Ulcers, Tissue Repair & Healing

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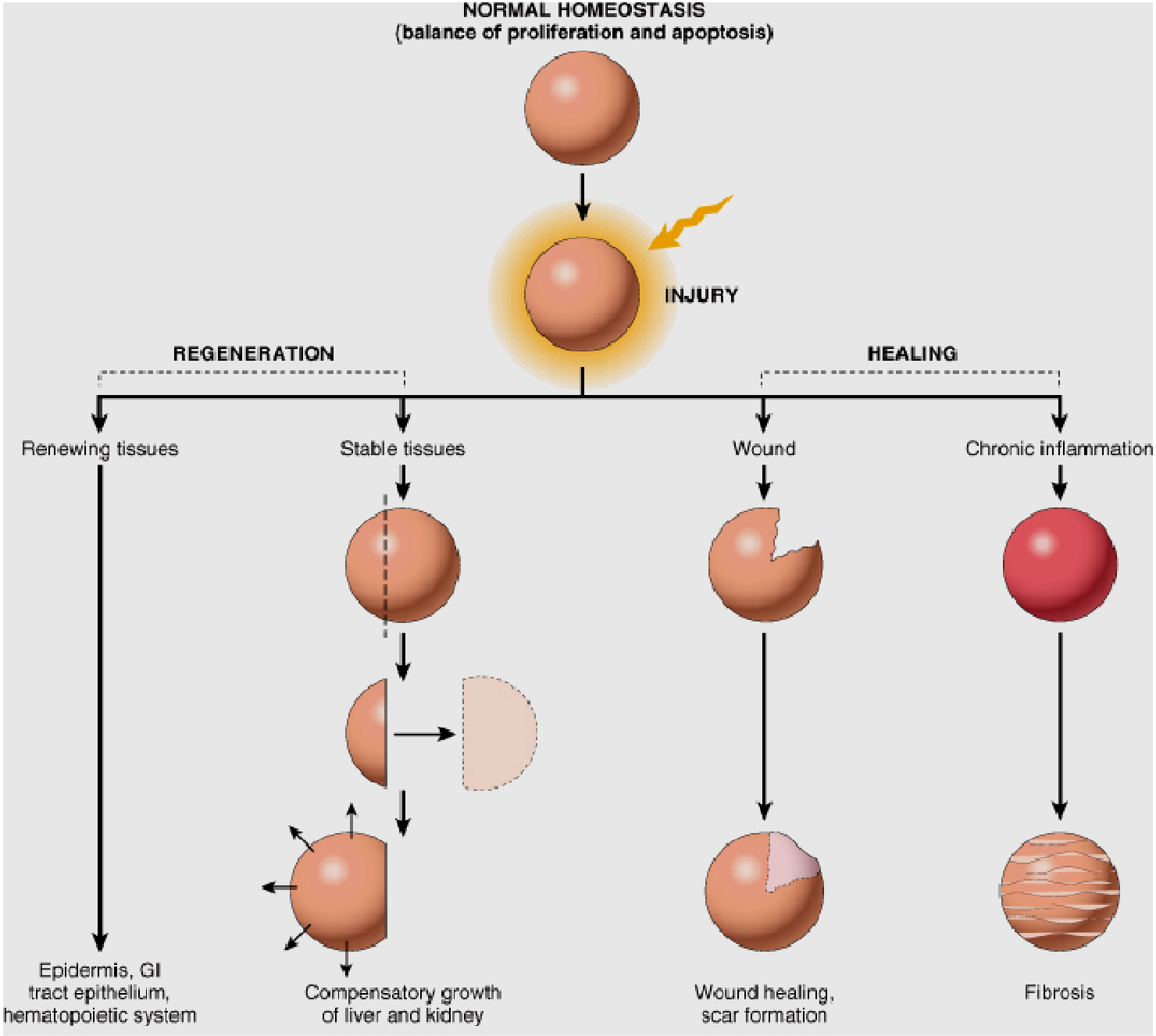
What Happens when a tissue is injured?

- Hemorrhage and clot formation
- Acute Inflammation
  - Resolution
  - Healing by Repair
  - Remodeling
  - Abscess formation
- Chronic inflammation
  - Ulcer – e.g. of persistent chronic inflammation
  - Healing by fibrosis/scaring



Tissue response to injury. Repair after injury can occur by regeneration, which restores normal tissue, or by healing, which leads to scar formation and fibrosis.

Cell Injury

- Cells respond to external stimuli by 3 ways:
- **Adaption** – response to prolonged stress.
- **Cell injury** – undergo reversible (hydropic change) or irreversible cellular changes
- **Cell death** – undergo cell death (necrosis) or apoptosis.

Cell Adaption

- **Atrophy** – reduction in organ size owing to cell loss or reduction in cell size.
- **Hypertrophy** – increase in organ size owing to constitutive cell enlargement.
- **Hyperplasia** – increase in organ size owing to increase in number of cells.
- **Metaplasia** – transformation of one tissue cell type to another.
- **Dysplasia** – premalignant transformation of normal epithelium

Cell Injury

- Causes of cell injury:
- Oxygen deficiency (hypoxia)
- Free radicals – superoxide, hydrogen peroxide, hydroxyl radical
- Chemical or physical agents
- Biological agents – cytokines, oncogenes

Cell Death

- Necrosis – morphological sign of cell death
- Several forms recognised – end result of inflammation
  - Coagulative necrosis
  - Liquefactive necrosis
  - Caseous necrosis
  - Fat necrosis
  - Fibrinoid necrosis

Types of Necrosis

- **Coagulative necrosis** – typically caused by ischaemia (infarct).
- **Liquefactive necrosis** – typically occur in brain or in an abscess.
- **Caseous necrosis** – typically occur in TB or fungal infections. Characterised by granular material surrounded by epitheloid & multinucleated giant cells.
- **Fat necrosis** – caused by trauma to adipose cells or release of lipolytic enzymes during disease states e.g. Acute pancreatitis.
- **Fibrinoid necrosis** – typically seen in arteries, arterioles or glomerular capillaries damaged by autoimmune diseases. Blood vessels impregnated by fibrin & serum proteins & appear magneta red in histological sections.

Acute Inflammation
Vascular events
Cellular events
Chemical mediators
Pathological types of acute inflammation

ACUTE INFLAMMATION

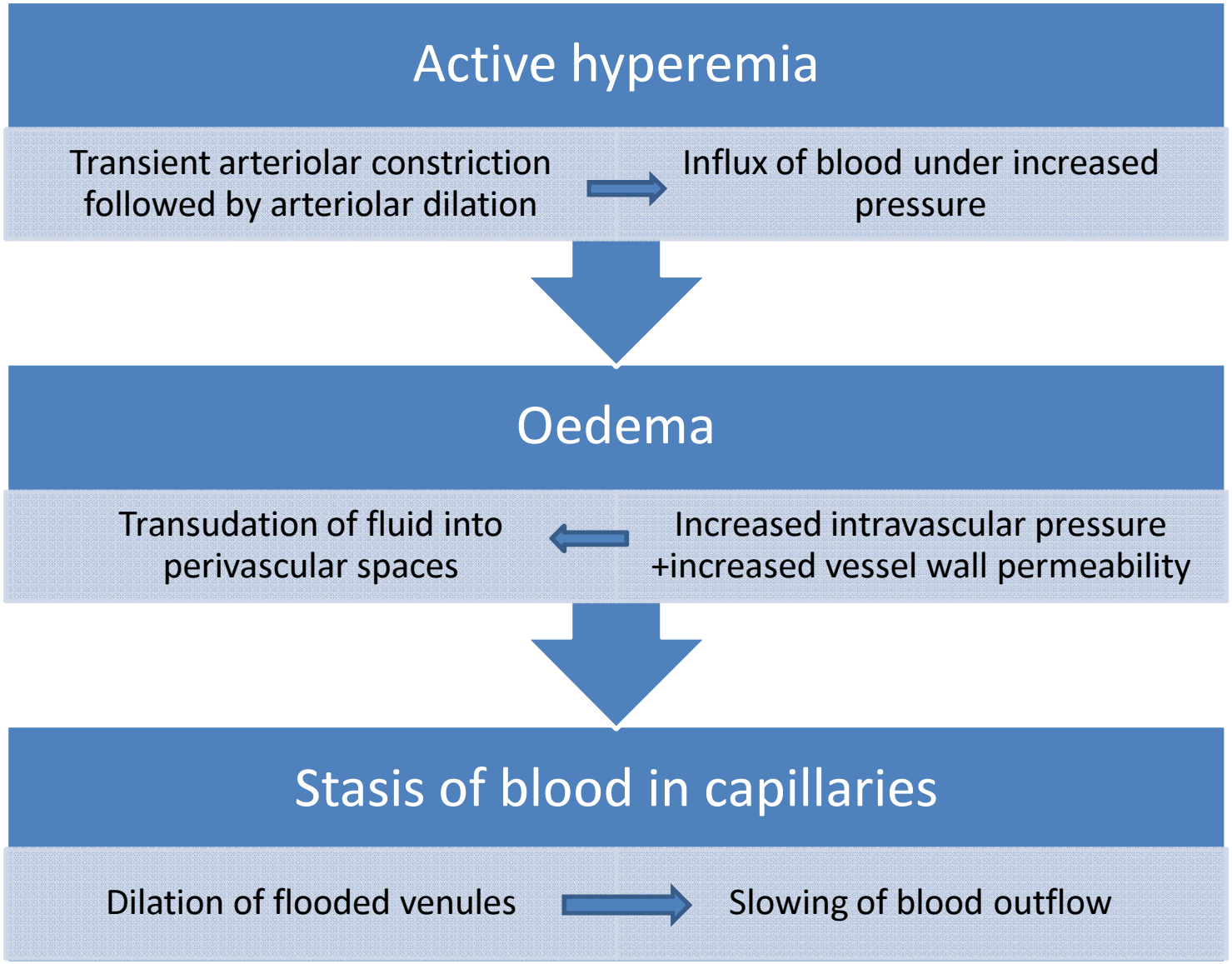
Inflammation & Repair

- Inflammation is the body's reaction to injury
- Purpose of reaction is 2 fold:
  - Eliminate cause of injury
  - Initiate repair & healing of injured tissue
- Type of inflammation
  - Acute
  - Chronic

Acute Inflammation

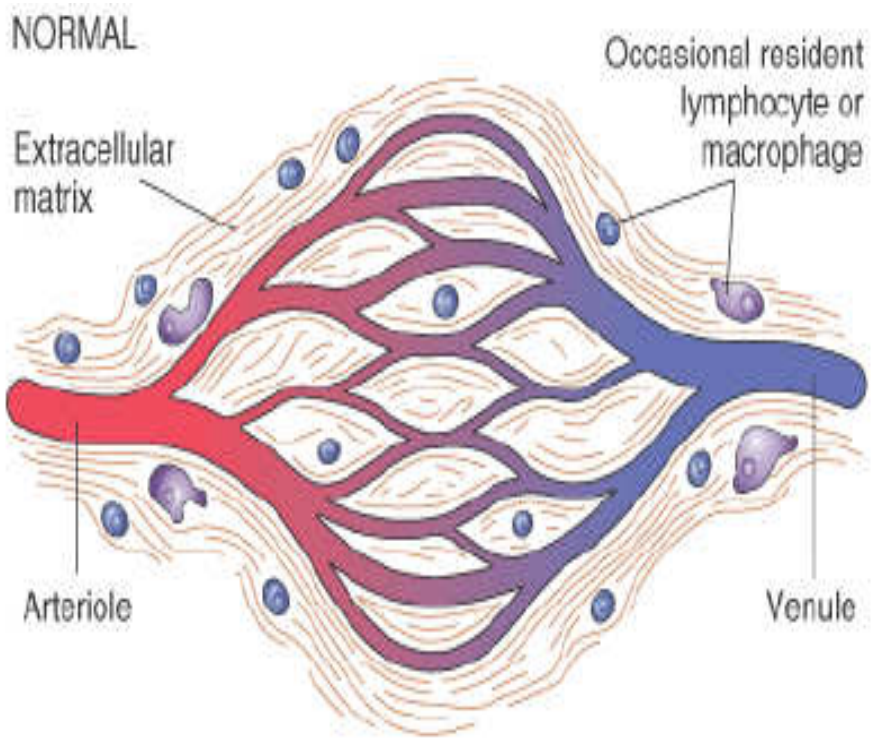
- Classic signs of acute inflammation:
  - Rubor (redness)
  - Tumour (swelling)
  - Calor (heat)
  - Dolor (pain)
  - Functio laesa (impaired function)
- Inflammatory response consists of:
  - Vascular events
  - Cellular events
- Mediated by chemical mediators

