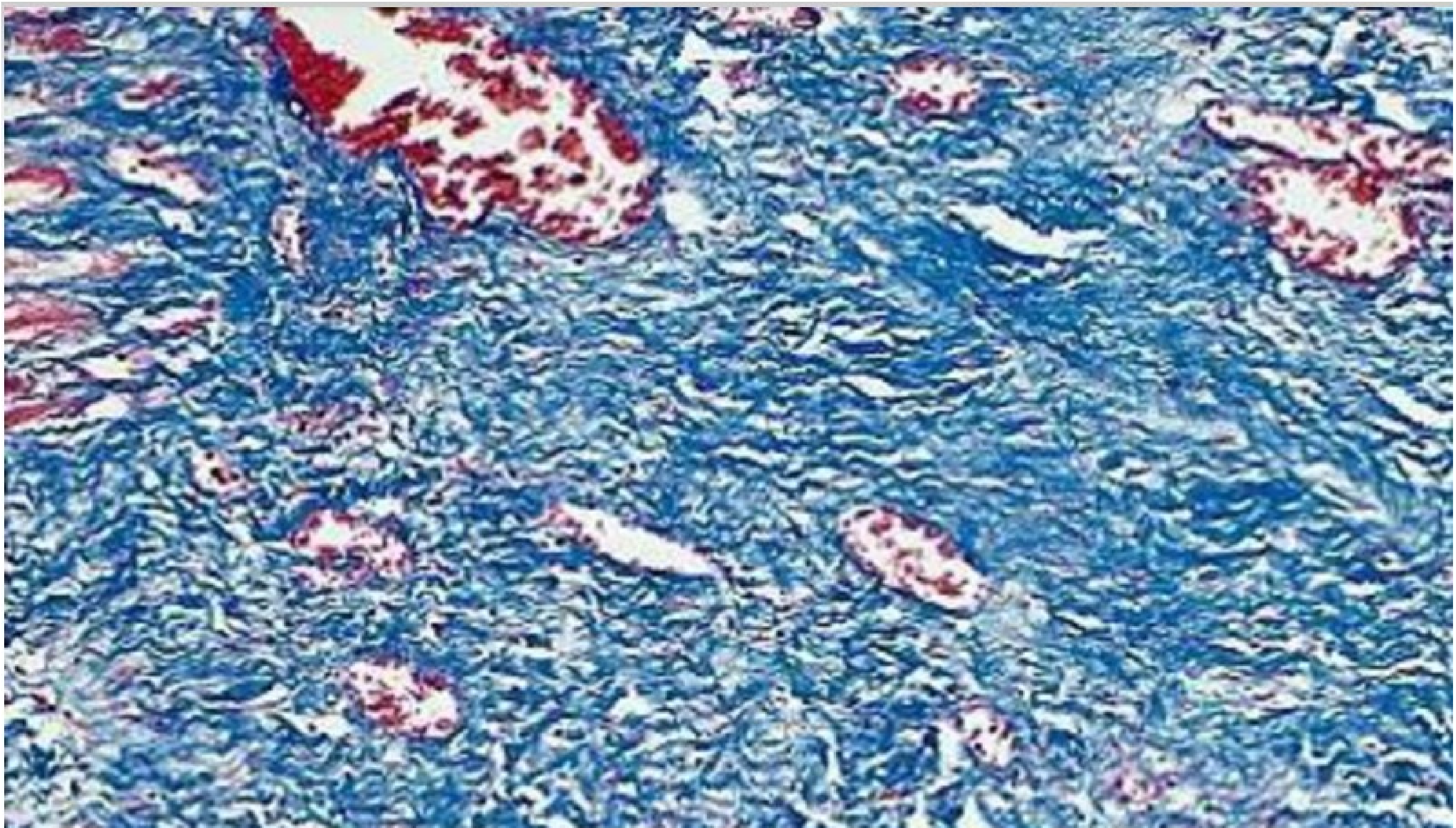
REMODELING OF CONNECTIVE TIISUE

- **Maturation and reorganization of connective tissue** …..REMODELING

  ……..produce a stable SCAR.

- Amount of connective tissue increases in granulation tissue ……..

- Eventually leads to SCAR formation …..



