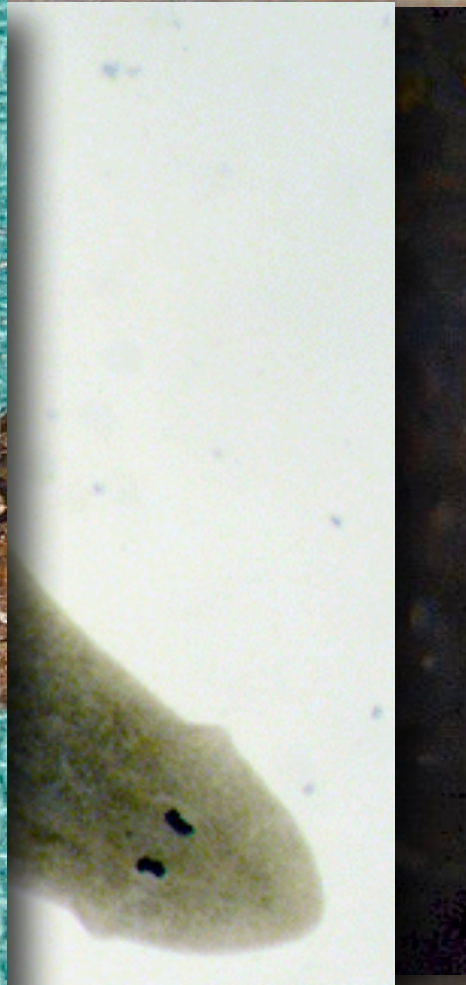




Tissue Repair: Regeneration, Fibrosis and Healing

Henry Sánchez, M.D.

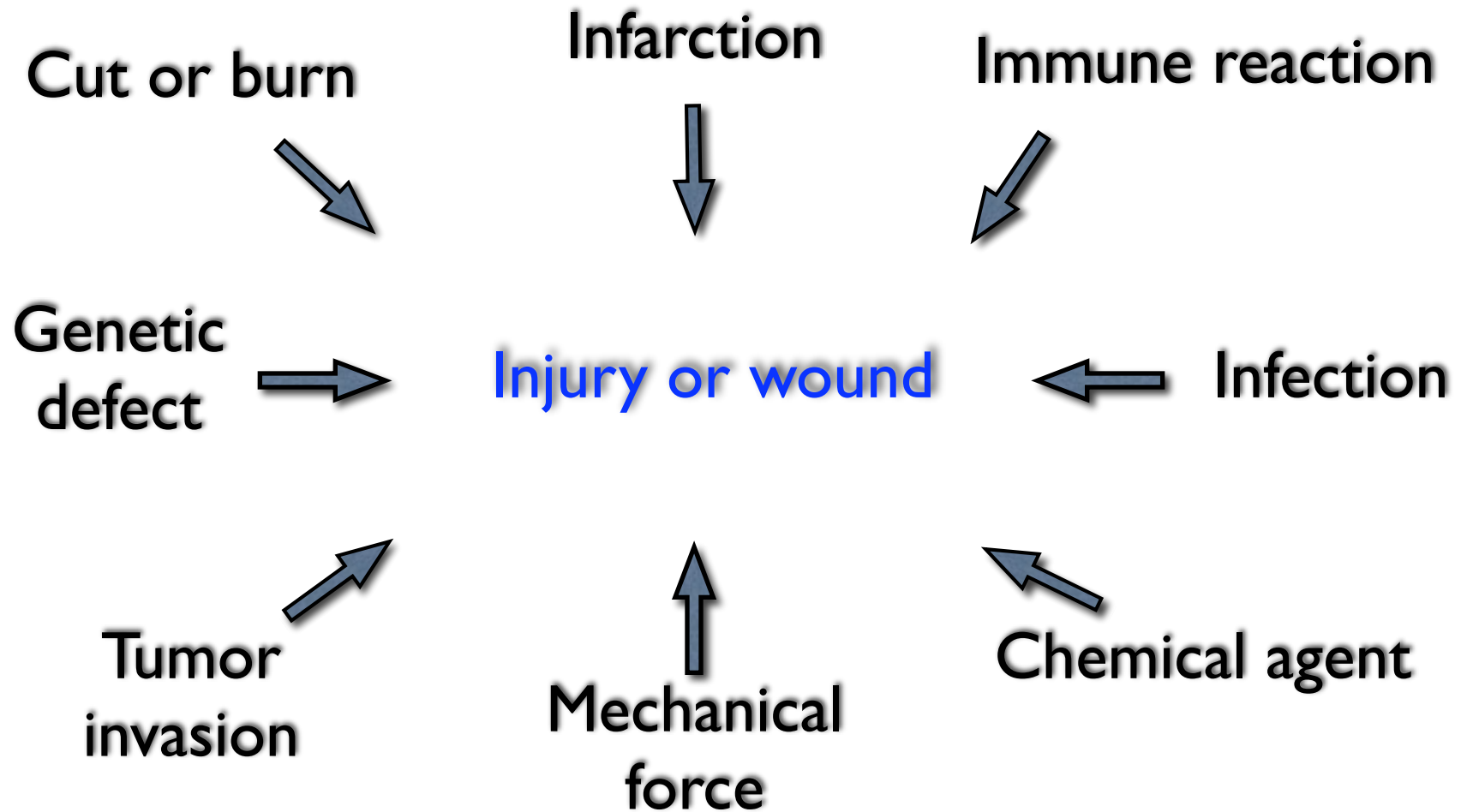


Lizard **Platyrrhinus**

Reparative Process

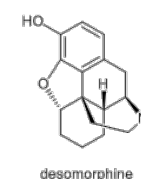
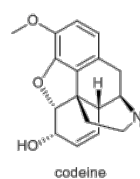
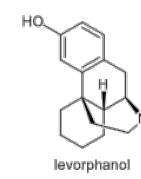
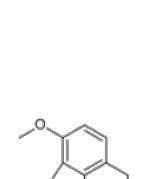
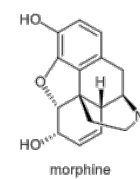
- **Regeneration** - anatomic structures are completely replaced by the growth of new cells and tissues
- **Healing** - a tissue response to injury leading to collagen deposition and scar formation (**fibrosis**)
- Mammals have a limited capacity for regeneration and a greater propensity for healing with fibrosis





Classification of Wounds

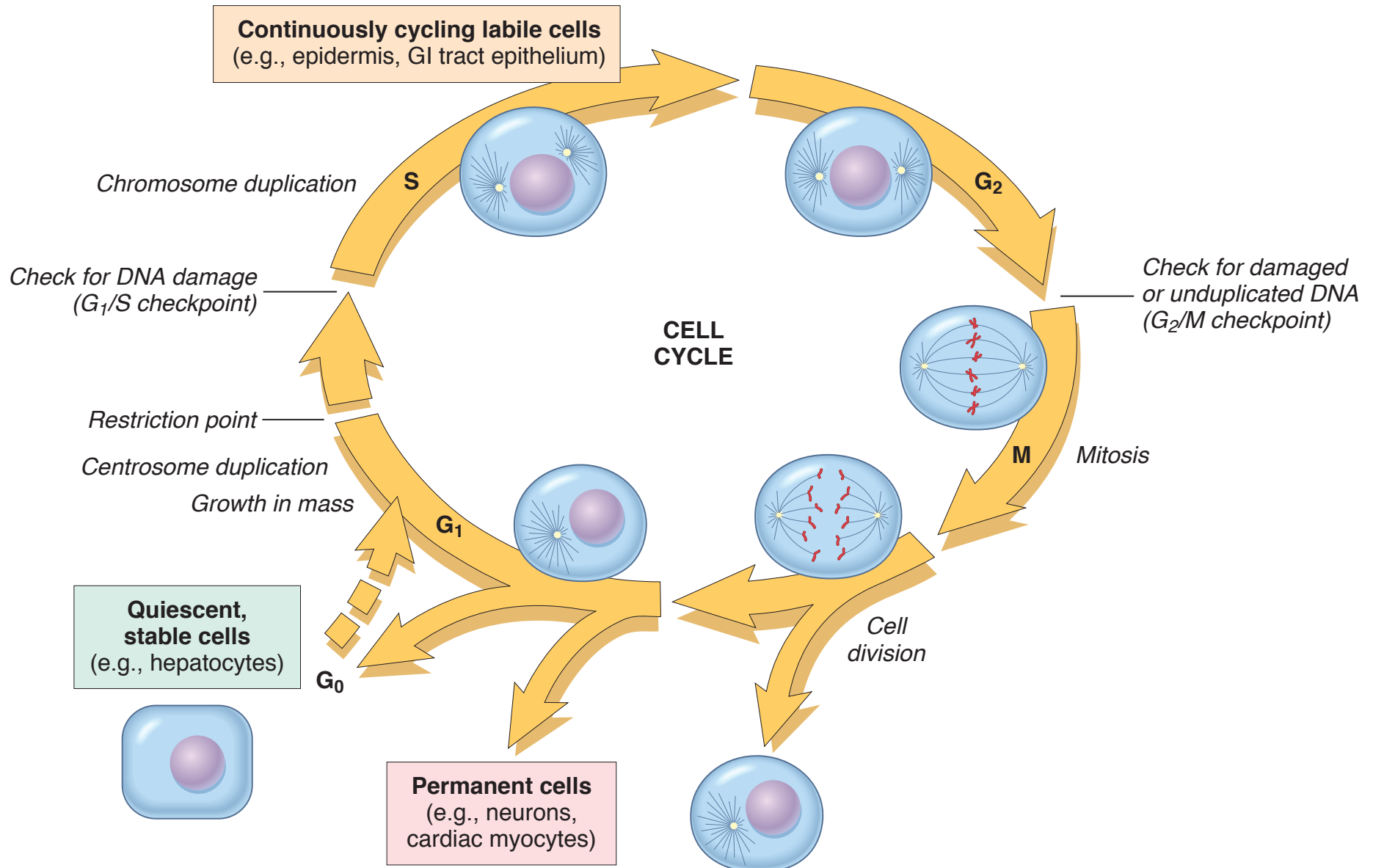
- **Acute wound** - an orderly and timely reparative process leading to complete or partial restoration
- **Chronic wound** - failed to proceed in an orderly and timely reparative process, or proceeded through the repair process without a sustained structure/function