Vascular Events in Acute Inflammation

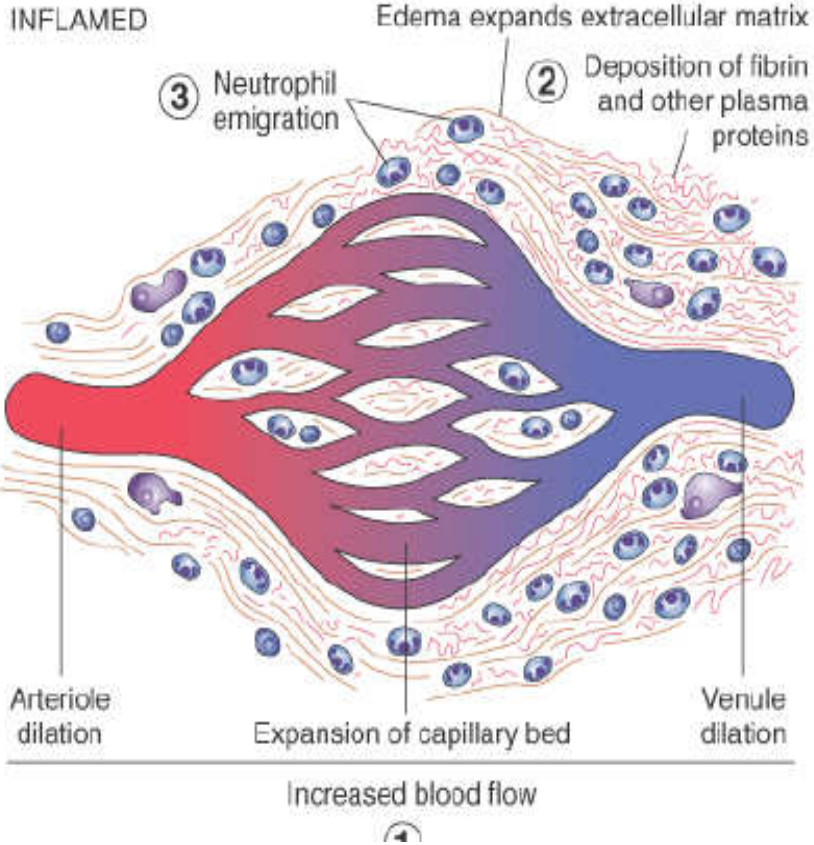


Vascular Events

NORMAL



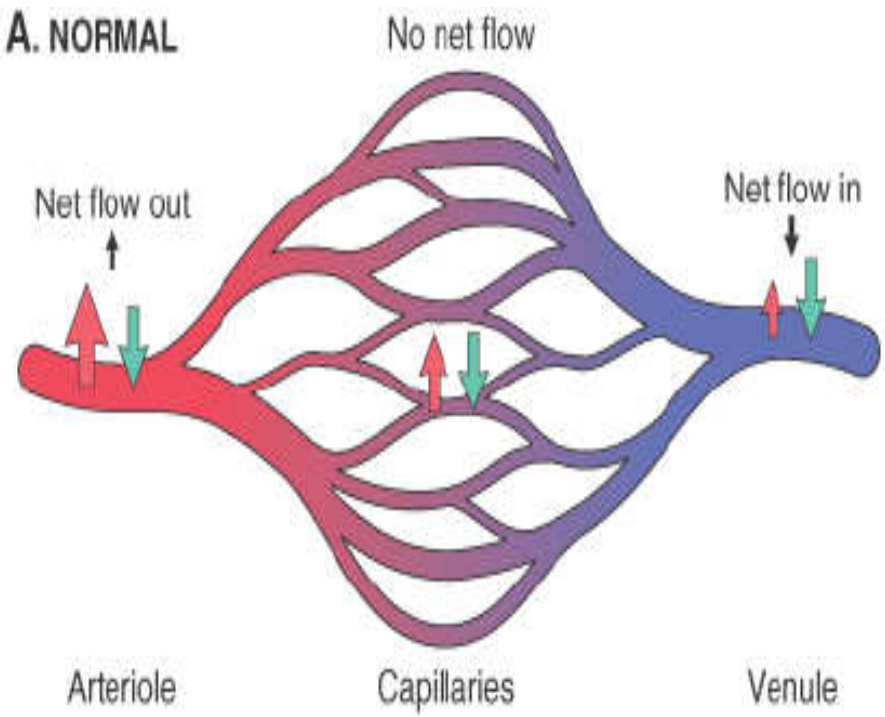
INFLAMED

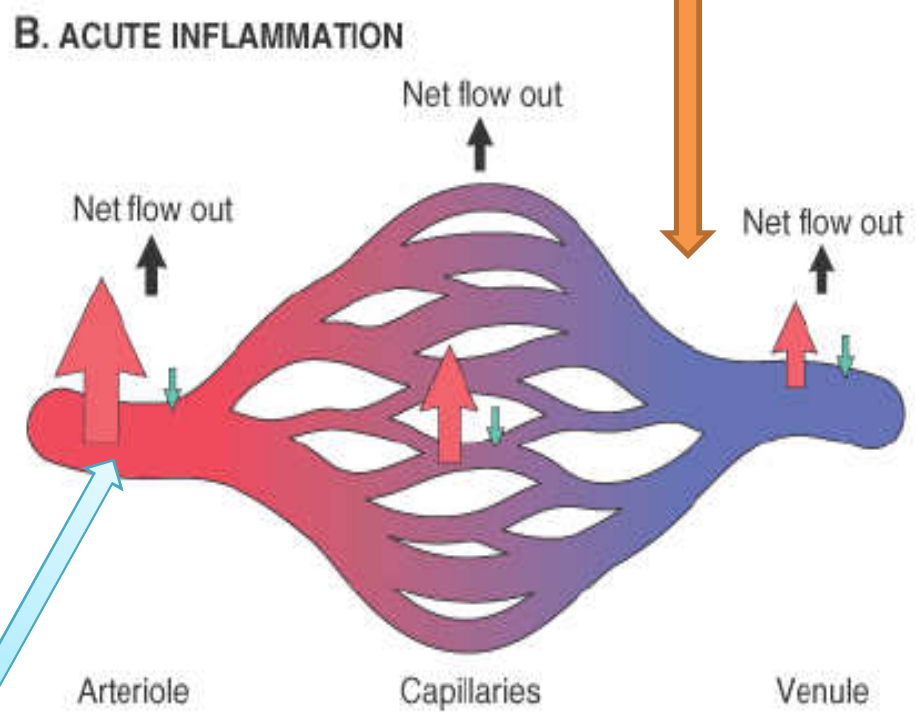


Ref: Robins Pathological Basis of Diseases, 7th Ed

BP & Plasma Colloid Osmotic Pressure Changes

Venous pressure increases, osmotic pressure reduced (due to protein leakage). **Net effect = decreased colloid osmotic pressure**



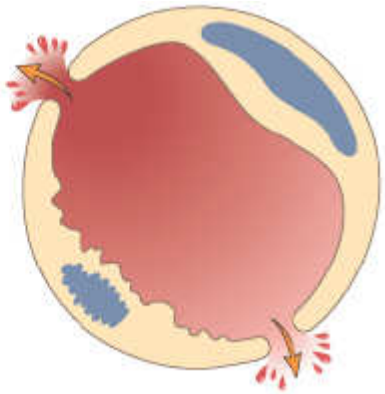


Increased arteriole pressure, mean capillary pressure increases (due to arteriolar dilation). **Net effect = increased hydrostatic pressure**

5 mechanisms of increased vascular permeability

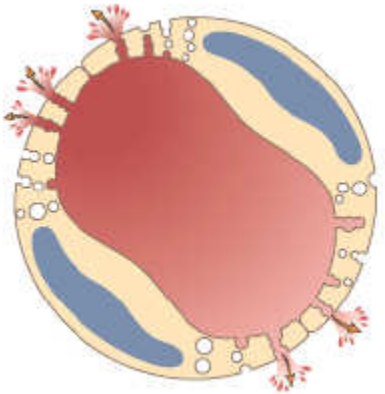
Gaps due to endothelial contraction

- Venules
- Vasoactive mediators (histamine, leukotrienes, etc.)
- Most common
- Fast and short-lived (minutes)



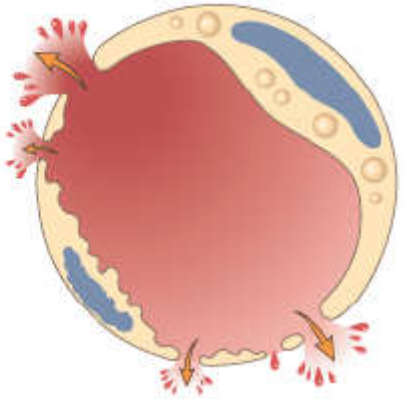
ncreased transcytosis

- Venules
- Vascular endothelium–derived growth factor



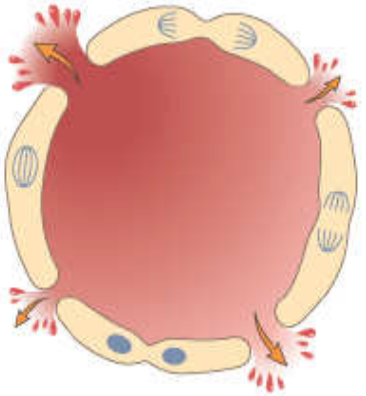
Direct injury

- Arterioles, capillaries, and venules
- Toxins, burns, chemicals
- Fast and may be long-lived (hours to days)