SCARRING

The role of macrophages in repair by connective tissue:

- **Cleanup of debris**
- **Recruitment of other cells**
- **Stimulation of matrix production**
- **Remodeling of the scar**

SCARRING

Myofibroblasts:

Myofibroblasts have hybrid properties of fibroblasts and smooth muscle cells

Myofibroblasts are found in the granulation tissue

Myofibroblasts are important for the contraction of wounds and the prevention of dehiscence

DEPOSITION OF CONNECTIVE TISSUE

Two steps:

1. Migration and proliferation of fibroblasts at site of injury
2. Deposition of ECM proteins produced by these cells.

- These processes are by……. Locally produced **CYTOKINES** and **GROWTH FACTORS** like PDGF, FGF-2, TGB-β…….produced by inflammatory cells……**ACTIVATED M2 MACROPHAGES**

DEPOSITION OF CONNECTIVE TISSUE

- **TRANSFORMING GROWTH FACTOR BETA (TGF- β)**….most important cytokine for synthesis and deposition of connective tissue proteins.
- Produced by cells in granulation tissue…..**M2 macrophages**
- **TGF- β…..**promotes fibroblasts migration and proliferation

  increase collagen synthesis and fibronectin

  decrease ECM degradation by inhibiting MMPs

DEPOSITION OF CONNECTIVE TISSUE

- **TGF- β……** involved in **scar formation after injury** , but also in
- Development of **fibrosis in LUNGS, LIVER, KIDNEYS** after chronic inflammation.
- Also an **anti-inflammatory cytokine**……limit and terminate inflammatory response…… by inhibiting lymphocyte proliferation

