Acute and Chronic Inflammation,

Tissue repair

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Objectives:

After learning, student should be able to

- Describe the basic knowledge and morphological patterns of acute and chronic inflammation
- Describe the knowledge of tissue repair
- Discuss pathological response in inflammation-associated tissue repair

Inflammation

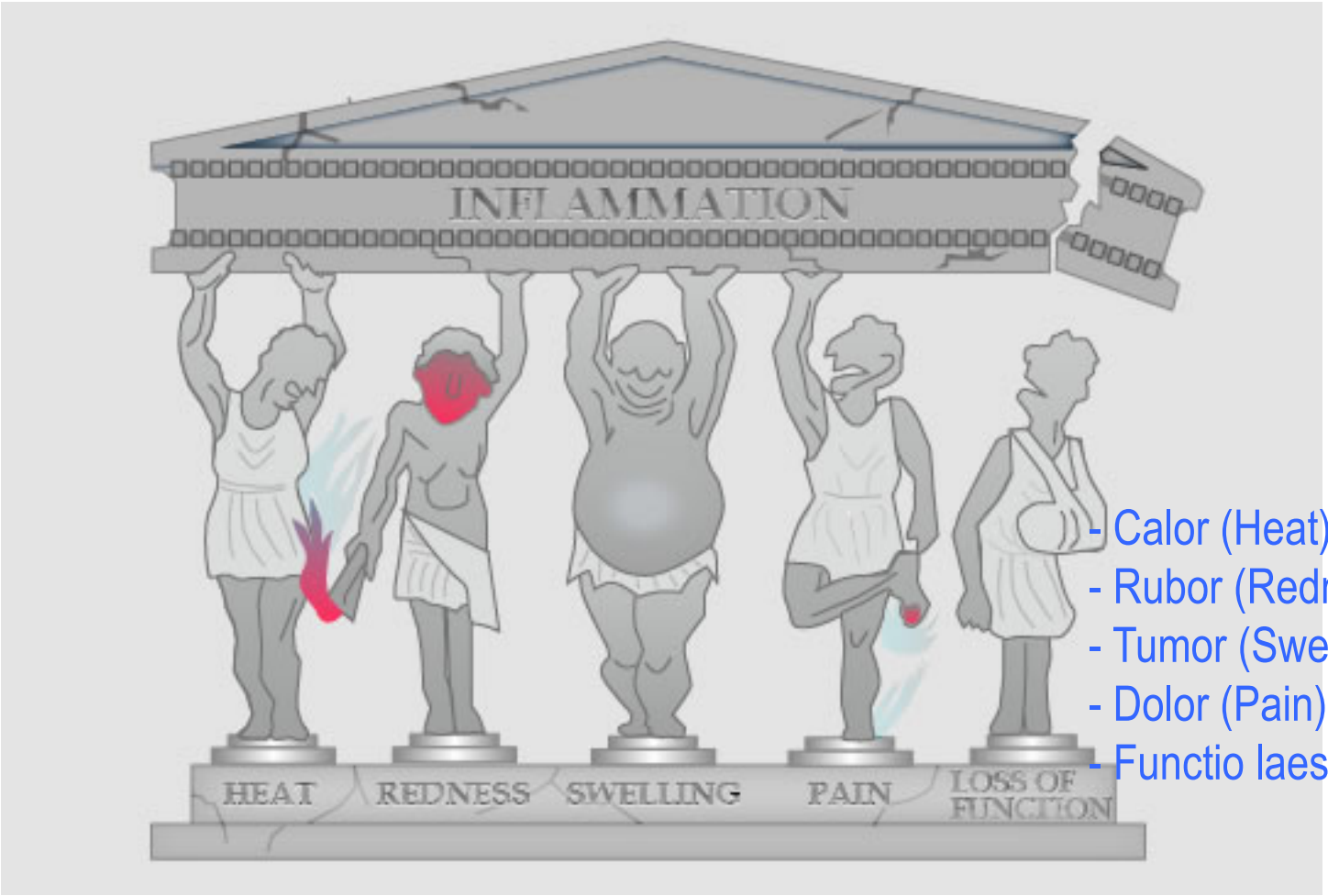
- It is a defensive host response to *foreign invaders* and *necrotic tissues.*
- To eliminate the initial cause of cell injury and necrotic tissues
- To initiate the process of *tissue repair*
- Two types of inflammation--- acute inflammation and chronic inflammation