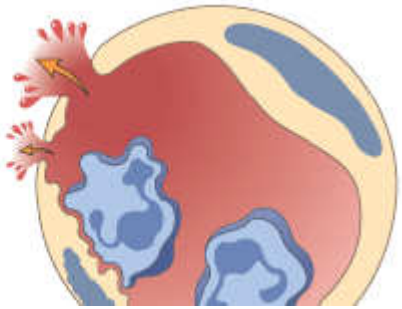
New blood vessel formation

- Sites of angiogenesis
- Persists until intercellular junctions form

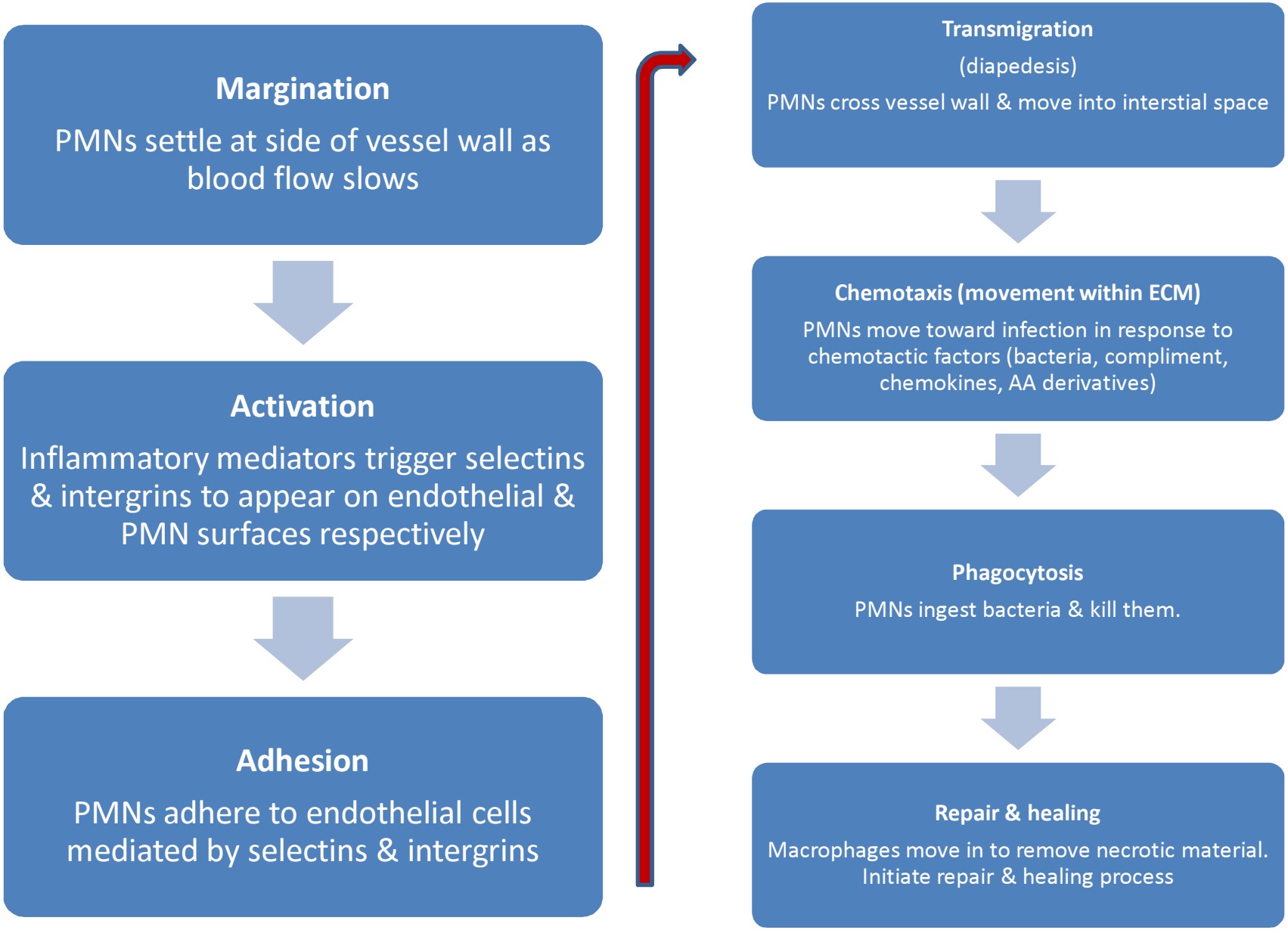


Leukocyte-dependent injury

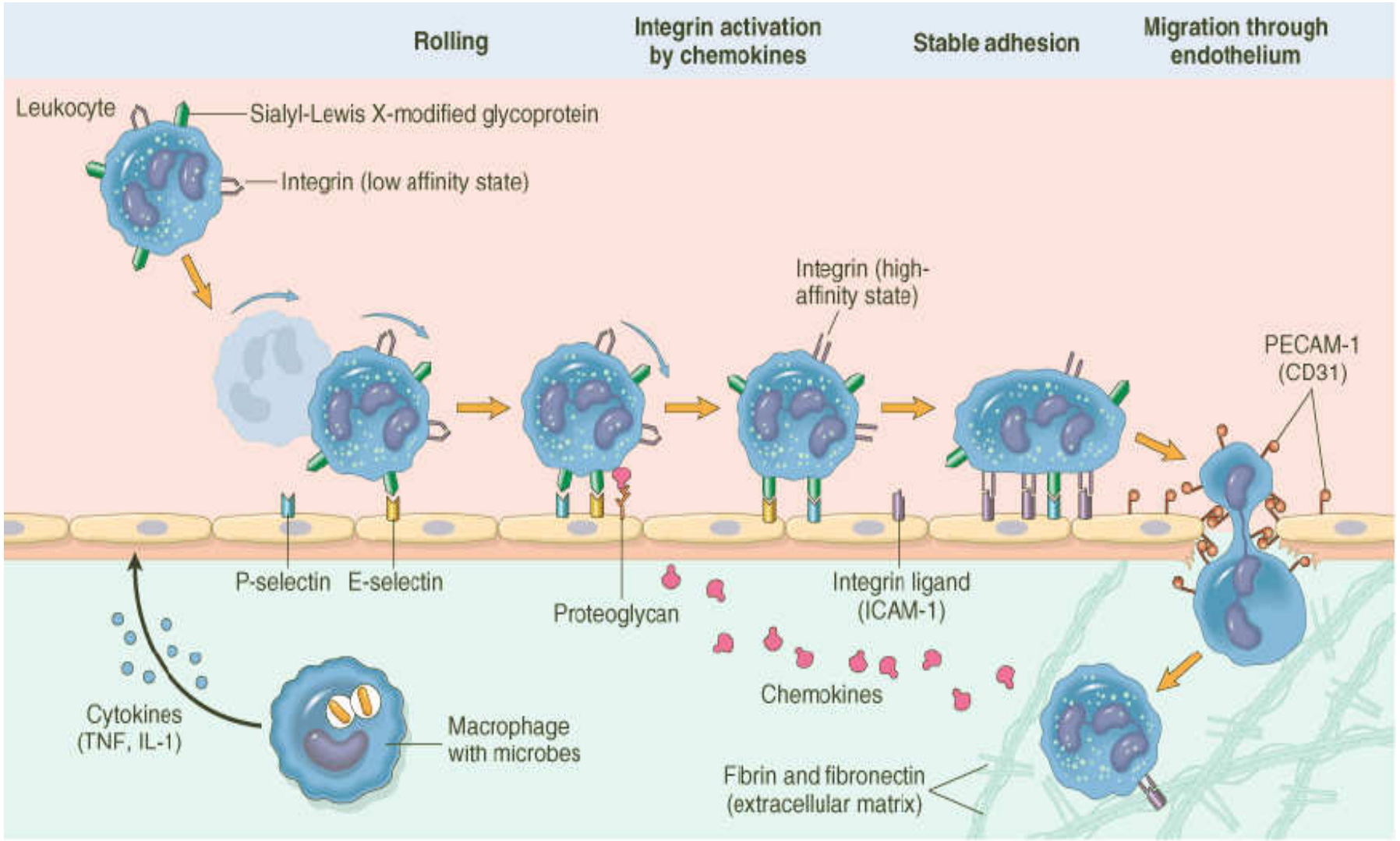
- Mostly venules
- Pulmonary capillaries
- Late response
- Long-lived (hours)



Cellular Events in Acute Inflammation



Cellular Events

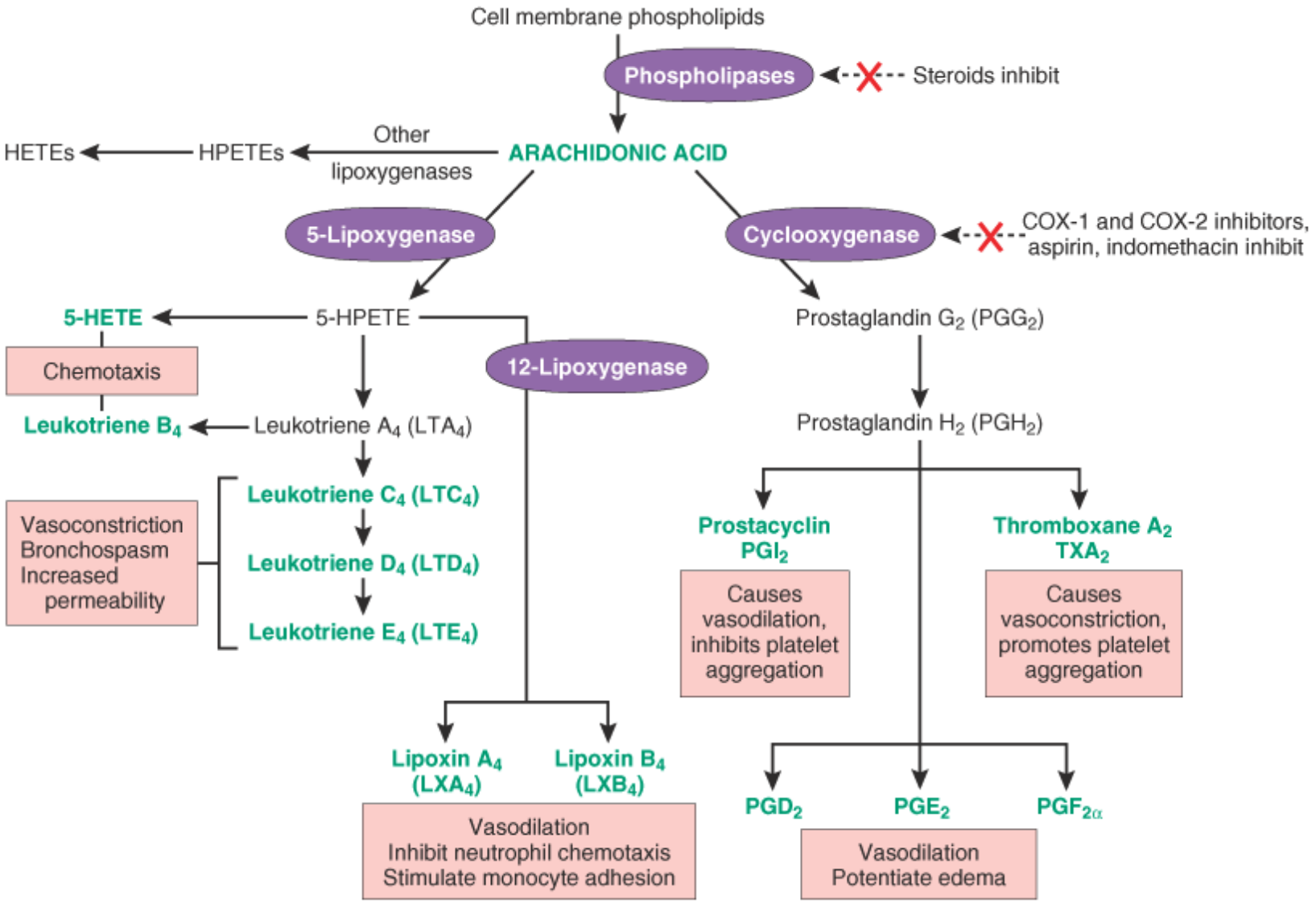


Ref: Robins Pathological Basis of Diseases, 7th Ed

Chemical Mediators

- Chemical mediators account for vascular & cellular events
- **Cell derived mediators**
  - Histamine
  - AA derivatives
    - Cyclooxygenase pathway
    - Lipoxygenase pathway
- **Plasma derived mediators**
  - Kinins
  - Coagulation proteins
  - Fibrinolytic proteins
  - Compliment components

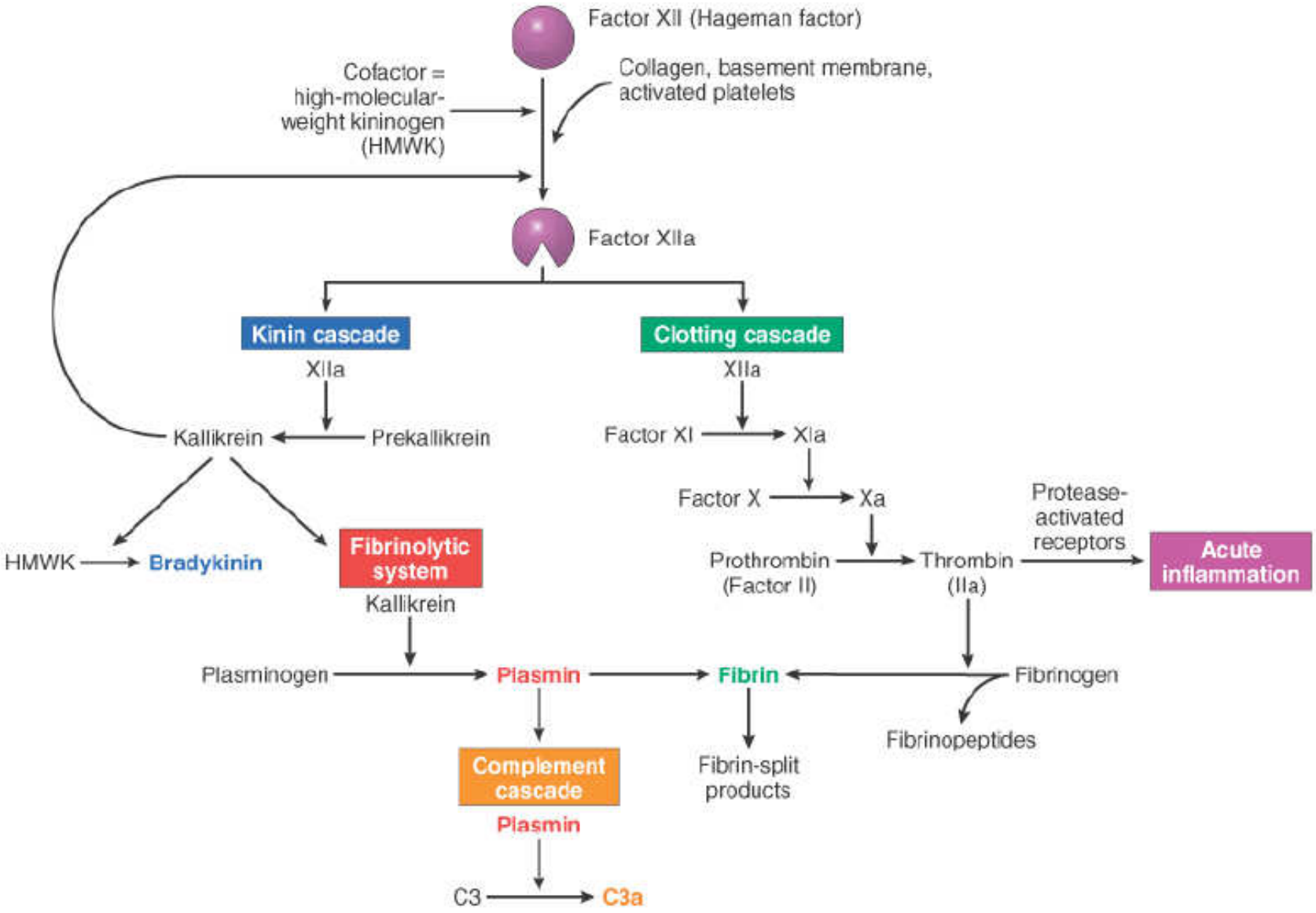
Arachidonic Acid Derivatives - Eicosanoids



Plasma Derived Mediators

- Kinins e.g. bradykinin
- Coagulation proteins e.g. fibrin, fibrin split products
- Fibrinolytic proteins e.g. plasmin
- Compliment
- These mediators are typically activated by **XIIa** (Hageman factor)

Plasma Derived Mediators



Outcomes of Acute Inflammation

- **Resolution –** repair, regeneration, healing and remodeling
- **Abscess** - cavity filled with pus and walled off by fibrous tissue
- **Ulcer** – loss of surface epithelium & break in mucuosa
- **Fistula** – abnormal communication between two organs or between an organ and a surface
- **Scar formation** – distortion of structure and sometimes function
- **Conversion to chronic inflammation** – marked by replacement of neutrophils & monocytes with lymphocytes, plasma cells & macrophages.