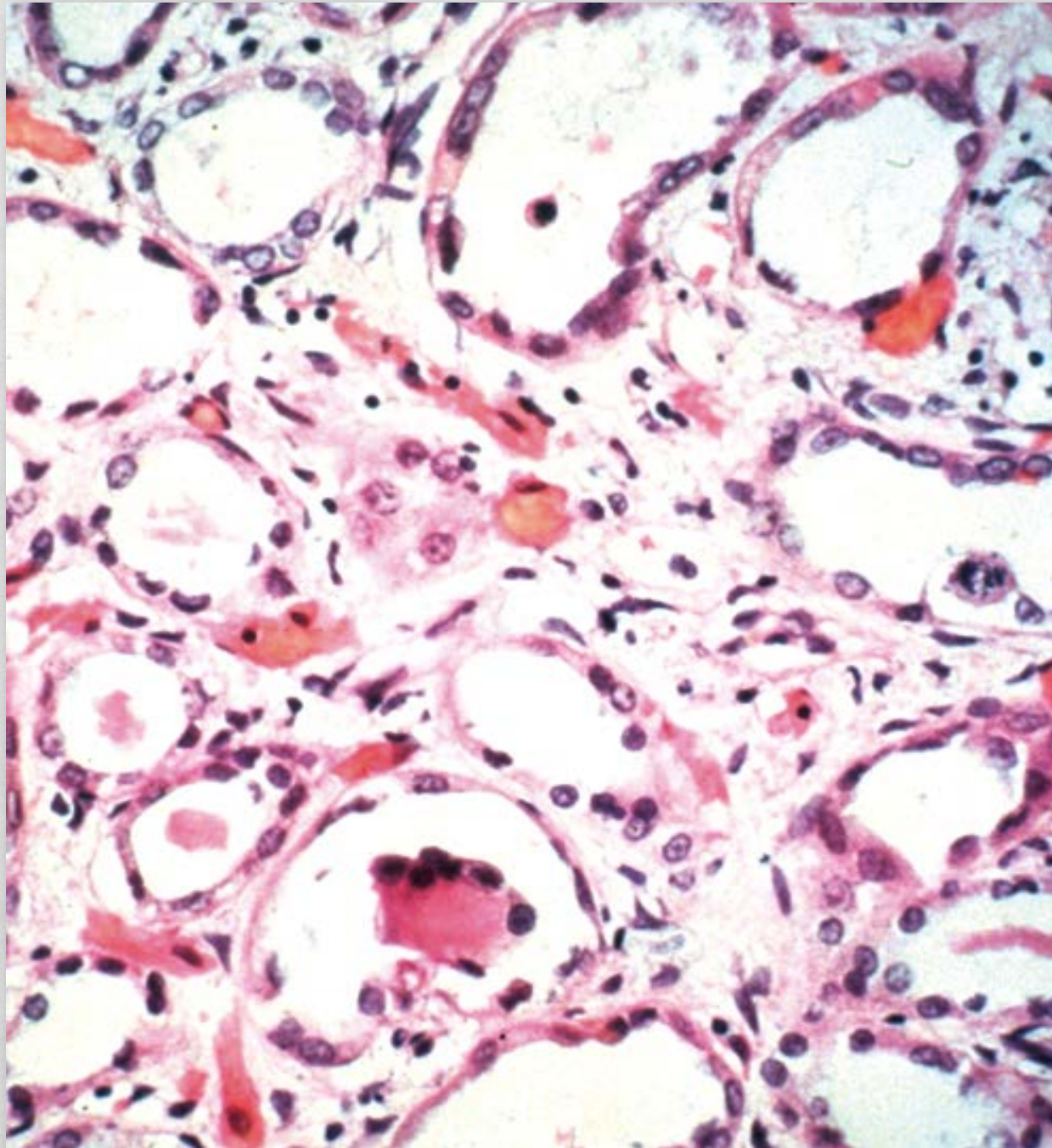
Tissue Types and Regenerative Capacity

- **Labile tissues** - constantly proliferating (derived from tissue stem cells)
- **Stable tissues** - normally a low level of replication and can undergo rapid division in response to stimuli (mitosis of differentiated cells + stem cells)
- **Permanent tissues** - loss the ability to replicate (no apparent stem cells)

Regenerative Capacity



Acute Tubular Necrosis



Components of Healing

- Multiple overlapping processes leading to wound closure
 - Hemostasis - platelets & fibrin
 - Inflammation - PMNs, macrophages & lymphocytes
 - Regeneration - re-epithelization
 - Fibrosis - angiogenesis, fibroblasts & ECM
 - Remodeling - collagen crosslinking/degradation

Hemostasis Phase

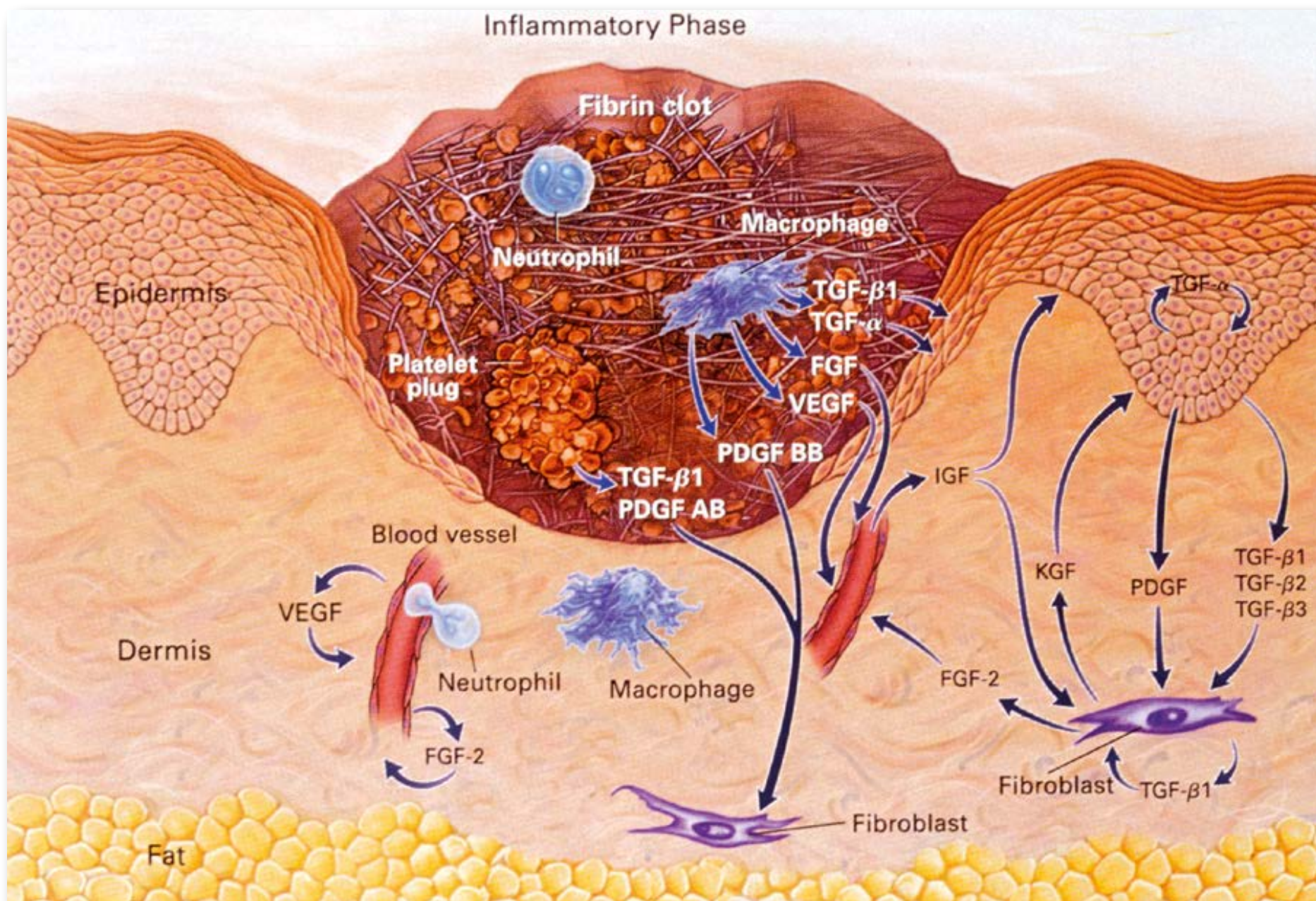
- Hemorrhage
- Release of vasoactive compounds
- Platelets and coagulation cascade form a blood clot (fibrin, platelets, red blood cells & leukocytes) - a protective covering (**eschar** or “**scab**”)
- Blood clot - provisional ECM