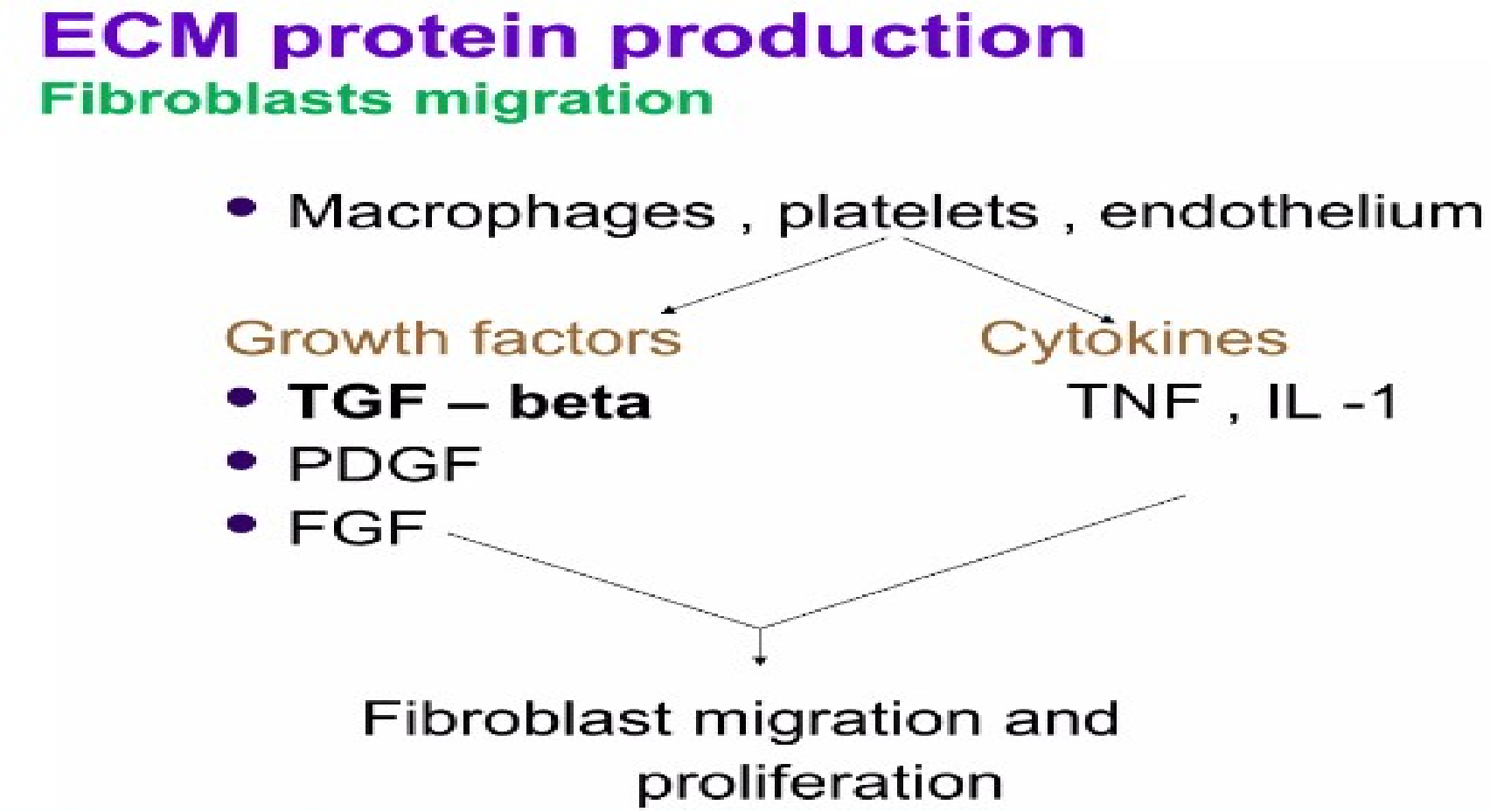
ECM PROTEIN PRODUCTION

- VEGF - (Angiogenesis and)
  increased vascular permeability

  ↓

  Exudation and deposition of plasma proteins
  Provides a stroma for the proliferating endothelial cells and fibroblasts

ECM PROTEIN PRODUCTION



ECM DEPOSITION AND SCAR FORMATION

- Growth factors (PDGF , FGF , TGF) & Cytokines (IL-1 & IL-13)
- Stimulate fibroblast to produce collagen
- Net collagen is dependant on both the production and degradation

REMODELLING OF CONNECTIVE TISSUE

Outcome of repair depends on :

- Balance between SYNTHESIS and DEGRADATION OF ECM PROTEINS.
- This is accomplished by **MMPs...MATRIX METALLOPROTEINASES**....dependent on metal ion Zinc (Zn) for their activity.
- **MMPs.... Produced by fibroblasts , macrophages, neutrophils, synovial cells and some epithelial cells.**
- Its secretion is regulated by **cytokines and growth factors** .
- Their activity is inhibited by **TIMPs ....TISSUE INHIBITORS OF METALLOPROTEINASES produced by mast cells**

IMPORTANT GROWTH FACTORS FOR WOUND HEALING

- Platelet derived growth factor:
  - Promotes migration and proliferation of fibroblasts
  - Is chemotactic for monocytes
- Epidermal growth factor
  - Promotes growth of endothelial, epithelial cells and fibroblasts

IMPORTANT GROWTH FACTORS FOR WOUND HEALING

- Fibroblast growth factor:
  - Promotes synthesis of ECM proteins including fibronectin.
  - Chemotactic for fibroblasts and endothelial cells
  - Promotes angiogenesis
- Vascular Endothelial Growth Factor (VEGF)
  - Angiogenesis
- Macrophage derived growth factors
  - IL-1 and TNF
    - Promote proliferation of fibroblasts and endothelial cells.

FACTORS AFFECTING WOUND HEALING

- **Infection:** most important cause of delayed wound healing.
- **Foreign bodies** such as fragments of steel, glass, or even bone impair healing.
- **Nutrition** : protein & vitamin C deficiency inhibit collagen synthesis & delay healing.

FACTORS AFFECTING WOUND HEALING

- **Poor perfusion**, due to arteriosclerosis, diabetes or obstructed venous drainage results in impaired healing.
- **Glucocorticoids (steroids)**
  - Have anti-inflammatory effects, and their administration may result in poor wound strength due to diminished fibrosis.
  - In some cases , e.g. corneal infections, glucocorticoids are sometimes prescribed (along with antibiotics) to reduce the likelihood of opacity that may result from collagen deposition.

FACTORS AFFECTING WOUND HEALING

- **The type of tissue injured:**
  - **Complete restoration** can occur only in **tissues** composed of **stable** and **labile cells.**
  - Injury to tissues composed of **permanent cells** result in **scarring** e.g. healing of a myocardial infarct.