❖ Features of acute and chronic inflammation

Features	Acute inflammation	Chronic inflammation
Onset	Fast: minutes or hours	Slow: days
Cellular infiltrate	Mainly neutrophils	Monocytes/macrophages and lymphocytes
Tissue injury, fibrosis	Usually mild and self-limited	Often severe and progressive
Local and systemic signs	Prominent	Less prominent; may be subtle

(Modified from Kumar et al., 2013)

❖ The external manifestations of inflammation



- Calor (Heat)
- Rubor (Redness)
- Tumor (Swelling)
- Dolor (Pain)
- Functio laesa (Loss of function)

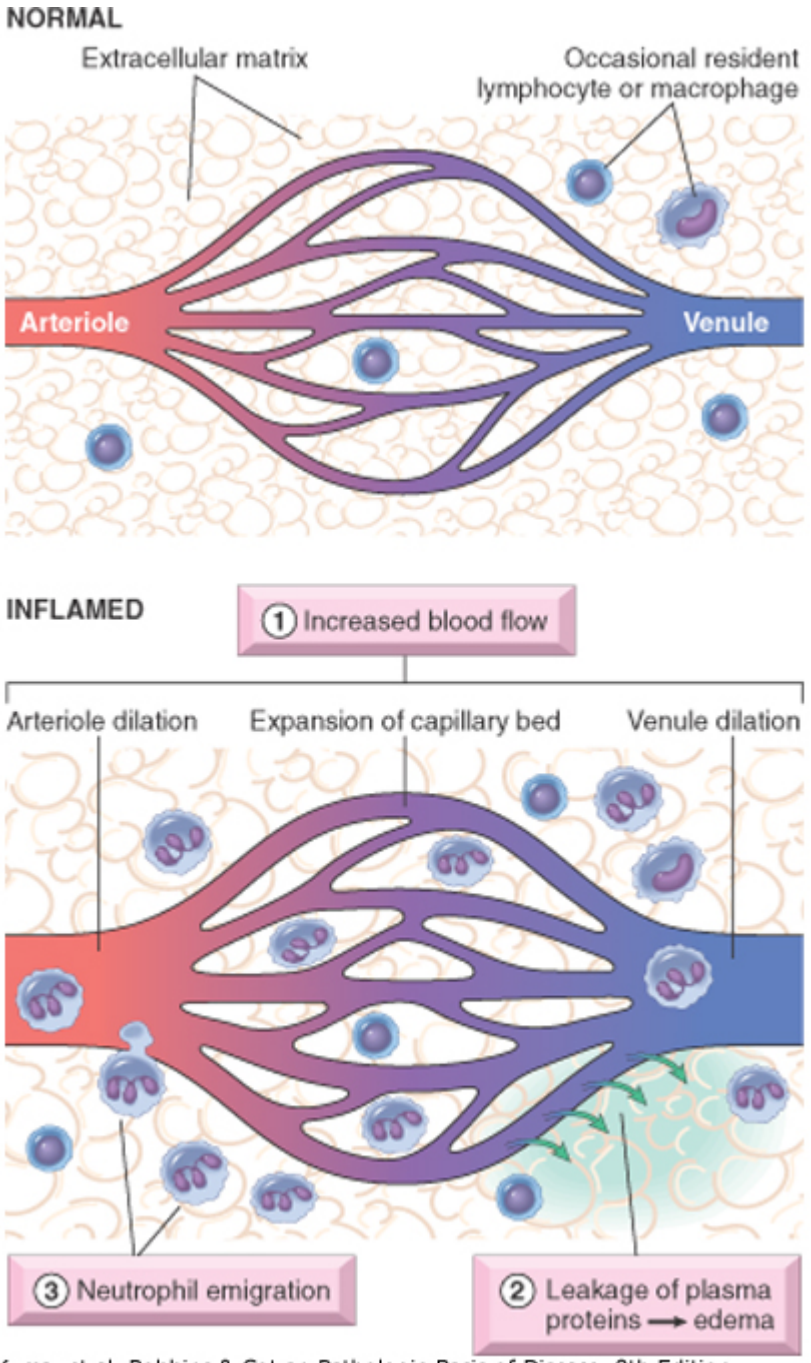
(inflam.jst.go.jp)