Inflammatory Phase

Injury → Inflammation → Repair

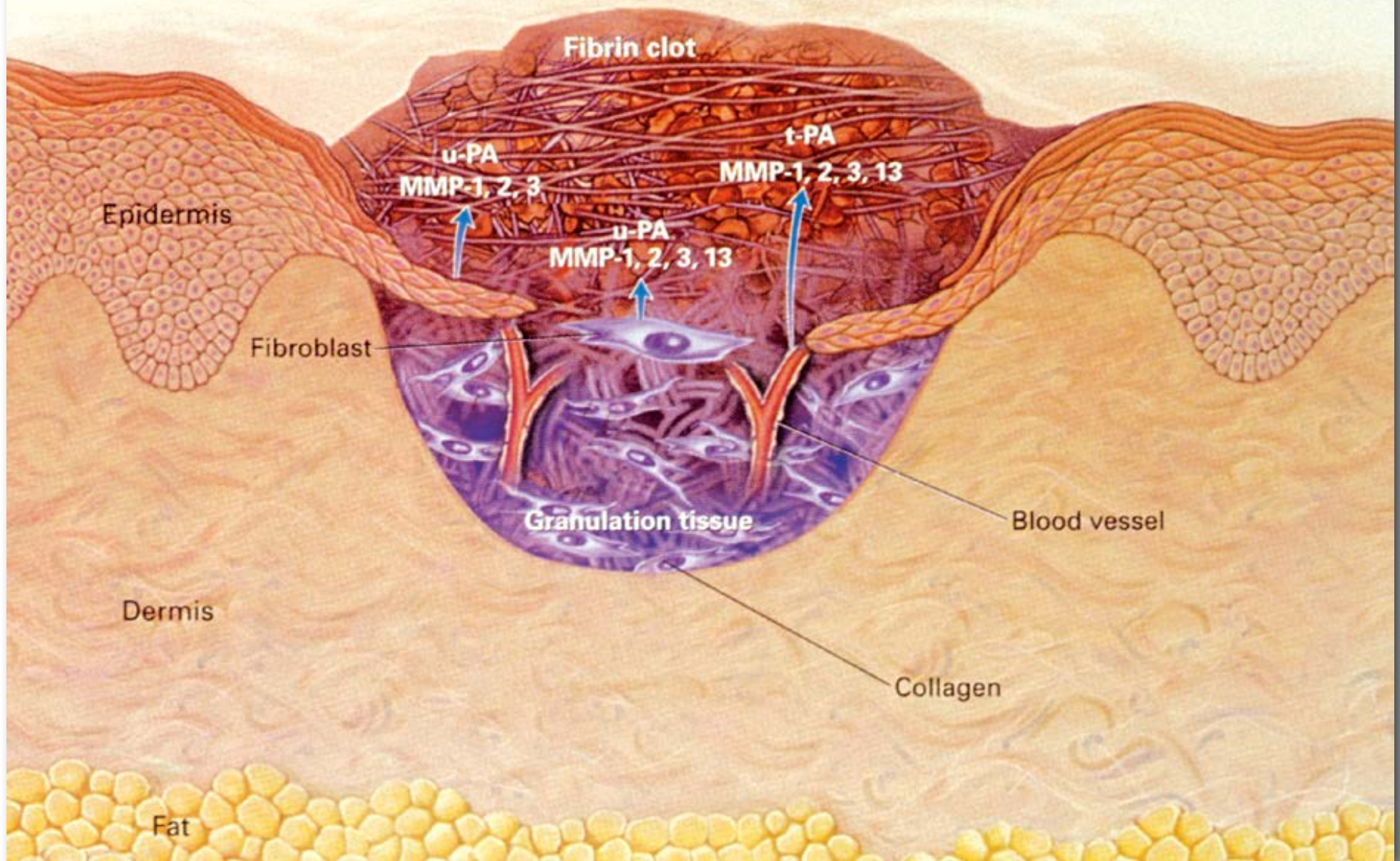
- Cells of inflammation - neutrophils, macrophages, lymphocytes
- Activated macrophage release growth factors leading to the formation of **granulation tissue** via **angiogenesis**
- **MACROPHAGE** orchestrates healing



Regeneration Phase (Re-epithelization)

- Two mechanisms
 - Migration - dominant process
 - Mitosis (replication)

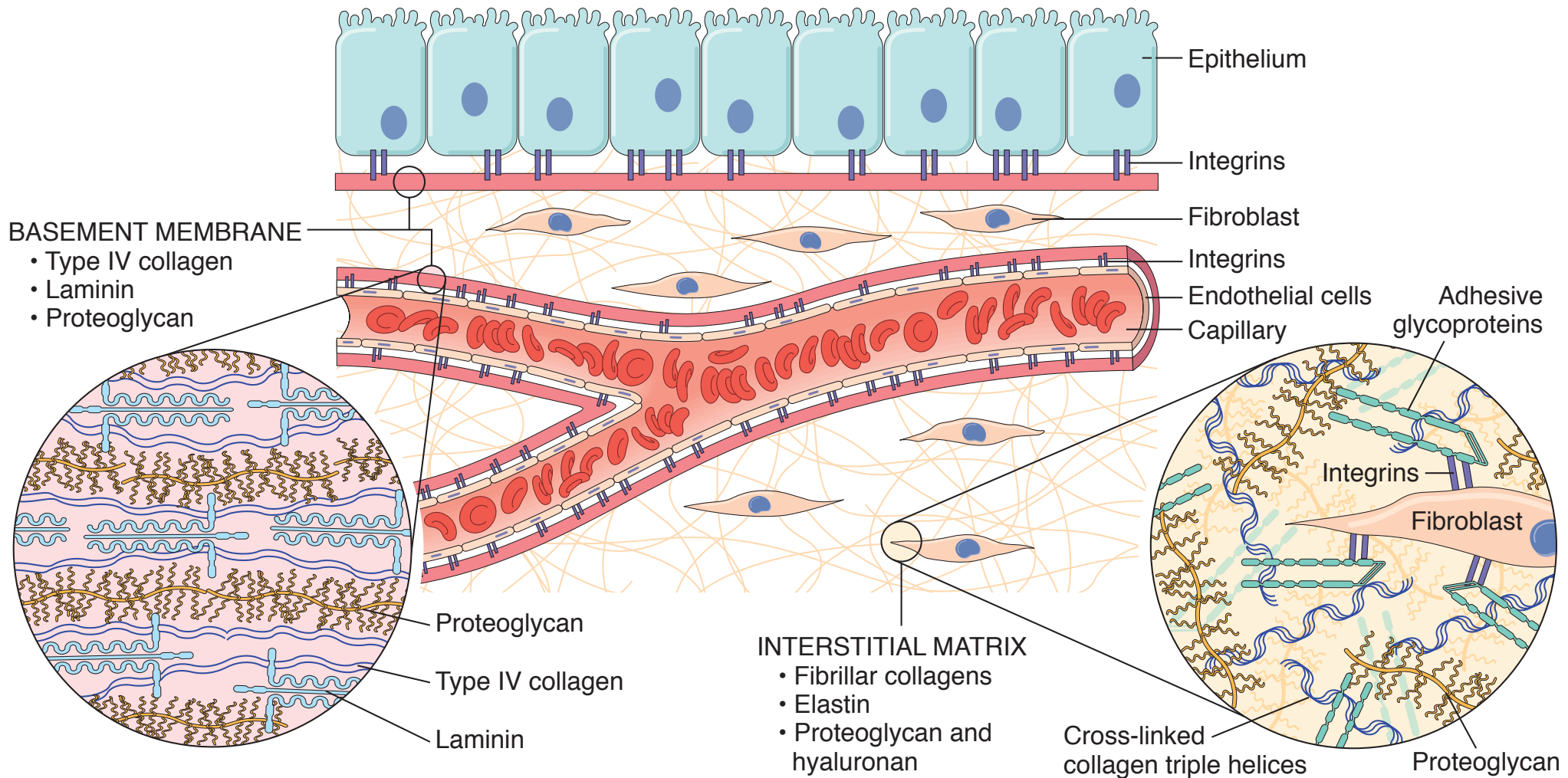
Reepithelialization and Neovascularization



Extracellular Matrix (ECM)

- **ECM** - adhesion and fibrous proteins embedded in a hydrated polysaccharide gel
 - Proteoglycans (glycoaminoglycans)
 - Fibrous structural proteins (collagen and elastin)
 - Fibronectin and laminin
- **Gel matrix** ("ground substance") - diffusion of nutrients, metabolites, growth factors, and hormones