Inflammatory response

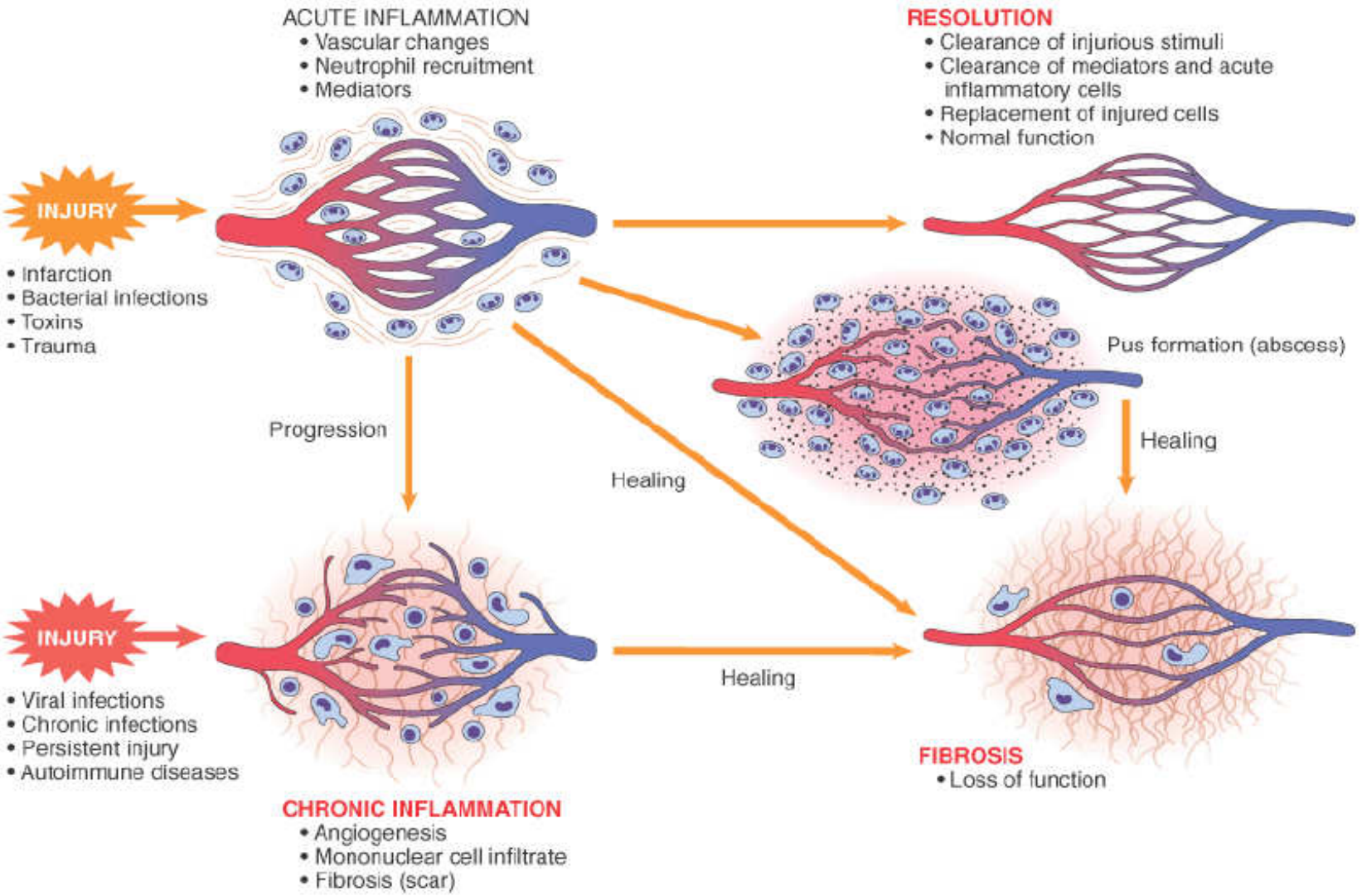
Vascular events

Cellular events

Pathological types of chronic inflammation

CHRONIC INFLAMMATION

Outcome of Acute Inflammation



Chronic Inflammation

- Prolonged inflammation & mediated by cells that have longer lifespan than PMNs
  - Involves tissue destruction & repair

- Vascular response – similar to acute inflammation but include angiogenesis
  - Cellular events – mediated by macrophages, lympocytes & plasma cells.
  - Eosinophils – respond to parasitic infections or allergic rxns (immune-mediated)

Factors affecting healing
Normal wound healing
Healing by primary intention
Healing by secondary intention
Abnormal wound healing

WOUND HEALING & REPAIR

Overview of Repair

- Repair: the process to restore the destroyed cells and tissue by regenerating the same cell type and connective tissue
- Involves restoration of normal structure: ECM & connective tissue is intact.
  - Surviving parenchymal cells have ability to regenerate
- Requires cellular proliferation: mediated by growth factors

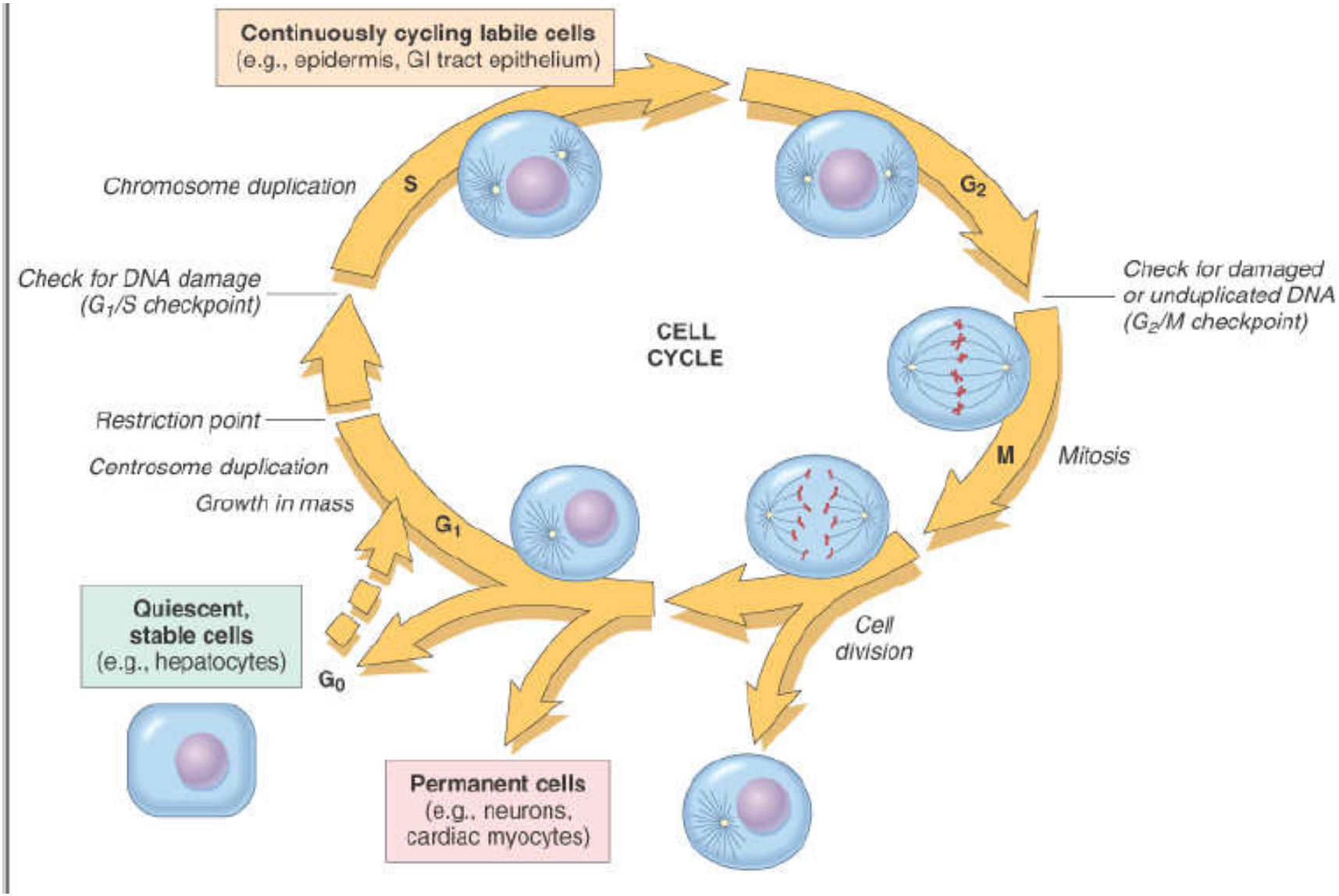
Overview of Repair

- Repair process involves:
  - Removal of debris
  - Granulation tissue formation
  - Scaring
- A complete restore or incomplete restore of injured tissue depends on
  - degree of injury (the original framework remains or not)
  - ability of regeneration of injured parenchymal cells

Outcome of Repair

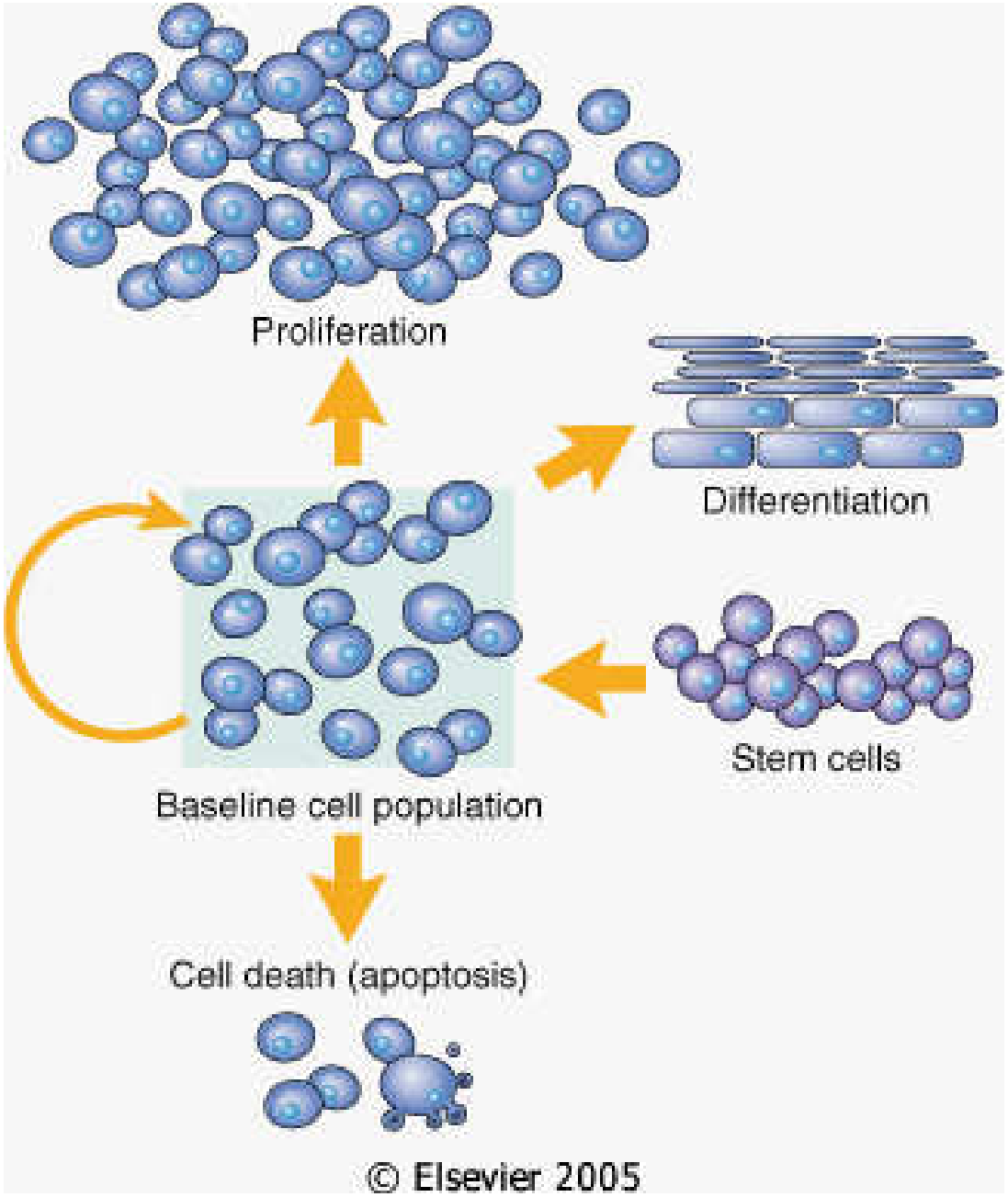
- Regeneration of injured tissue by parechymal cells of the same type
- Replacement by connective tissue (fibrosis), resulting in a scar
- In most cases tissue repair involves both of these two processes.