❖ Cardinal signs of inflammation

Cardinal Signs	Physiological responses
Dolor (Pain)	Stretching of pain receptors and nerves by inflammatory exudates and chemical mediators
Tumor (Swelling)	Exudation of fluid
Rubor (Redness)	Increased blood flow
Calor (Heat)	Increased blood flow, Release of inflammatory mediators
Functio laesa (Loss of function)	Disruption of tissue structure

Acute inflammation

- The response rapidly delivers leukocytes and plasma proteins to sites of injury.
- Once there, leukocytes clear the invaders and begin the process of digesting and getting rid of necrotic tissues.
- Acute inflammation has two major components:
  - *Vascular changes*
  - *Cellular events*



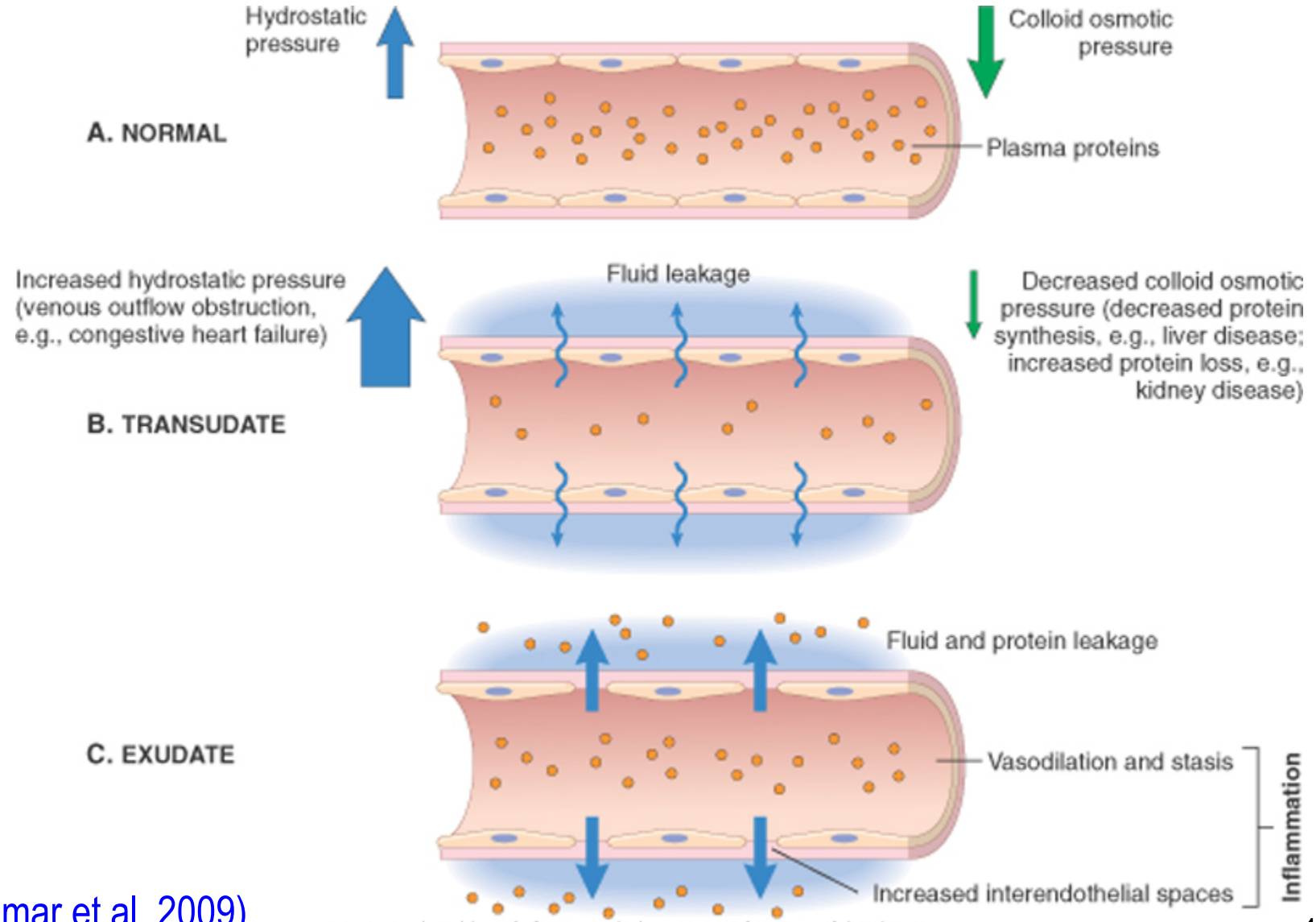
1. Vascular dilation and increased blood flow--- *erythema and warmth*
2. Extravasation of plasma fluid and proteins--- *edema*
3. Leukocyte emigration and accumulation--- *mainly neutrophils*