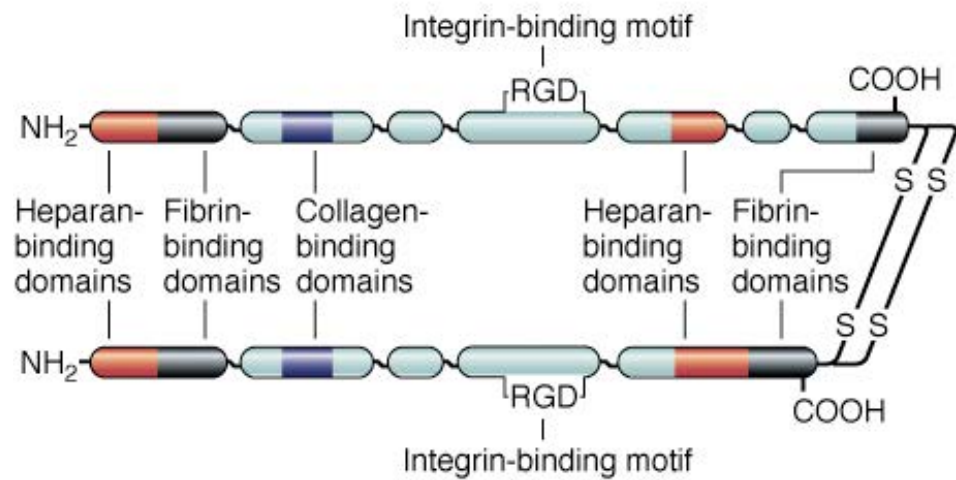
Extracellular Matrix Components



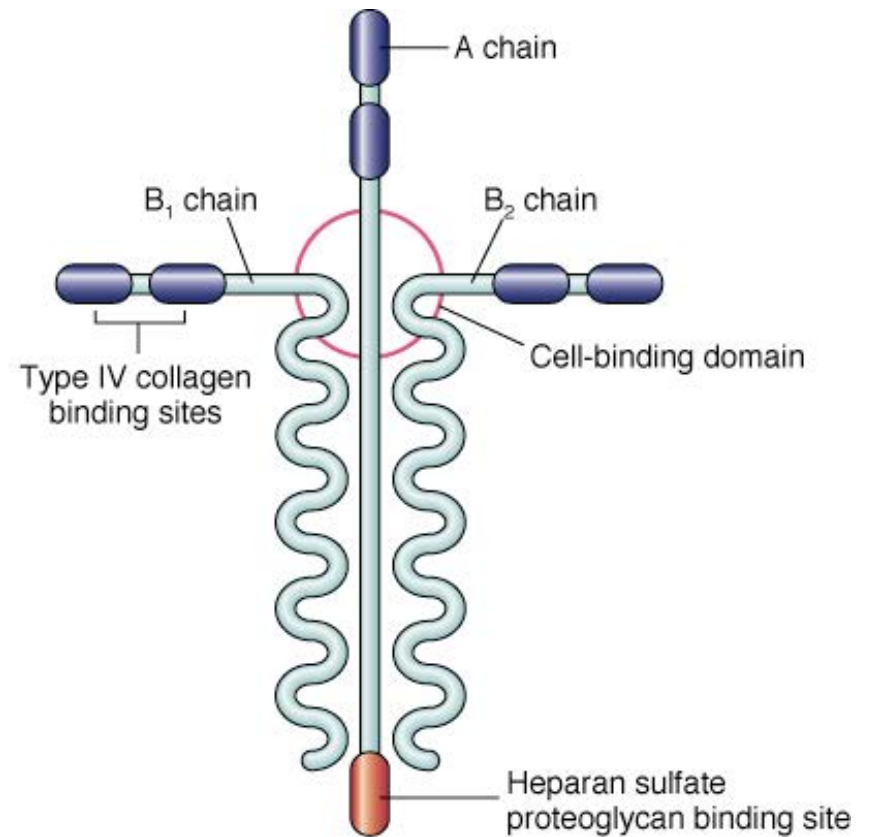
Major Collagens

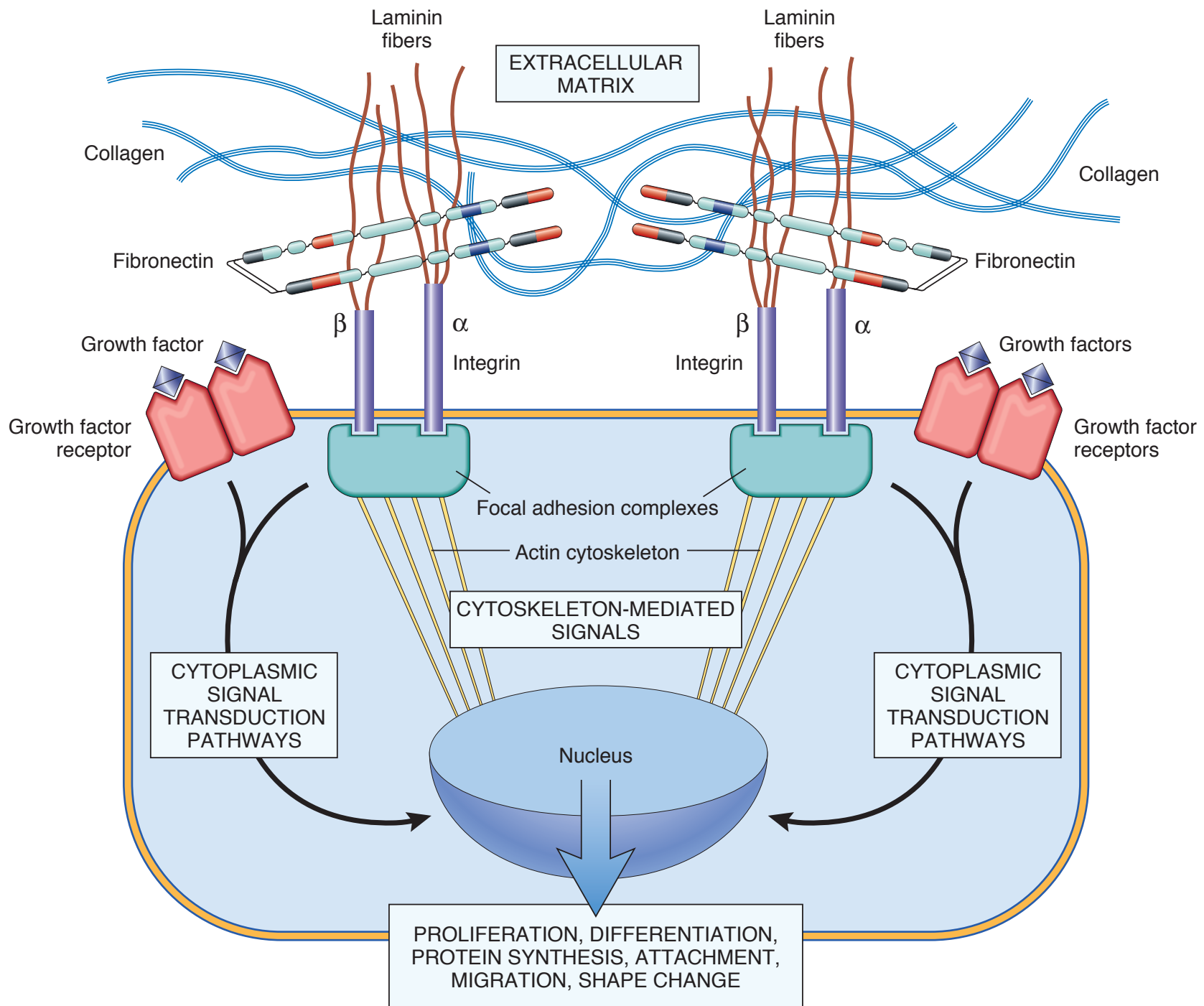
Collagen	Location	Cells
Type I	Skin, bone, tendon: hard mature scar tissue late in fibrosis and in late cirrhosis, constituting 90% body collagen	Primarily fibroblasts, but in other cells also
Type II	Cartilage	Chondrocytes
Type III	Blood vessels, smooth muscle in uterus, GI tract, and other hollow organs; in rapidly proliferating tissues; during embryogenesis, wound healing, organ regeneration; early cirrhosis and fibrosis	Smooth muscle cells, primitive fibroblasts and stem cells
Type IV	Basement membranes	Epithelial cells and highly specialized stromal cells such as endothelial and muscle cells