Type of cell & Wound Healing



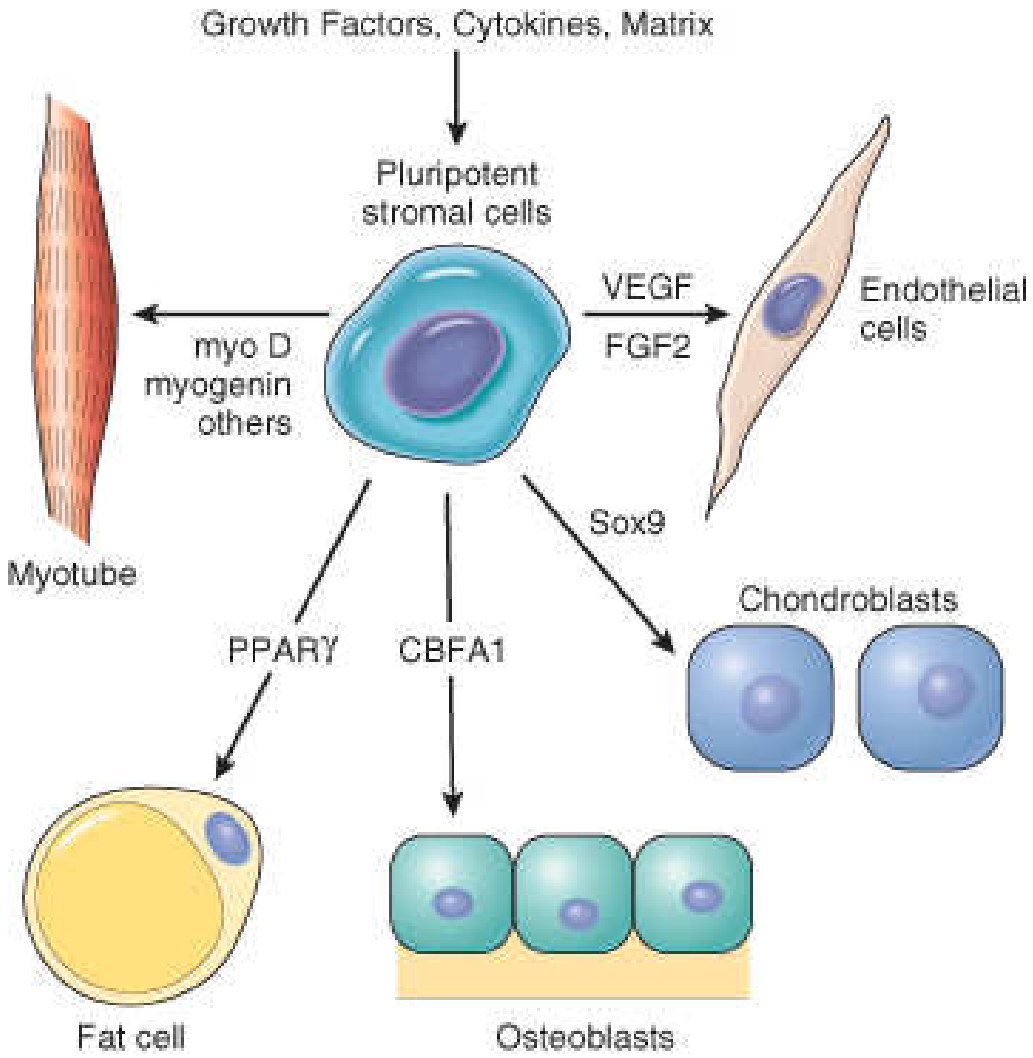
Cell Type & Wound Healing

- **Cell types – according to cell cycle**
- **Labile cells**
  - Divide continuously
  - Organs derived from these cells heal completely
  - Skin, GIT mucosa
- **Quiescent Stable cells (facultative mitotic)**
  - Replaced by regeneration from remaining cells stimulated to enter cell cycle
  - Liver & kidneys
- **Permanent (post-mitotic) cells**
  - Cannot be replaced
  - Scar tissue laid down in their stead
  - Neurones, cardiac myocytes

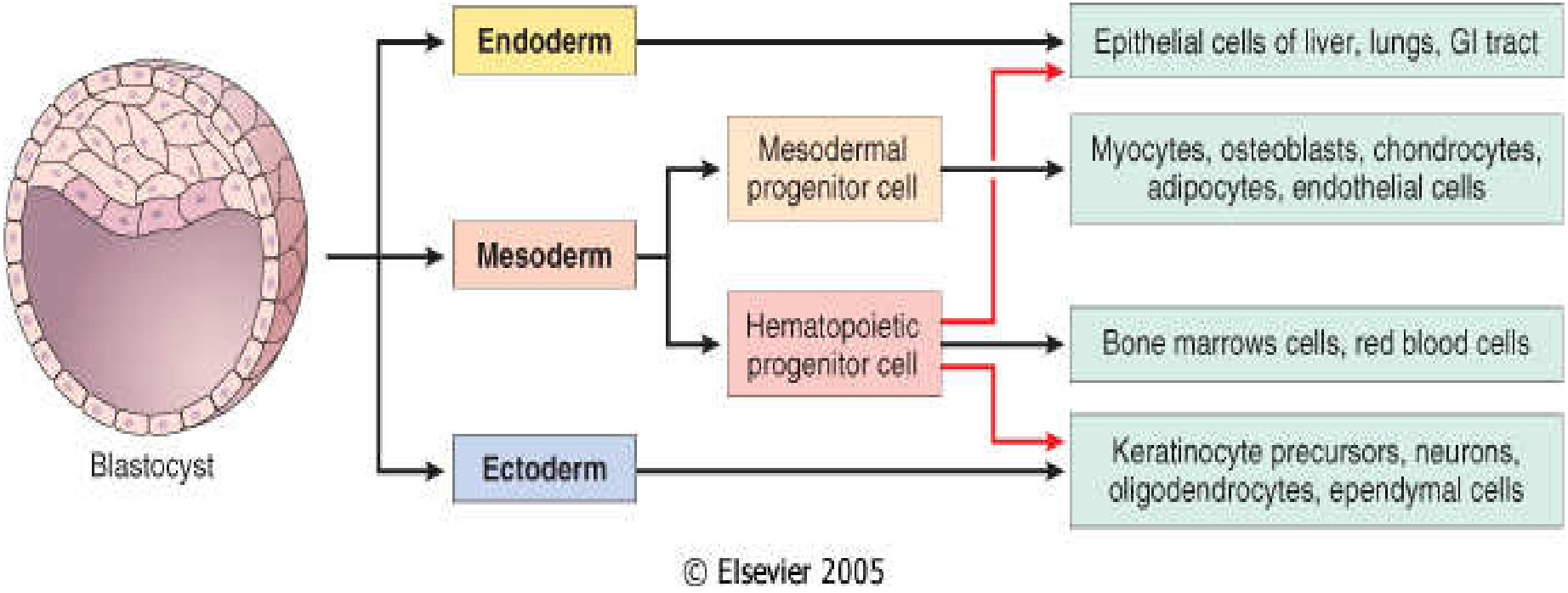


Mechanisms regulating cell populations.

Cell numbers can be altered by increased or decreased rates of stem cell input, by cell death due to apoptosis, or by changes in the rates of proliferation or differentiation.



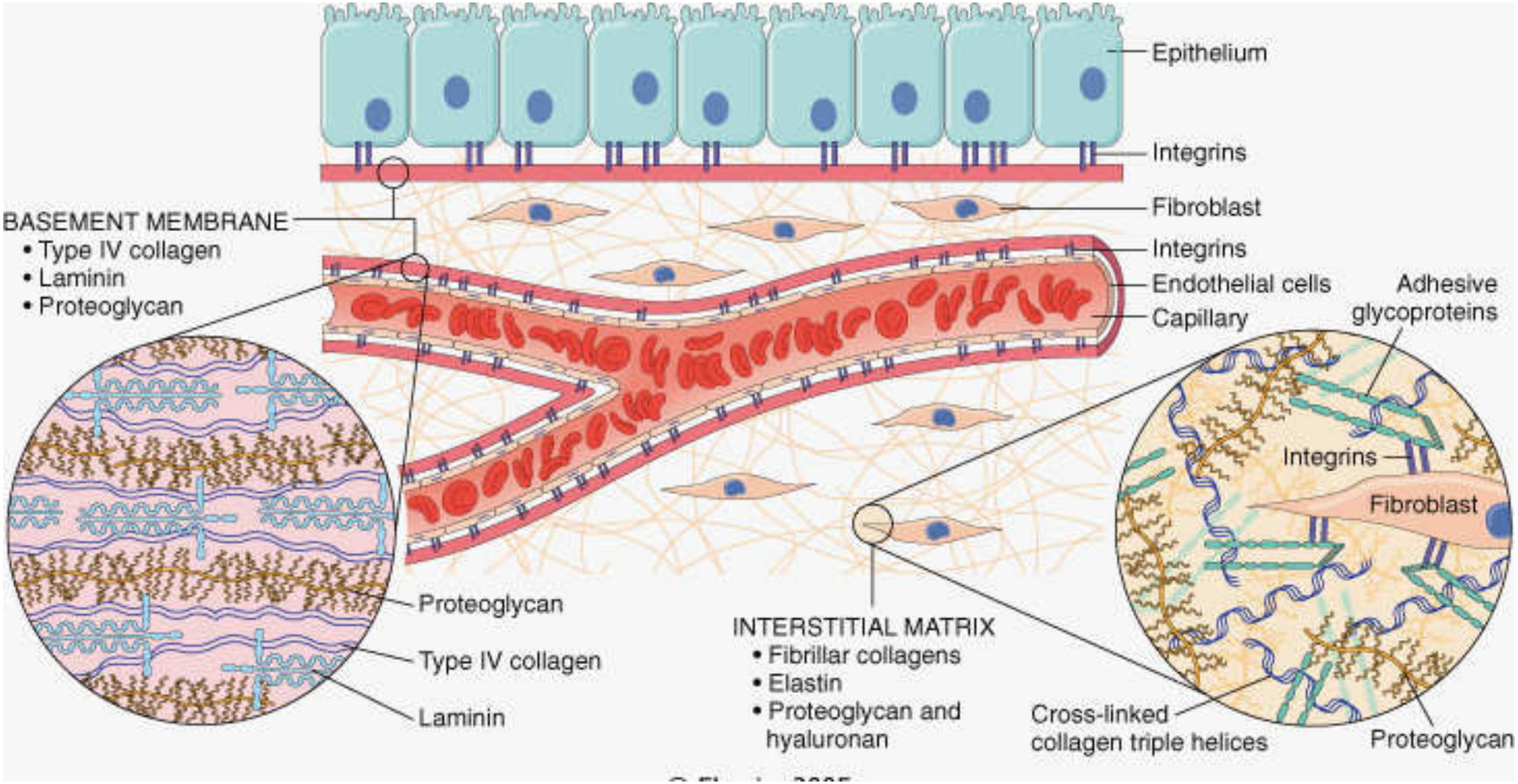
Differentiation pathways for pluripotent bone marrow stromal cells. Activation of key regulatory proteins by growth factors, cytokines, or matrix components leads to commitment of stem cells to differentiate into specific cellular lineages. Differentiation of myotubes requires the combined action of several factors (e.g., myoD, myogenin); fat cells require PPARγ, the osteogenic lineage requires CBFA1 (also known as RUNX2), cartilage formation requires Sox9, and endothelial cells require VEGF and FGF-2.