(Kumar et al, 2009)

❖ Vascular changes

- The main vascular reaction of acute inflammation are increased blood flow, vasodilation, and increased vascular permeability.
- Increasing *vascular permeability*--- the movement of protein-rich fluid (*transudate, exudate*) and *blood cells* into the extravascular tissues.
- The changes in blood vessels are initiated rapidly after infection or injury.

Formation of transudates and exudates

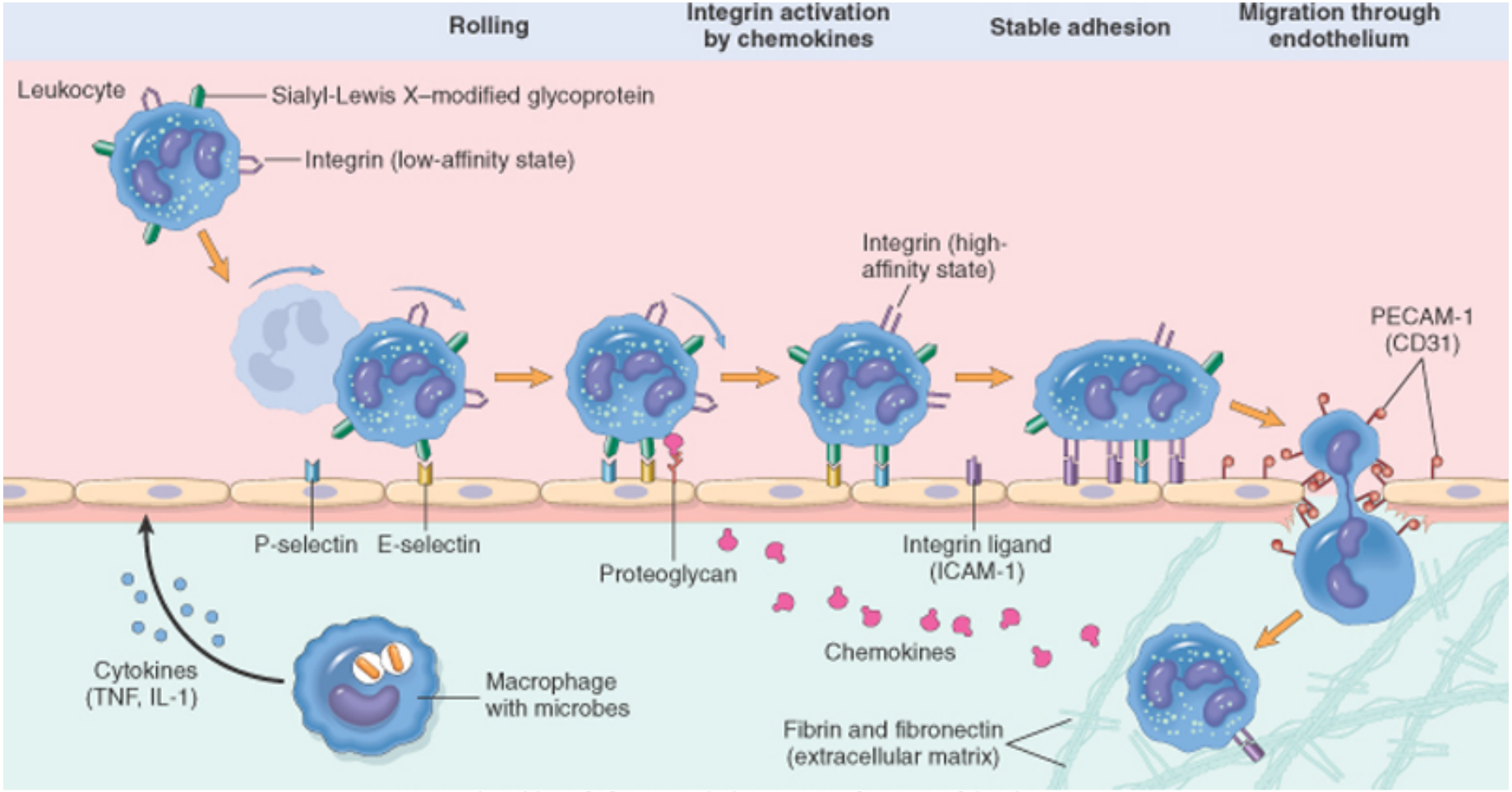


(Kumar et al, 2009)

❖ Cellular events

- ❑ Leukocyte recruitment and activation