COMPLICATIONS OF WOUND HEALING

1. **Infection** of wound
2. **Implantation (epidermal) cysts**…. Due to persistence of epithelial cells in the wound after healing .
3. **Deficient scar formation** …… Inadequate formation of granulation tissue

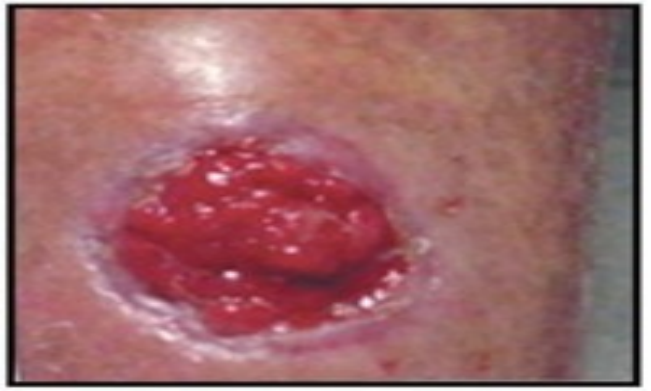
   May lead to wound splitting , incisional

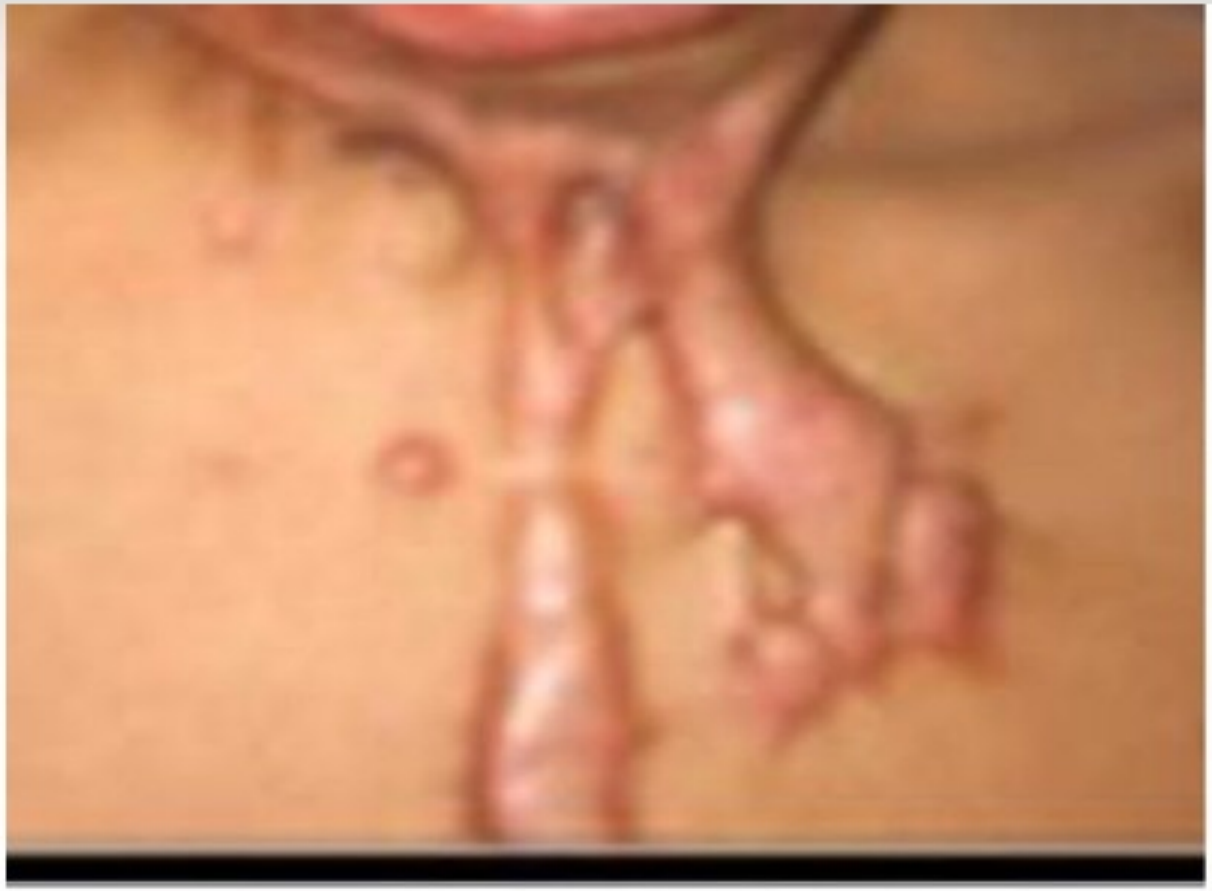
   hernia and ulceration

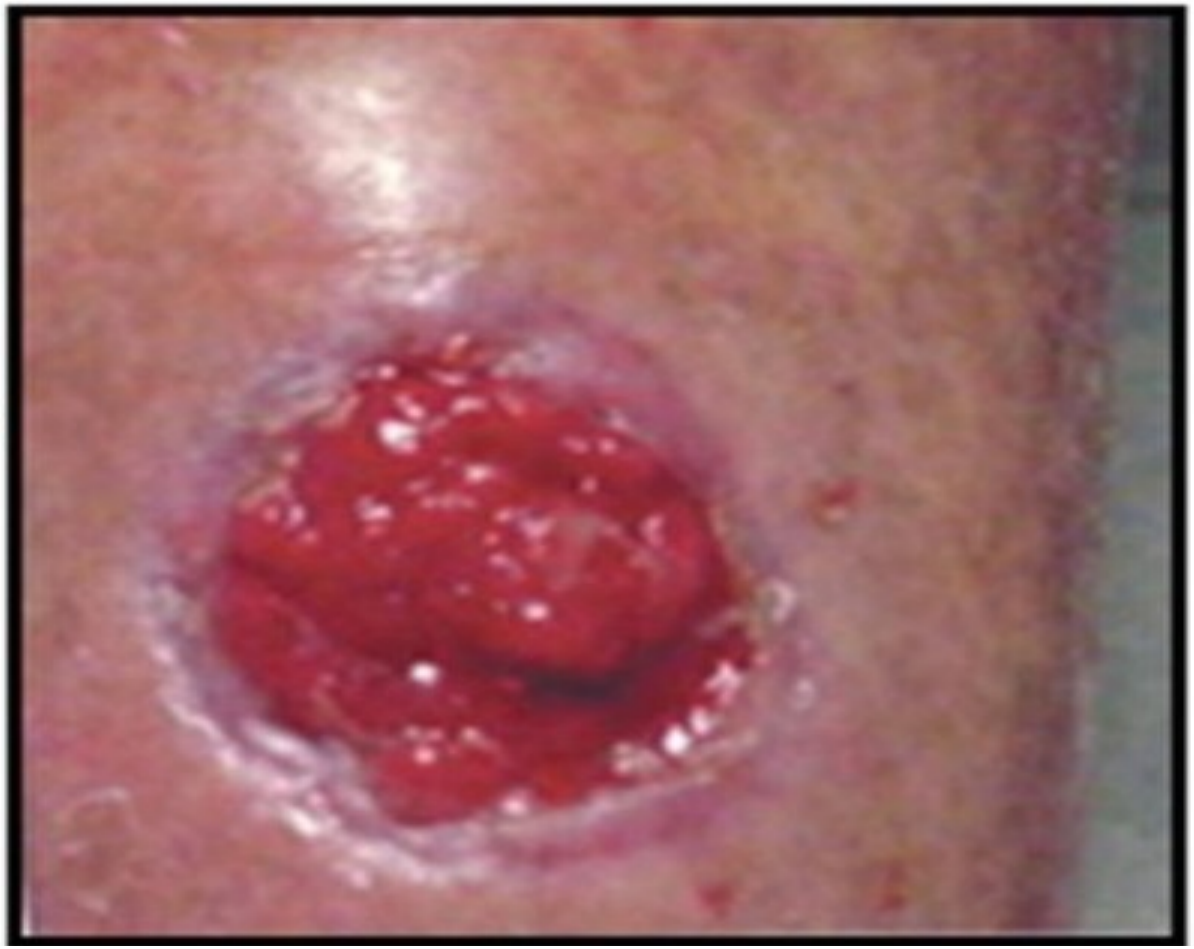
COMPLICATIONS OF WOUND HEALING

. **Exuberant granulation tissue:**

- Excessive **granulation tissue**
- Protrudes **above** the level of the surrounding **skin**
- Hinders **re-epithelialization**







COMPLICATIONS OF WOUND HEALING

6- Excessive contraction

- Termed **contracture** or **cicatrisation**
- Results in severe **deformity** & limit joint **mobility**
- healing of **severe burns**

7- Pigmentation:

- **in h**ealed wounds,
- may have rust-like color
- due of **haemosiderin**.

8- Malignant change: later, e.g. squamous cell carcinoma in **Marjolin`s ulcer**.