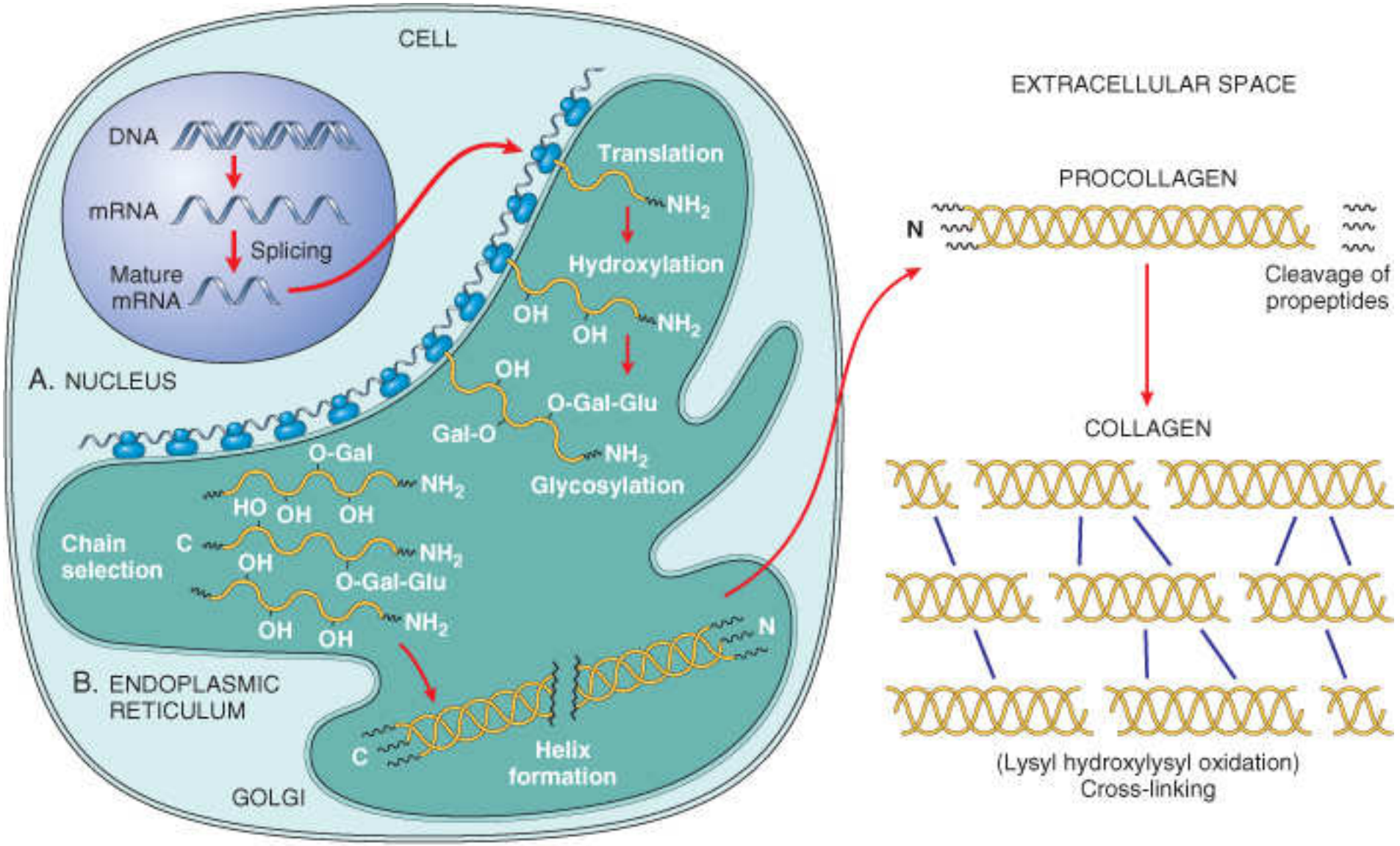


Differentiation of embryonic cells and generation of tissue cells by bone marrow precursors. During embryonic development the three germ layers-endoderm, mesoderm, and ectoderm-are formed, generating all tissues of the body. Adult stem cells localized in organs derived from these layers produce cells that are specific for the organs at which they reside. However, some adult bone marrow stem cells, in addition to producing the blood lineages (mesodermal derived), can also generate cells for tissues that originated from the endoderm and ectoderm (indicated by the *red lines*).

The Extracellular Matrix

- A dynamic, constantly, remodeling, macromolecular complex
  - Interstitial matrix
  - Basement membrane (BM)
- Major components
  - Collagens
  - Elastic fibers
  - Fibronectin
  - Laminin
  - Proteoglycans


Epithelium
Integrins
Fibroblast
Integrins
Endothelial cells
Capillary
BASEMENT MEMBRANE
• Type IV collagen
• Laminin
• Proteoglycan
Adhesive glycoproteins
Integrins
Fibroblast
Proteoglycan
Type IV collagen
Laminin
INTERSTITIAL MATRIX
• Fibrillar collagens
• Elastin
• Proteoglycan and hyaluronan
Cross-linked collagen triple helices
Proteoglycan



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Steps in collagen synthesis

The Extracellular Matrix

- Roles of ECM
  - mechanical support for cell anchorage
  - determination of cell orientation (polarity)
  - control cell growth
  - maintenance of cell differentiation
  - scaffolding for tissue renewal
  - establishment of tissue microenvironments, storage and presentation of regulatory molecules

Definition - Healing

- Healing is a response to tissue injury, and represents an attempt by the organism to restore integrity to an injured tissue.
- It overlaps the inflammatory process, and it is only for didactic purposes that the two are discussed separately.

Wound Healing

- The orderly process by which a wound is eventually replaced by a scar
- Destruction of epithelium only is termed an erosion, and heals exclusively by regeneration
- If destruction of the basement membrane occurs (extracellular matrix), then a scar will form

Steps in Wound Healing

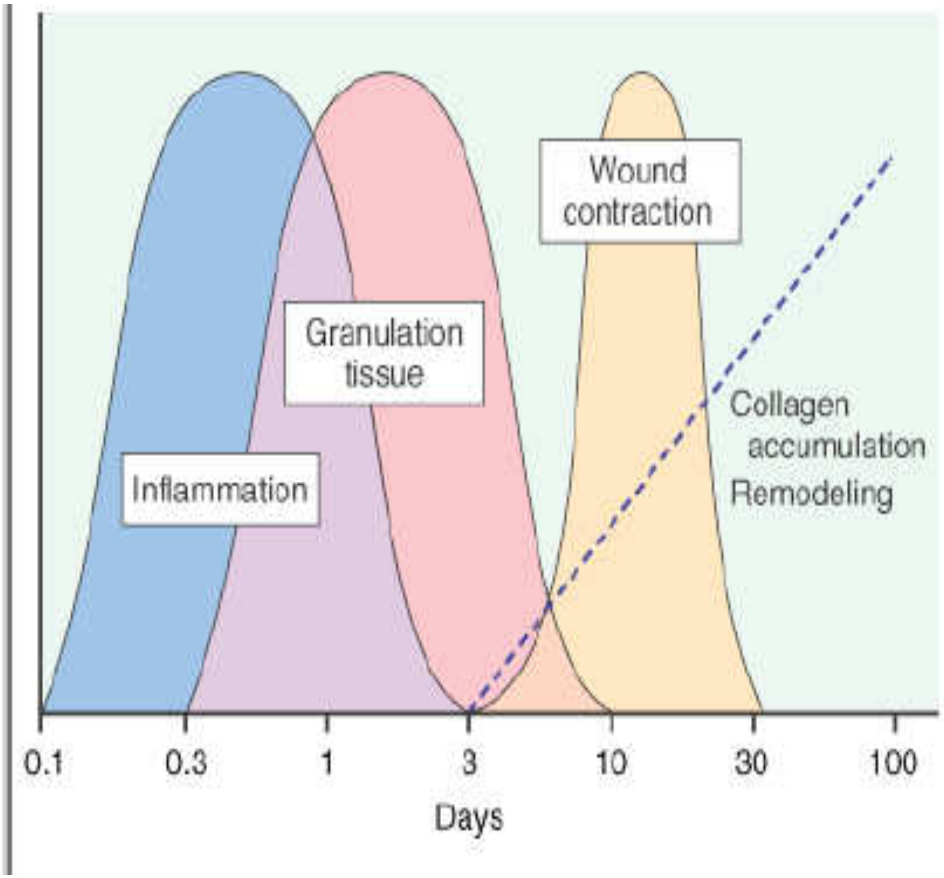
- Induction of an acute inflammatory response
- Regeneration of parenchymal cells
- Migration and proliferation of both parenchymal and connective tissue cells
- Synthesis of extracellular matrix proteins (collagen III)
- Remodeling
- Collagenization and maturation of wound

Wound Healing

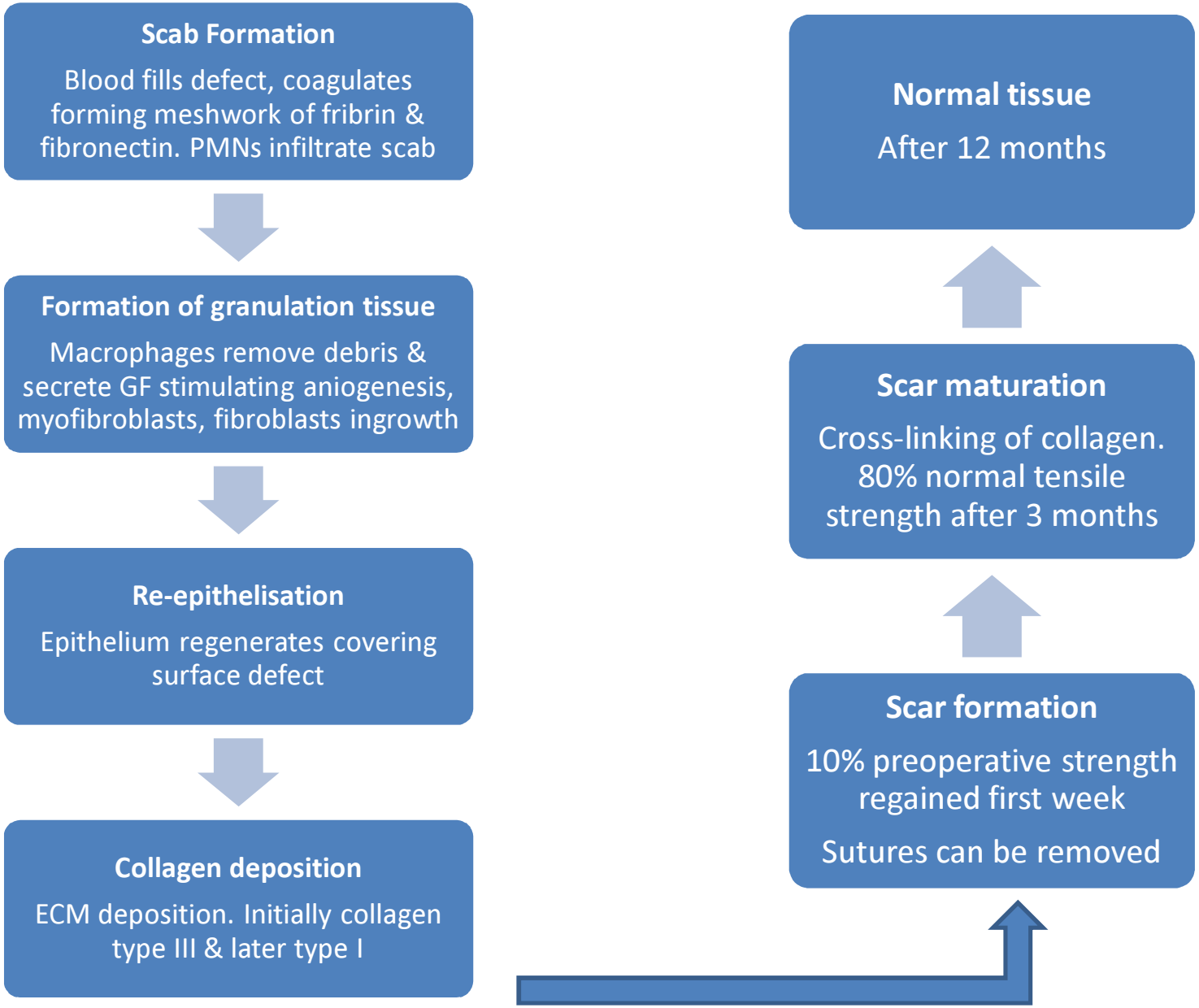
- Contraction
  - Accounts for a reduction in size of the defect primarily by the action of myofibroblasts
  - This process produces faster healing, since only one-third to one-half of the original defect must be repaired
  - Myofibroblasts account for contraction, and represent an intermediate type of cell, between a fibroblast and a myocyte

Normal Wound Healing Process

- Skin wound healing can occur via 2 ways:
- Healing by primary intention
  - Clean surgical wounds
- Healing by secondary intention
  - Large gaping wounds
  - infected wounds