- ❑ The recruitment of *leukocyte* from vascular lumen to the extravascular space
  - Margination and rolling along the vessel wall
  - Adhesion to the endothelium
  - Transmigration between endothelial cells
  - Chemotaxis--- migration in interstitial tissues toward a chemotactic stimulus.

Mechanisms of leukocyte migration through blood vessels



(Kumar et al, 2009)

❑ Major roles of leukocyte adhesion molecules in the leukocyte migration

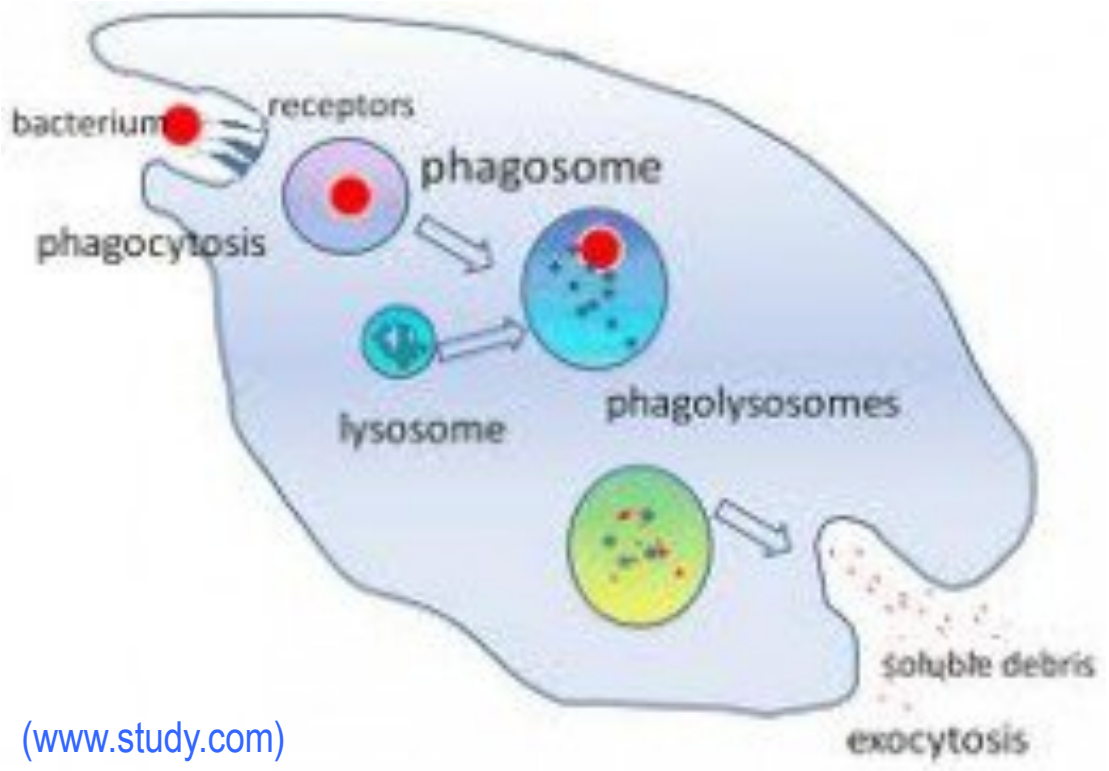
Table 2–2 Endothelial and Leukocyte Adhesion Molecules