Fibronectin



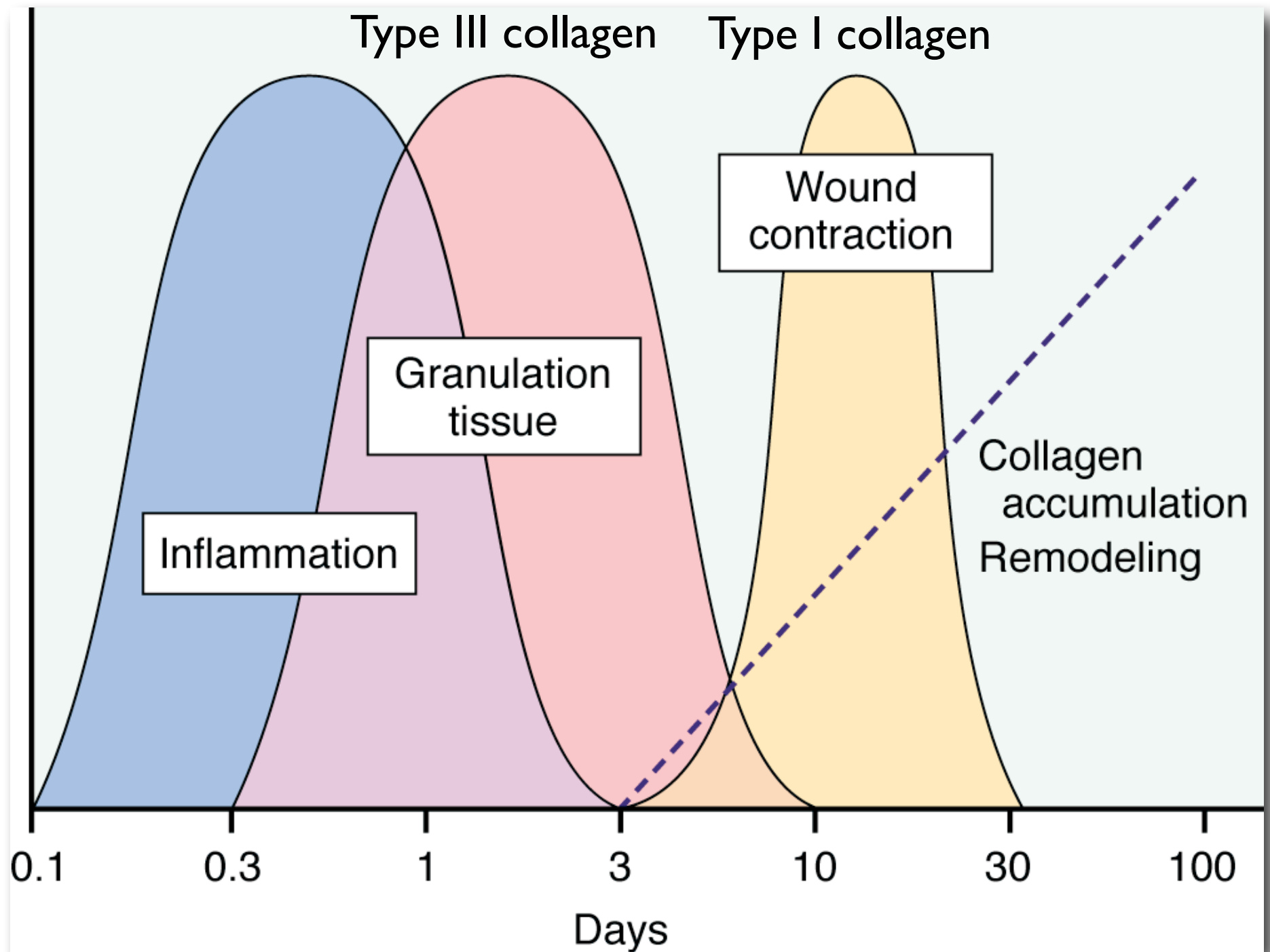
Laminin





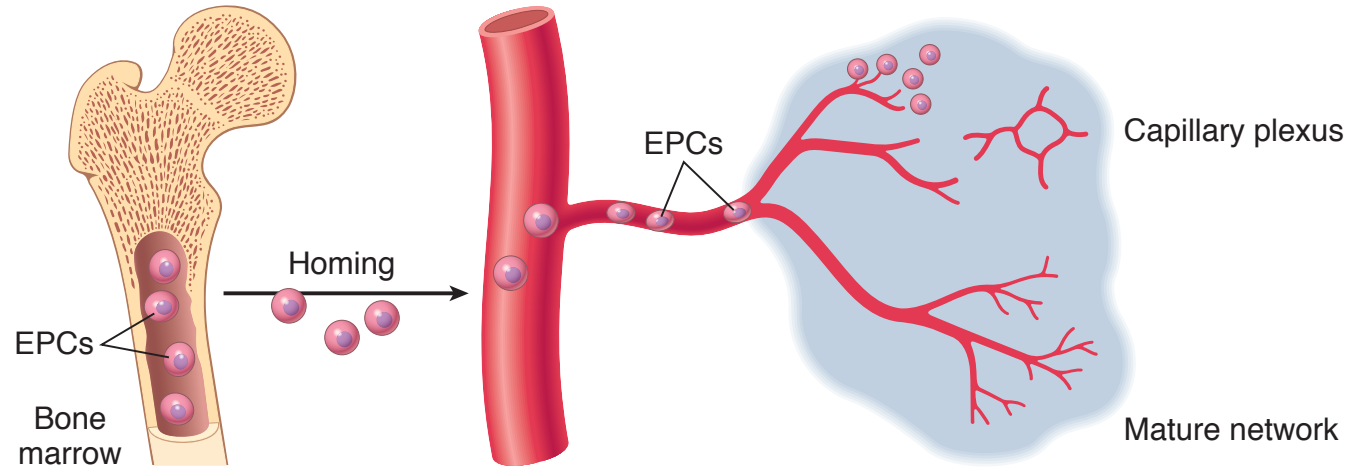
Fibrosis Phase

- Increased collagen synthesis - PDGF, FGF, TGF-beta and interleukins (IL-1 & IL-13)
- Granulation tissue - type III collagen
- Scar formation - type I collagen
- Myofibroblasts - wound contraction
- Angiogenesis (neovascularization) - Vascular Endothelial Growth Factor (VEGF)

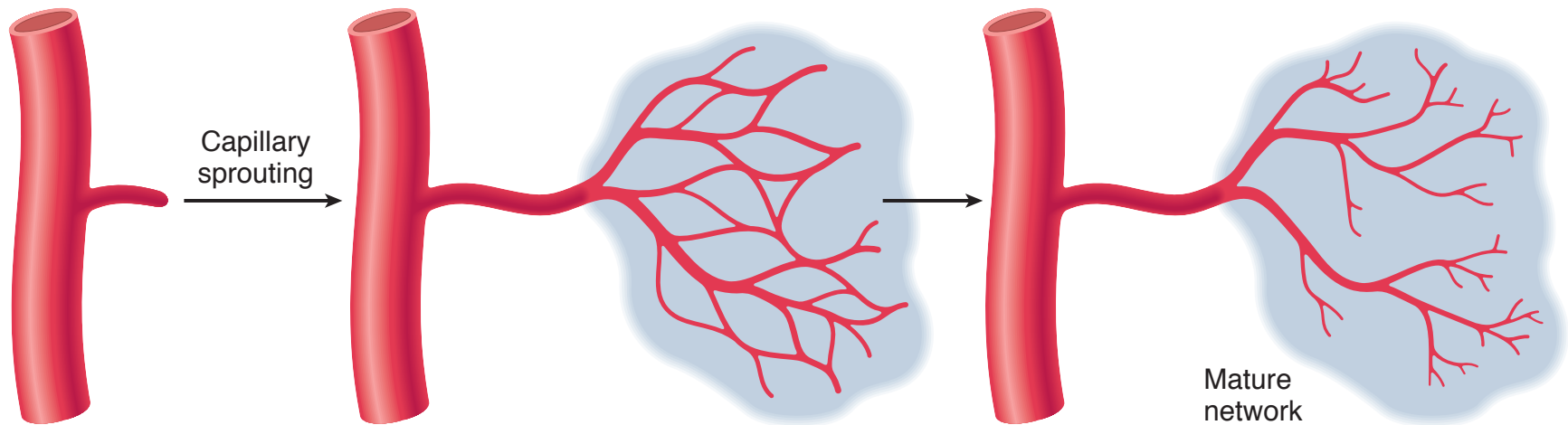


Angiogenesis in Tissue Repair

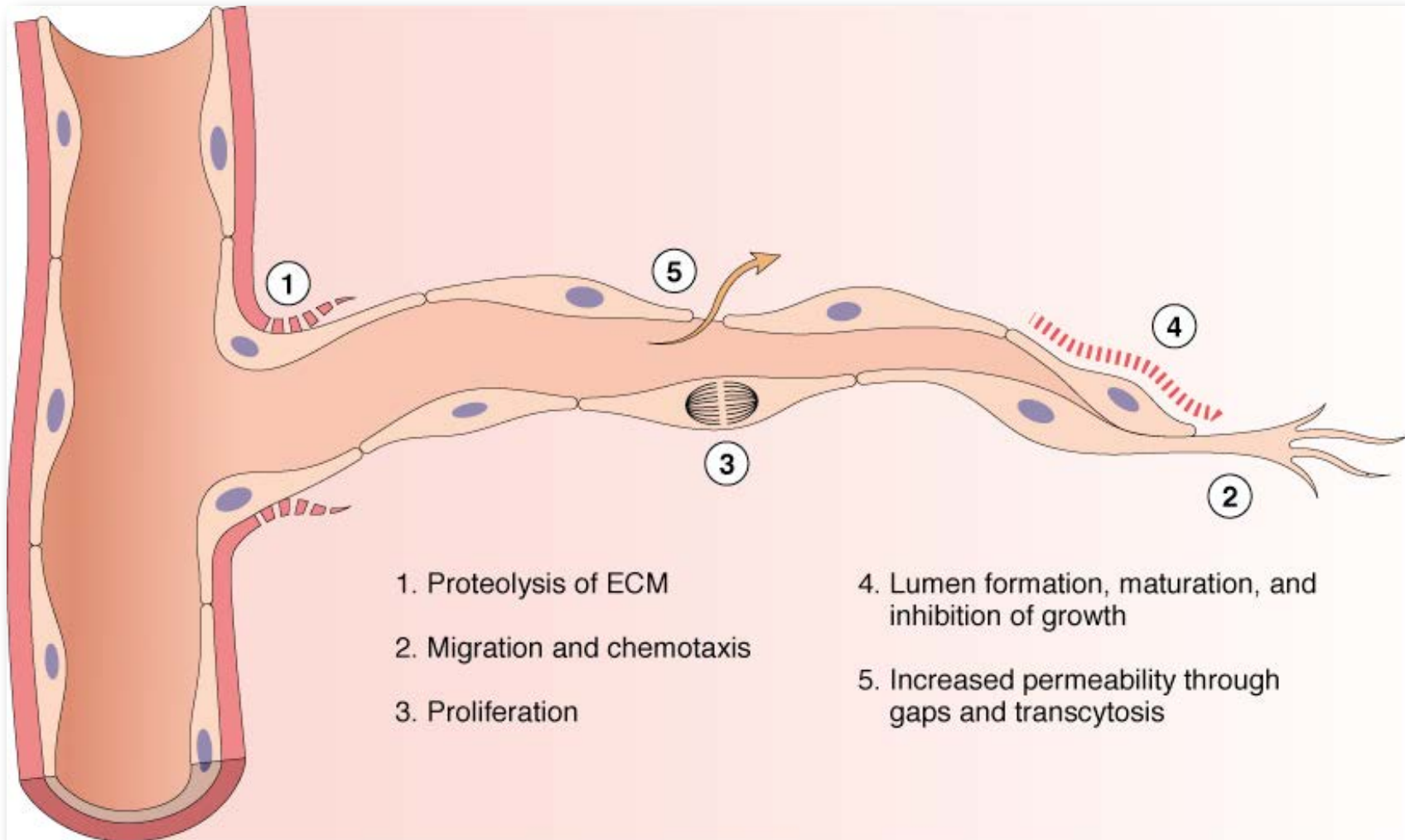
A. Angiogenesis by mobilization of EPCs from the bone marrow