Healing by Primary Intention

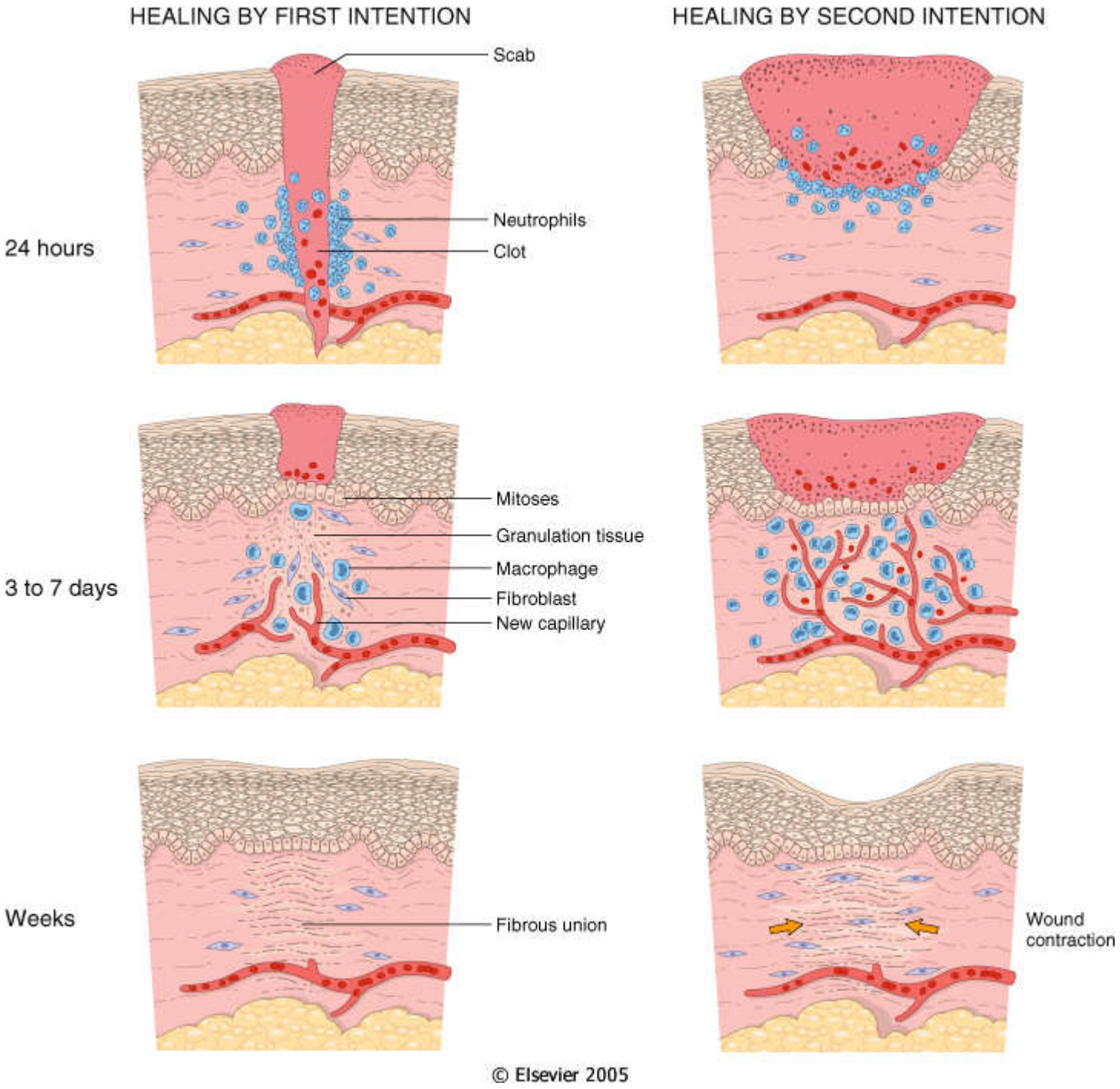


Selected Growth Factors

Growth Factor	Function
PDGF. Synthesized by plts & other cells	Promote proliferative reposes of fibroblasts, smooth muscle cells. Requires other growth factors for effective function. •Chemotactic for fibroblasts & smooth muscle cells •Chemotactic for monocytes
Epidermal growth factor	Promote growth of endothelial cells, fibroblasts & epithelial cells
Fibroblast growth factor	Promote synthesize of ECM proteins by fibroblasts, endothelial cells, monocytes
Fibronectin	Chemotactic for fibroblasts & endothelial cells, links ECM components to cell-surface intergrins (intergrins mediate interactions between cells & ECM)
Transforming growth factors	Growth inhibitor. Aid in modulation

Wound Healing by Secondary Intention

- More pronounced & prolonged inflammatory phase in which PMNs may persists for days
- More abundant granulation tissue
- Wound contraction by myofibroblasts to help draw margins of wound closer to one another



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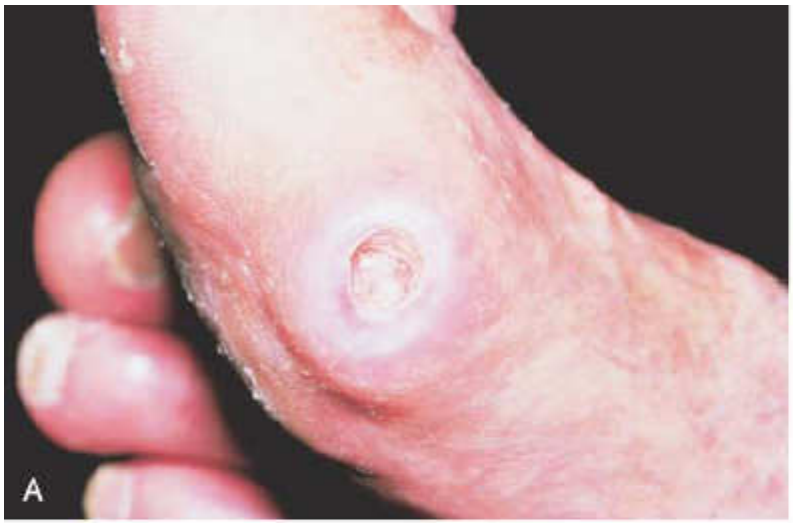
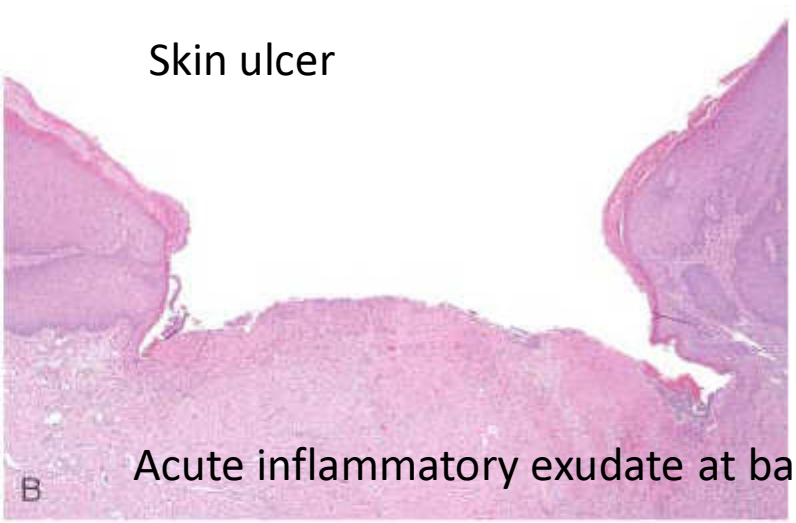
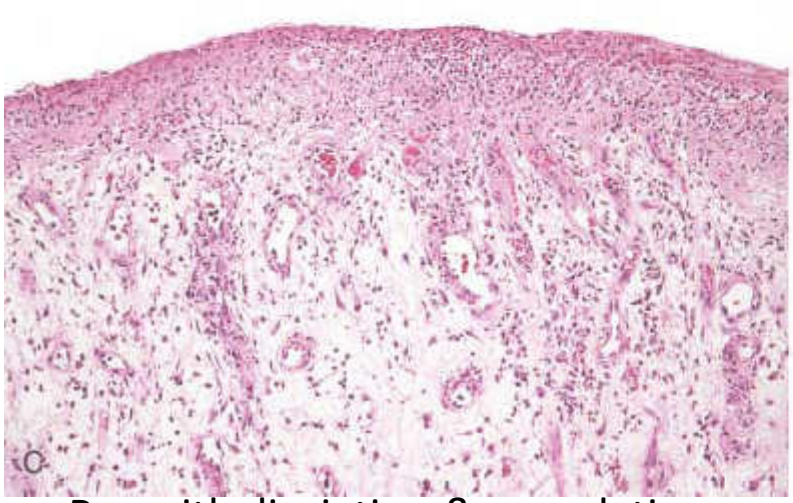
Healing



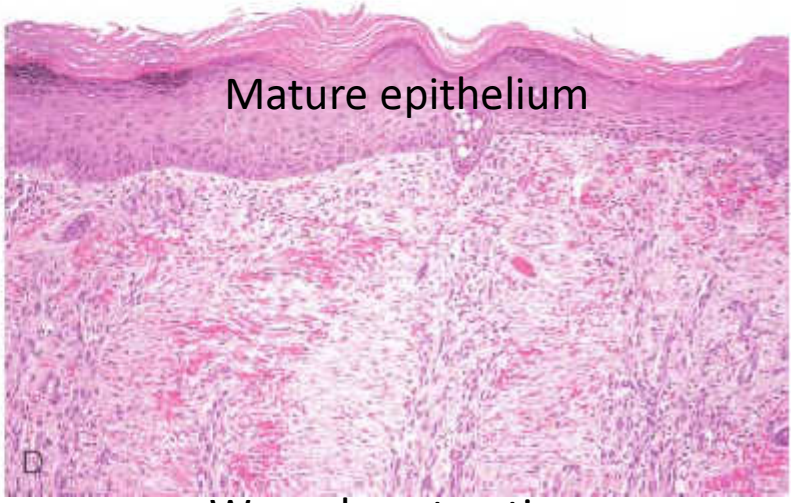
Skin ulcer



Acute inflammatory exudate at base



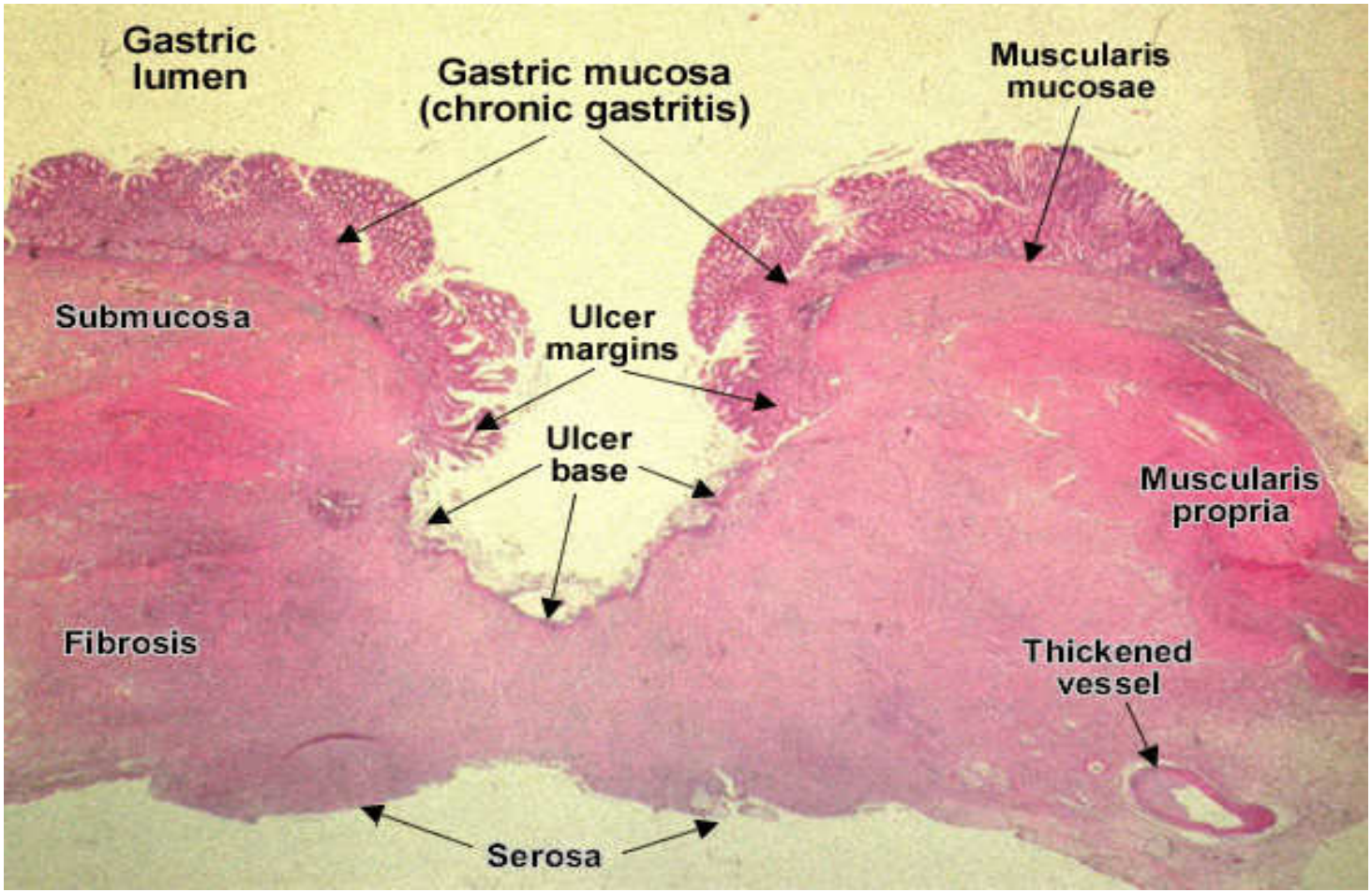
Re-epitheliaziation & granulation



Mature epithelium

Wound contraction

Chronic Ulcer



Example of ulcer: peptic ulcer

Factors that Influence Wound Healing

- Type, size, and location of the wound
- Vascular supply (diabetics heal poorly)
- Infection - delays wound healing and leads to more granulation tissue and scarring
- Movement - wounds over joints do not heal well due to traction
- Radiation - ionizing radiation is bad, UV is good