Endothelial Molecule	Leukocyte Molecule	Major Role(s)
Selectins and Selectin Ligands		
P-selectin	Sialyl–Lewis X–modified proteins	Rolling
E-selectin	Sialyl–Lewis X–modified proteins	Rolling and adhesion
GlyCam-1, CD34	L-selectin*	Rolling (neutrophils, monocytes)
Integrins and Integrin Ligands		
ICAM-1 (immunoglobulin family)	CD11/CD18 integrins (LFA-1, Mac-1)	Firm adhesion, arrest, transmigration
VCAM-1 (immunoglobulin family)	VLA-4 integrin	Adhesion
Others		
CD31	CD31 (homotypic interaction)	Transmigration of leukocytes through endothelium

*L-selectin is also involved in the binding of circulating lymphocytes to the high endothelial venules in lymph nodes and mucosal lymphoid tissues, and subsequent homing of lymphocytes to these tissues.
ICAM-1, intercellular adhesion molecule-1; LFA-1, leukocyte function–associated antigen-1; Mac-1, macrophage-1 antigen; VCAM-1, vascular cell adhesion molecule-1; VLA-4, very late antigen-4.

(Kumar et al, 2015)

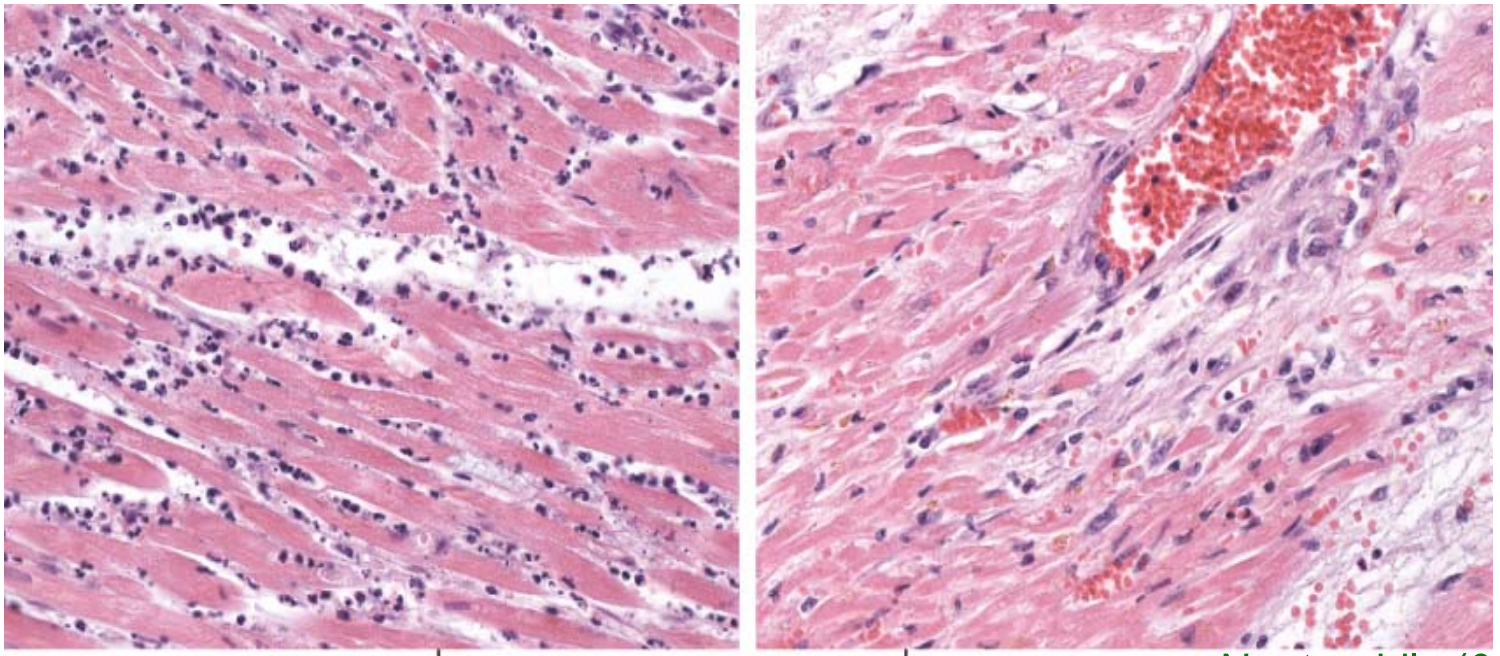
- The first immune cells that arrive at an injured site are mostly *neutrophils*.
- Neutrophils have several different types of receptors that recognize several different pathogen-associated molecular patterns.

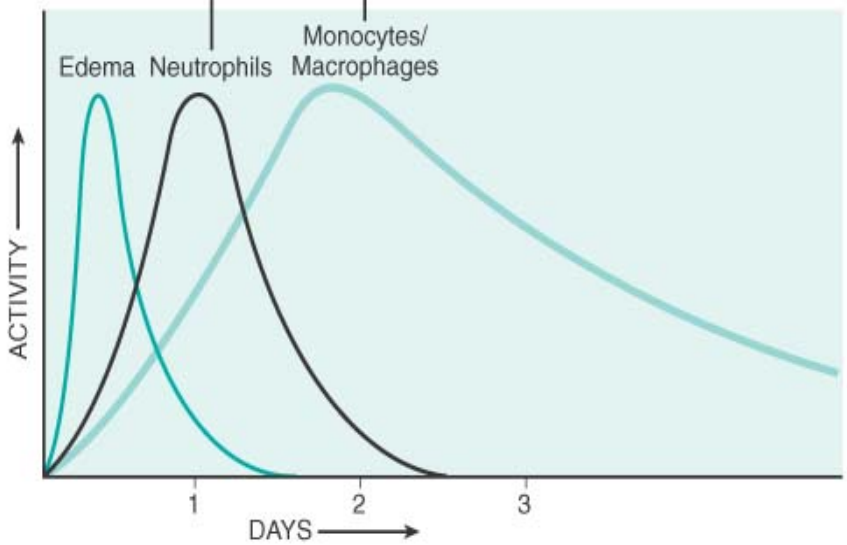


(www.study.com)