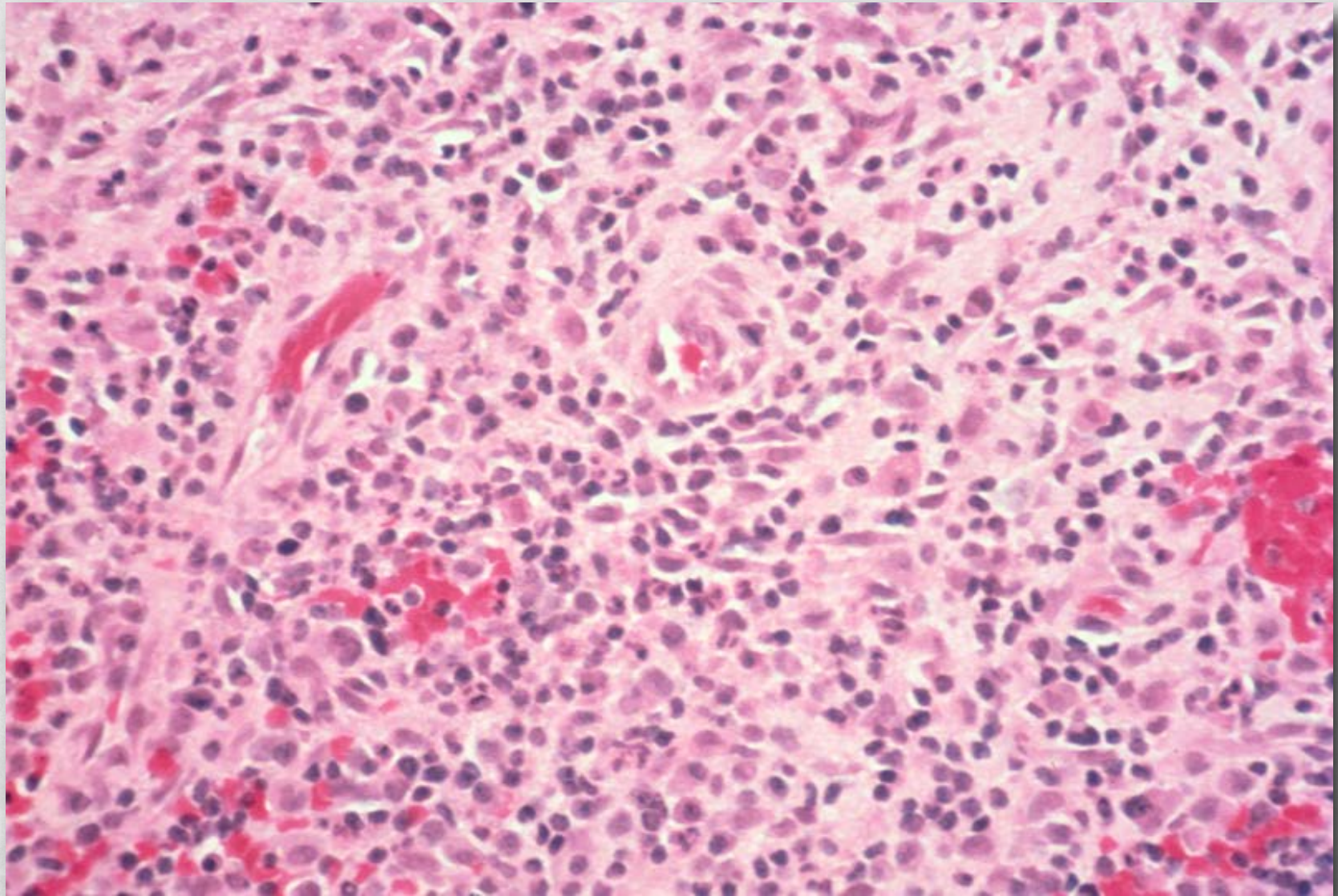


B. Angiogenesis from pre-existing vessels



Angiogenesis



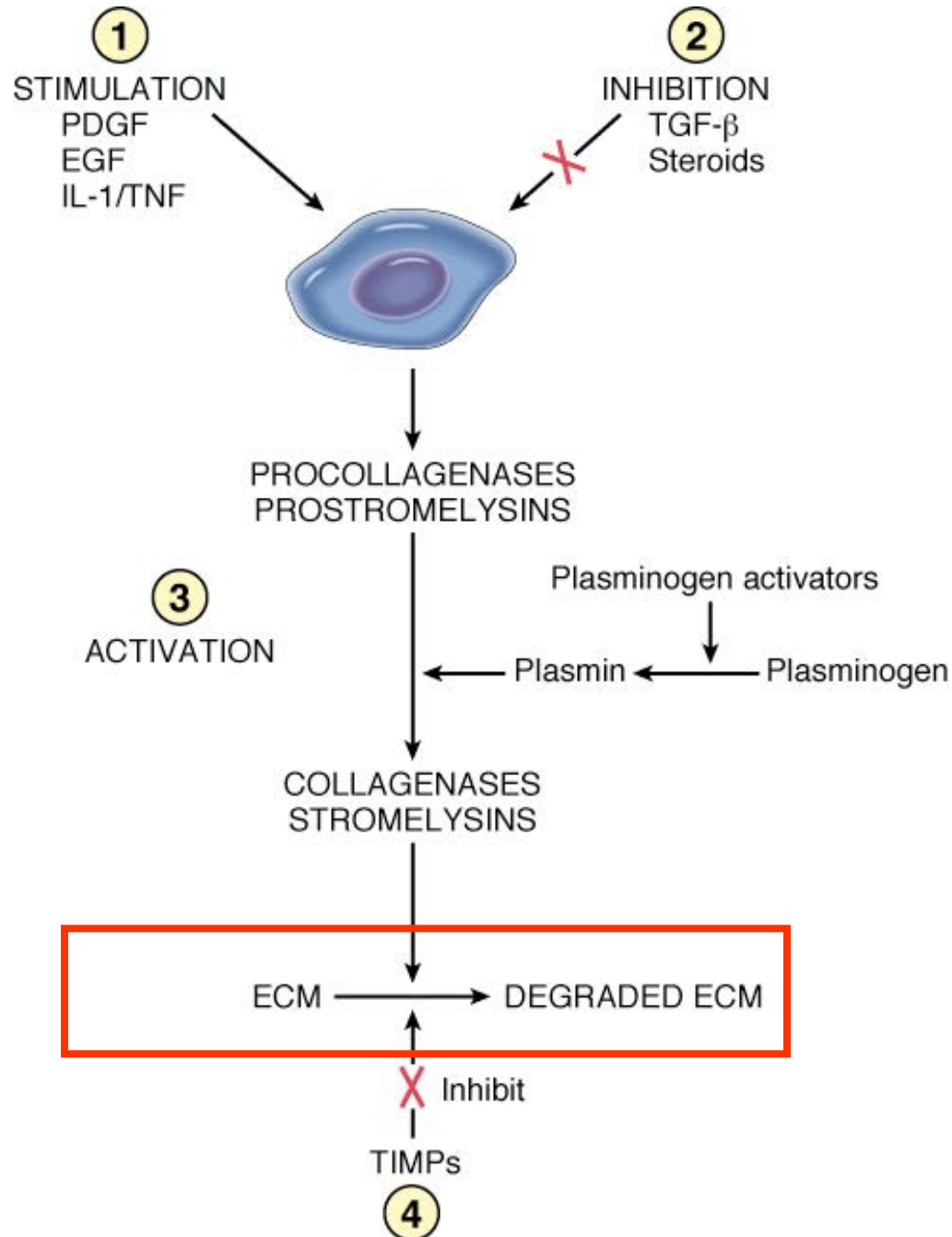


Granulation tissue

Tissue Remodeling Phase

- Granulation tissue evolves into scar
- Balance between extracellular matrix synthesis and degradation
- Matrix metalloproteinases (MMPS) - interstitial collagenases, gelatinases & stromelysins require zinc as a cofactor
- Tissue inhibitors of metalloproteinases (TIMPS)

Tissue Remodeling Phase



Fibrosis

PERSISTENT STIMULUS
(chronic inflammation)

Activation of macrophages and lymphocytes

Growth factors
(PDGF, FGF, TGF β)

Cytokines
(TNF, IL-1, IL-4, IL-13)

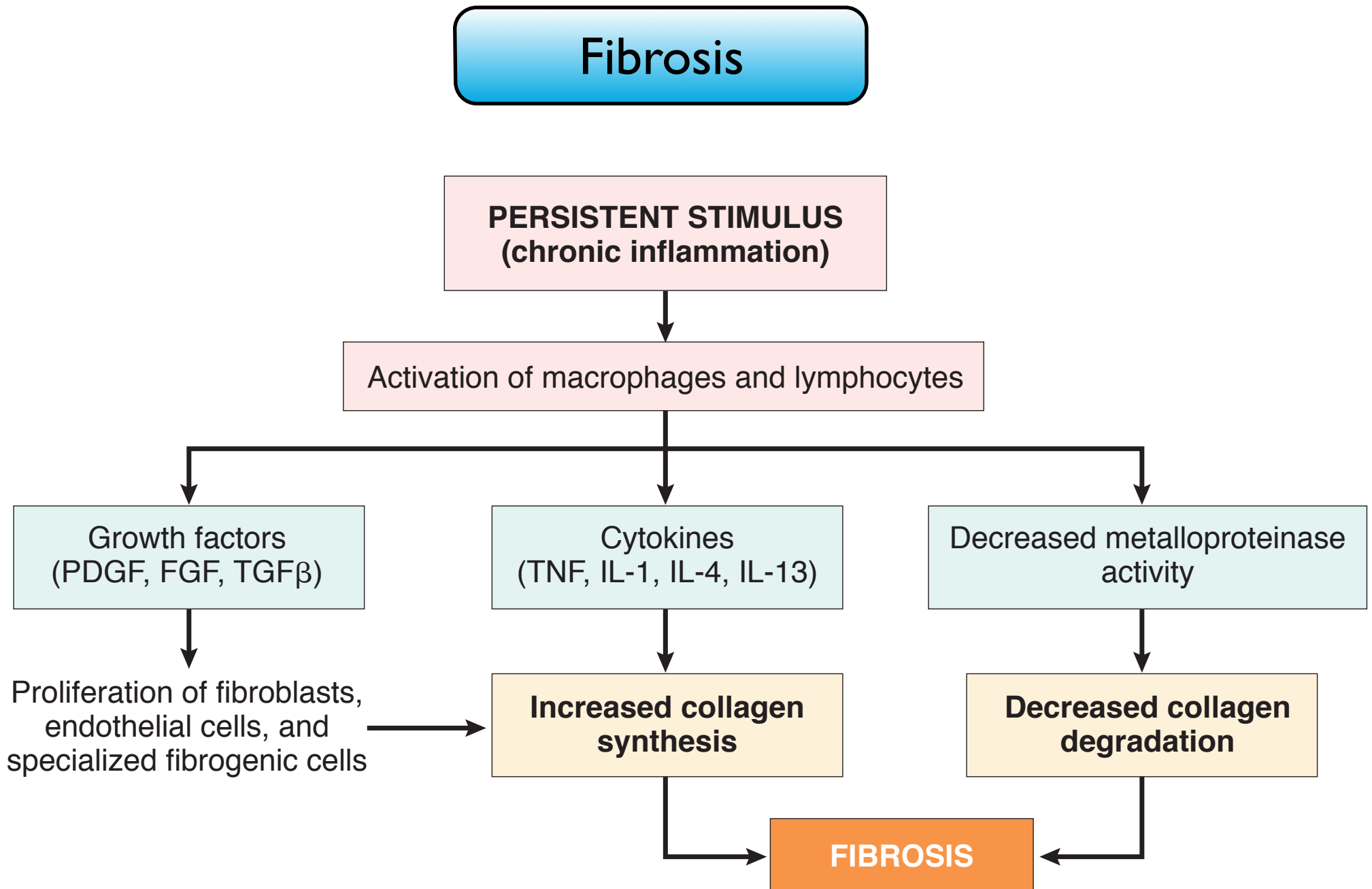
Decreased metalloproteinase
activity

Proliferation of fibroblasts,
endothelial cells, and
specialized fibrogenic cells