Factors that Influence Wound Healing

- Overall nutrition: vitamin and protein deficiencies lead to poor wound healing, especially vitamin C, which is involved in collagen synthesis
- Age: younger is definitely better!
- Hormones - corticosteroids drastically impair wound healing, because of their profound effect on inflammatory cells

Complications of Wound Healing

- Defective scar formation
- Contraction
- Poor healing and defective or weak scar formation
  - Dehiscence (separation of margins) or ulceration is usually due to:
    - **Wound infection (common)**
    - **Malnutrition (scurvy - rare)**
    - **Hypoxia with ulceration, usually due to inadequate vascularity in a skin flap (common).**
    - **Tension**

Abnormal Wound Healing

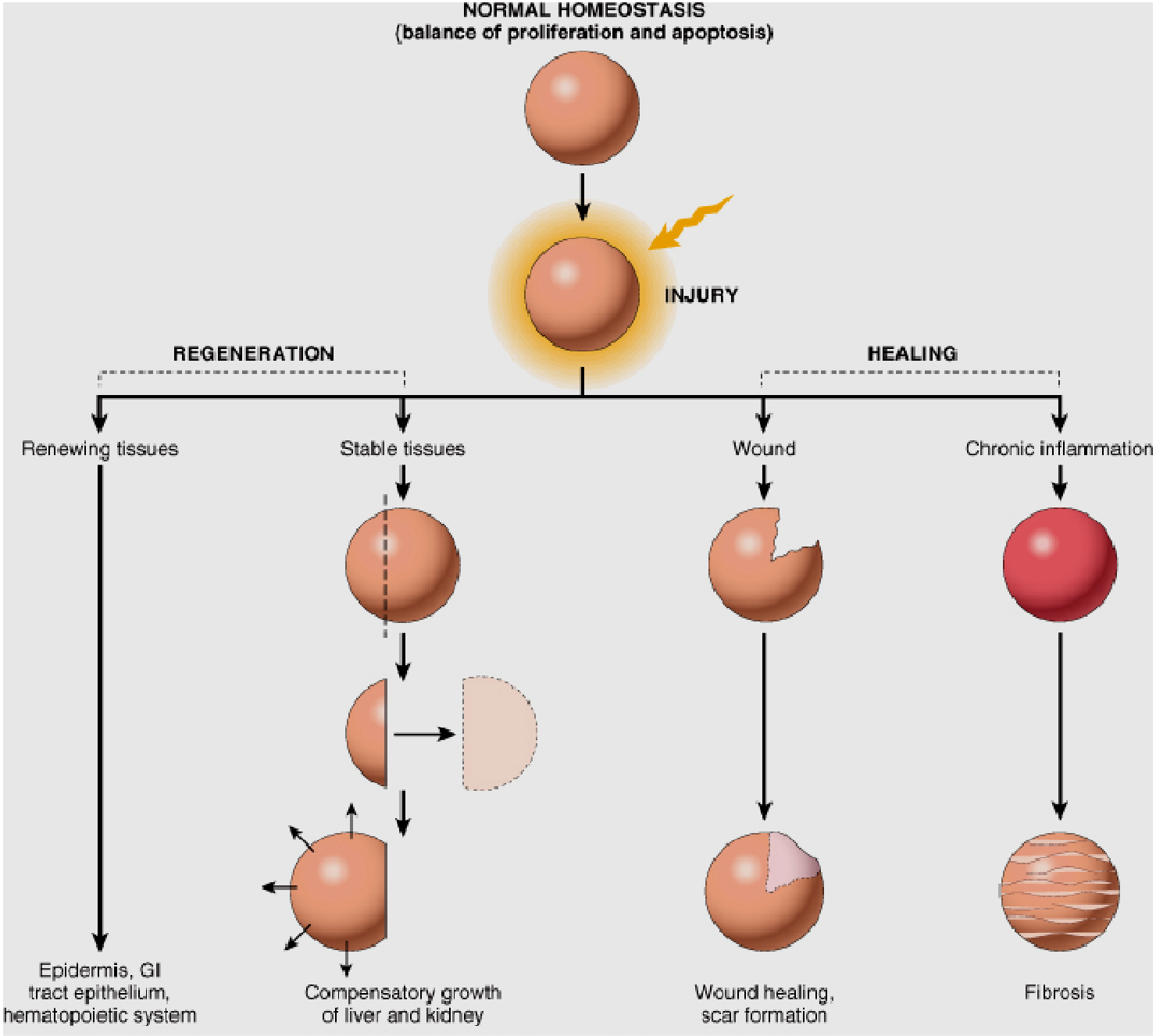
- Excessive scar formation (keloid)
- Delayed wound healing
  - Infection
  - Mechanical factors (trauma, tension, foreign bodies)
  - Malnutrition, poor circulation or old age
  - Drugs e.g. corticosteroids, cytotoxic drugs

Excessive Scar Formation

- Keloids (hypertrophic scars) are the result of over-exuberant production of scar tissue, which is primarily composed of type III collagen
- The cause is thought to be due to genetic factors, perhaps due to lack of the proper *metalloproteinases (collagenases)* to degrade type III collagen

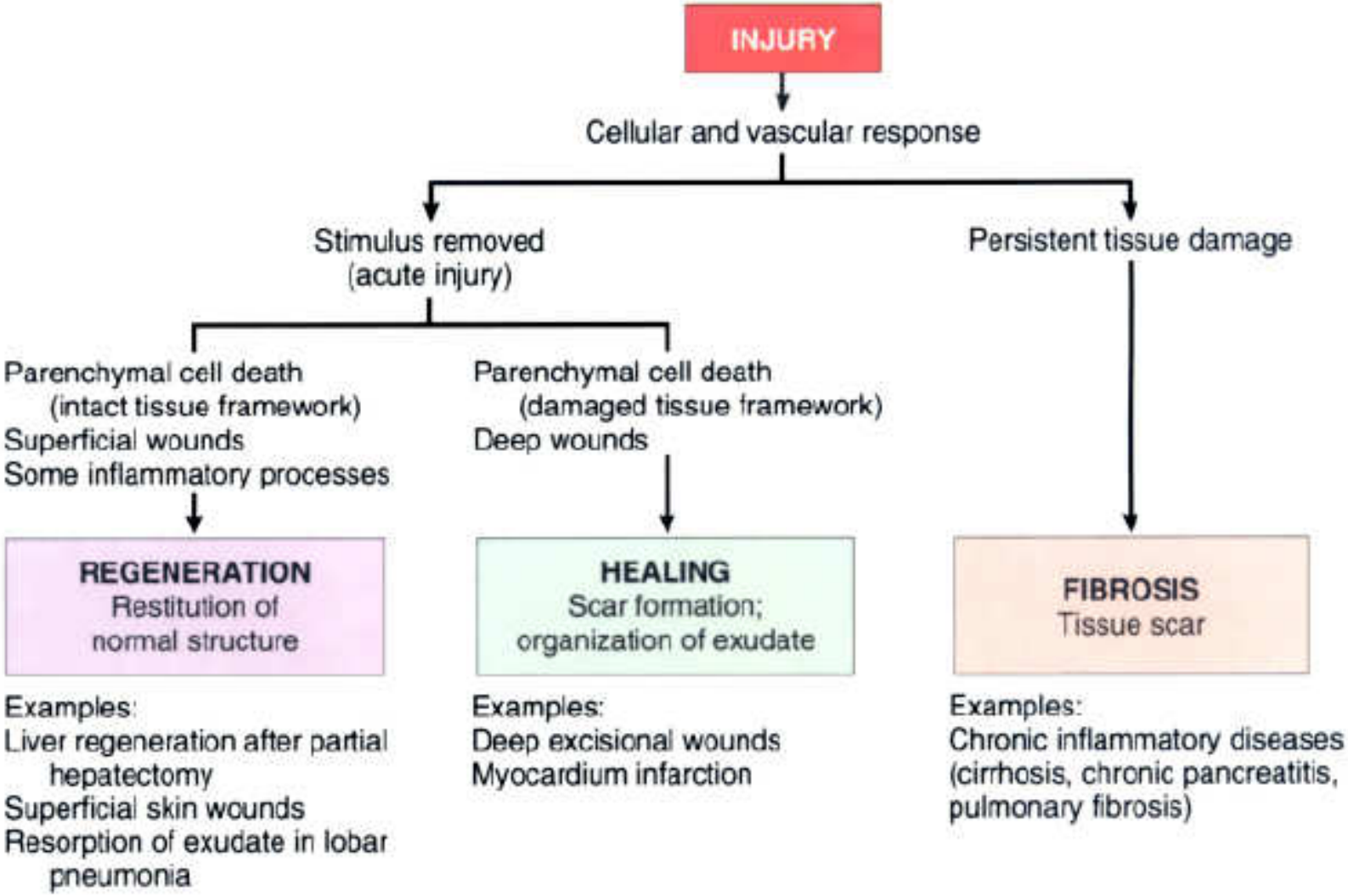
Contraction

- Excessive contraction of a wound is known as a contracture. They are a special problem in the treatment of extensive burns
- Several diseases of unknown cause are characterized by the formation of contractures
  - Peyronie disease of the penis

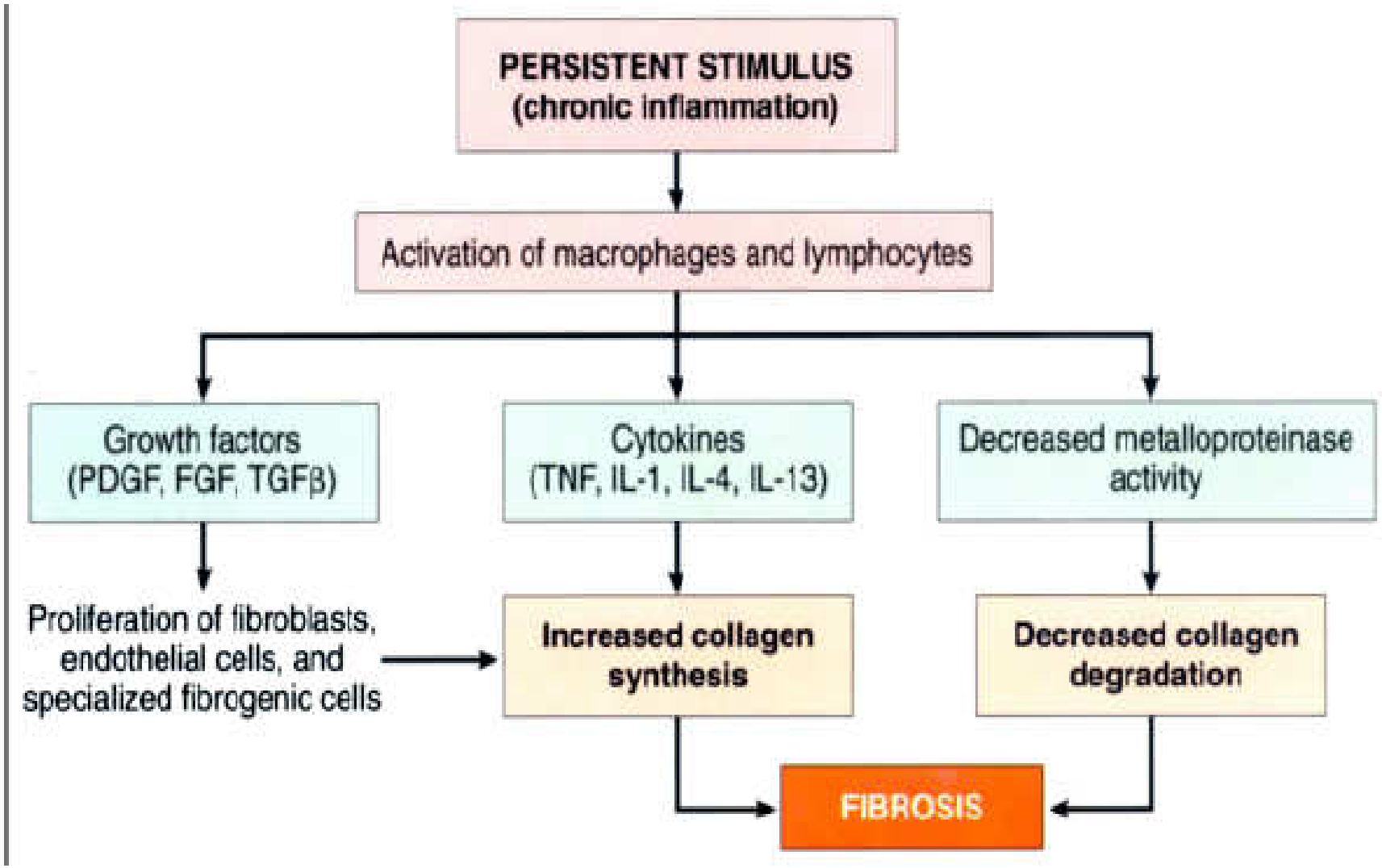


Tissue response to injury. Repair after injury can occur by regeneration, which restores normal tissue, or by healing, which leads to scar formation and fibrosis.

Repair response after injury



Fibrosis in chronic inflammation



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