**Increased collagen
synthesis**

**Decreased collagen
degradation**

FIBROSIS



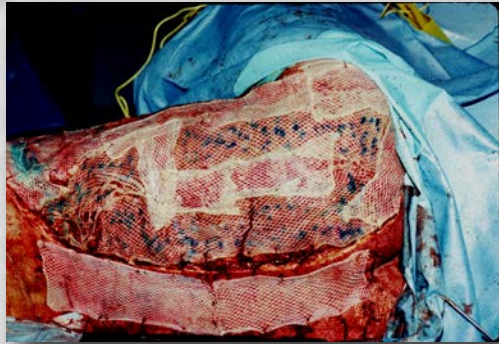
Cutaneous Tissue Repair



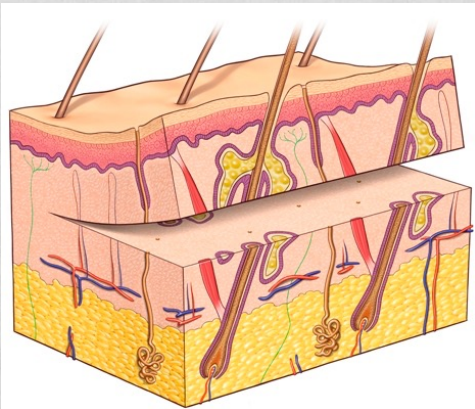
Eschar



Meshing Device



Grafts



Split Skin Graft

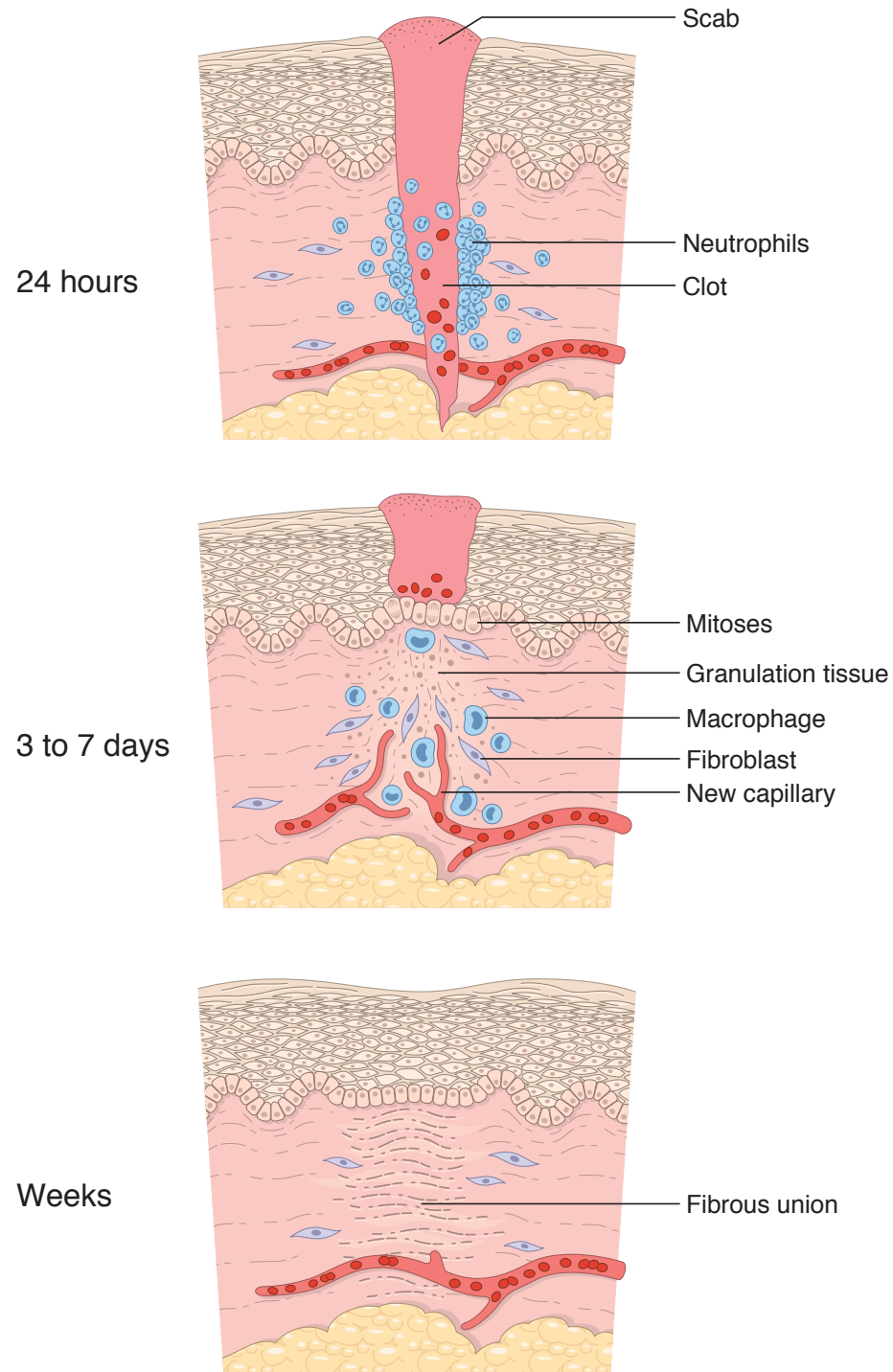


Regeneration



Fibrosis & Remodeling

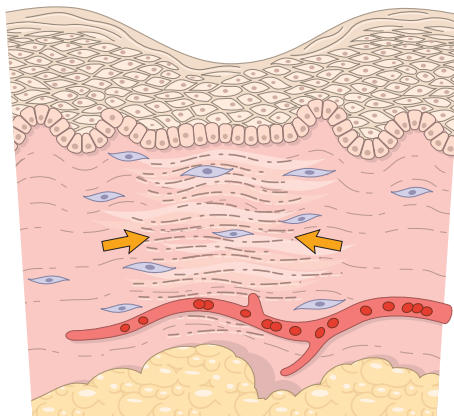
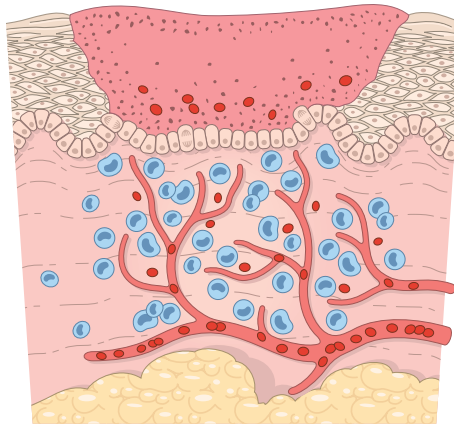
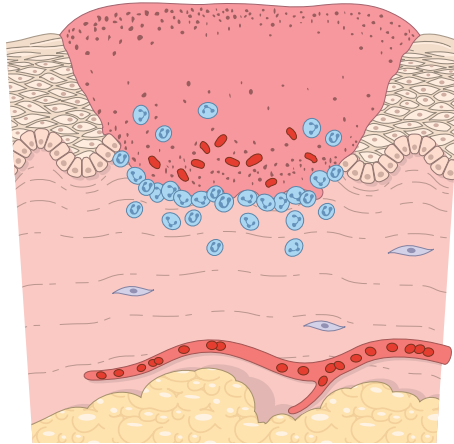
HEALING BY FIRST INTENTION





Primary Union ("healing by first intention")

HEALING BY SECOND INTENTION



Wound
contraction



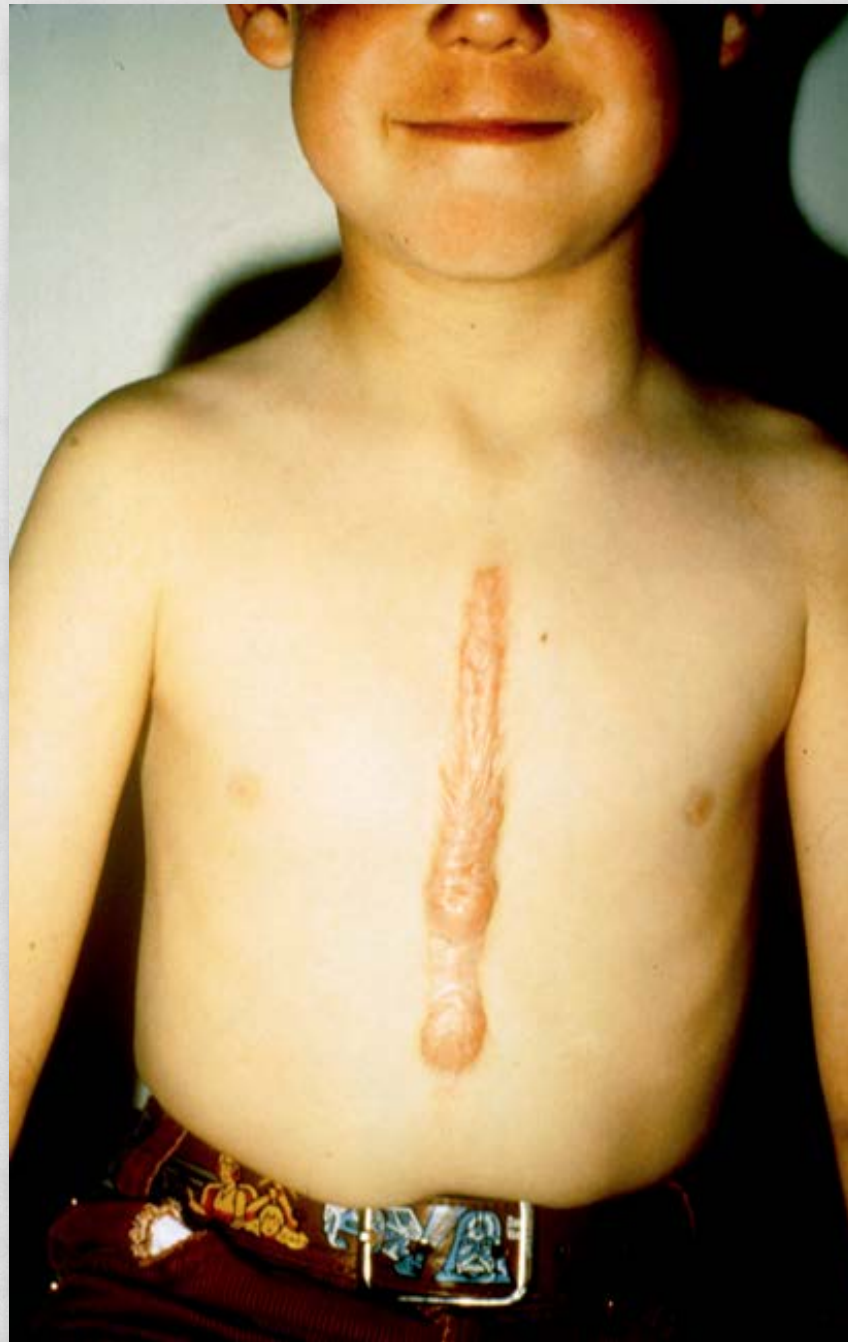
tention")

Secondary Union

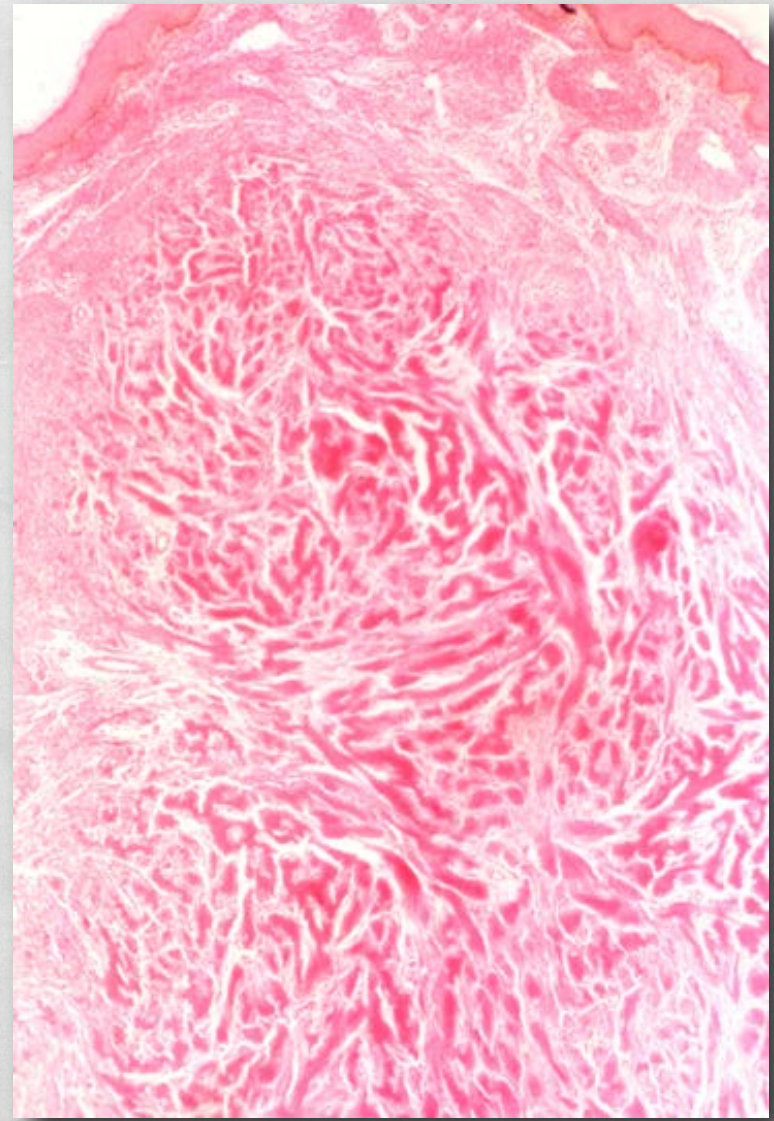
- Amount of granulation tissue greater than primary union
- Wound contraction and scar is more prominent
- Increased risk of bacterial contamination
- Epidermis migration is slow
- Advantages
 - Large defects can be closed
 - Contaminated wounds may heal

Complications of Cutaneous Wound Healing

- Wound dehiscence - rupture of a wound
- Wound contraction
- Exuberant granulation tissue ("proud flesh")
- Excessive collagen formation and/or decreased degradation
- Hypertrophic scar
- Keloid



Hypertrophic scar



Keloid



Hypertrophic Scar

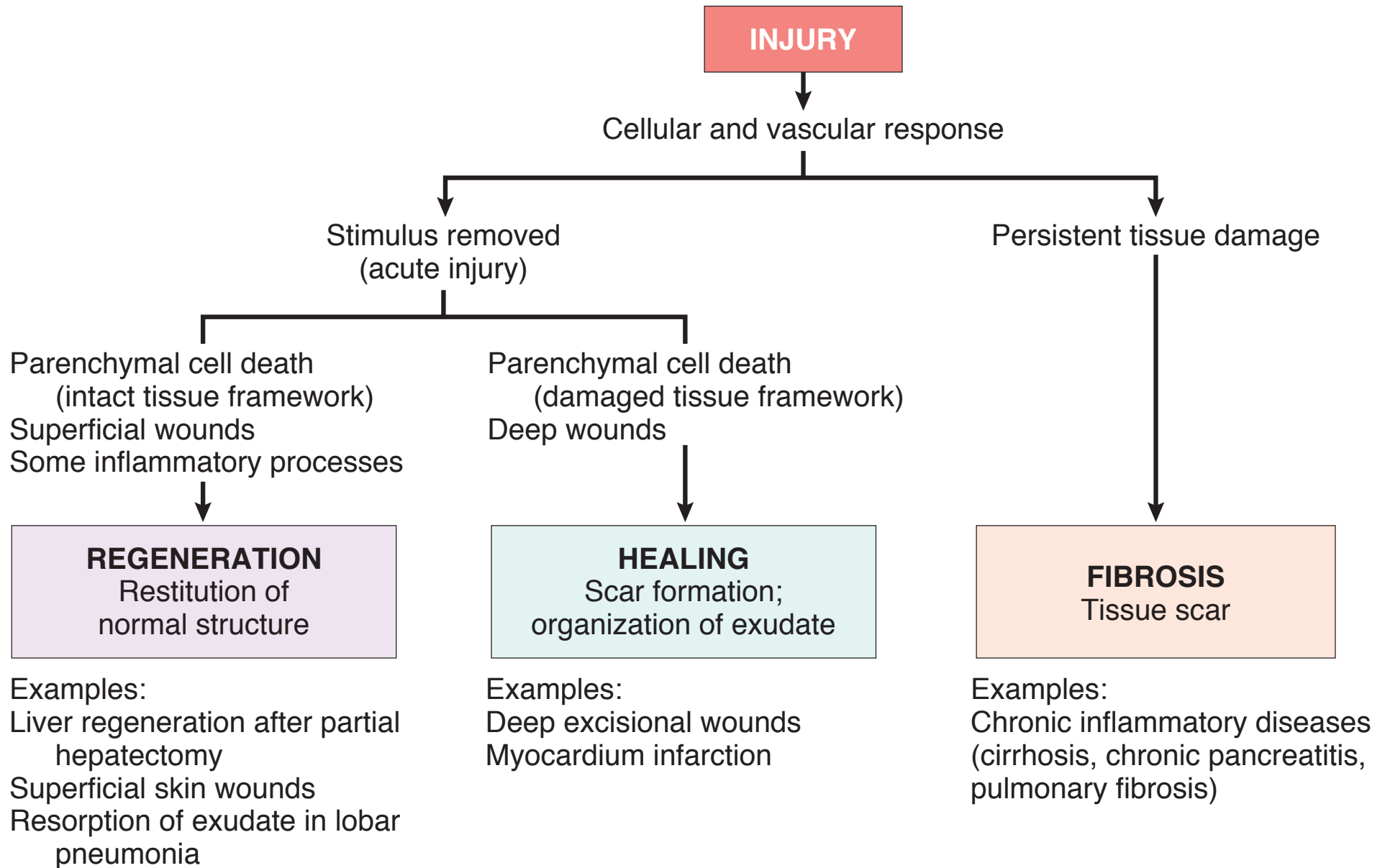
Factors that Retard Tissue Repair

Local Factors	Systemic Factors
Blood supply	Age
Denervation	Anemia
Local infection	Drugs (e.g., steroids, cytotoxic medications, intensive antibiotic therapy)
Foreign body	Genetic disorders (e.g., osteogenesis imperfecta, Ehlers-Danlos syndromes, Marfan syndrome)
Hematoma	Hormones
Mechanical stress	Jaundice
Necrotic tissue	Malignant disease
Protection (dressings)	Malnutrition
Surgical techniques	Obesity
	Systemic infection
	Temperature
	Trauma, hypovolemia and hypoxia
	Uremia
	Vitamin deficiency (e.g., vitamin C)
	Trace metal deficiency (e.g., zinc and copper)

Organization

- Replacement of wound healing exudate by granulation tissue leading to fibrosis
- **Body cavities** - fibrous adhesions
- **Heart valves** - stenosis, or regurgitation
- **Lungs** - reduces total lung capacity
- **Joint space** - immobilized/fused joint
- **Abscess** - walled off by a fibrous capsule

Overview of Tissue Repair



Summary

- Tissue repair is a very important biological process
- Each tissue has evolved a complex array of biochemical and cellular reparative responses to injury