- Phagocytosis
- Phagosome
- Lysosome

❑ Leukocyte infiltrates in inflammatory reactions

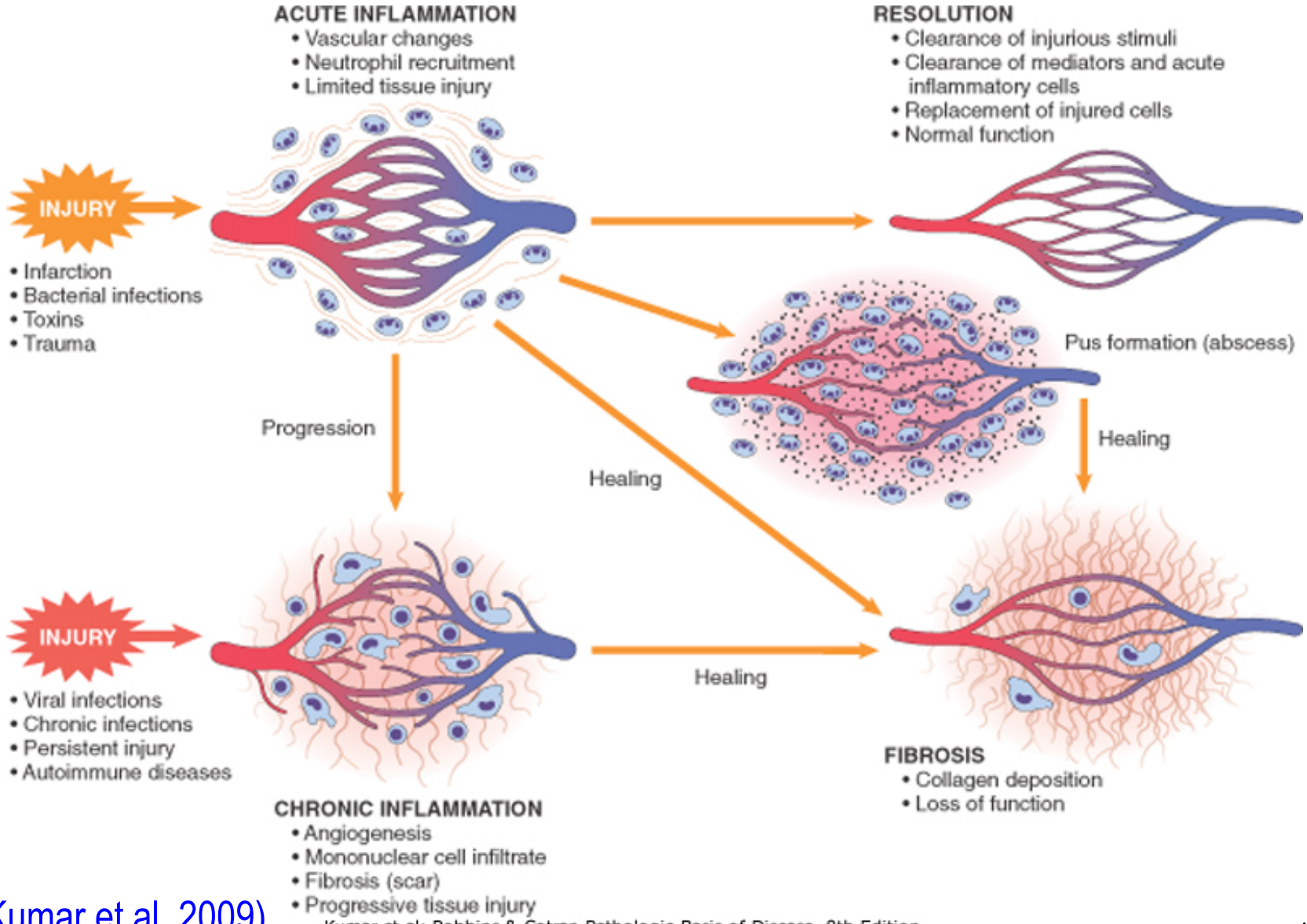




- Neutrophils (6-24 h)
- Monocytes (24-48 h)

(Kumar et al, 2015)

❖ Outcomes of acute inflammation



(Kumar et al, 2009)

❖ The stimuli for acute inflammation

- ❑ Infections--- most common and medically important causes of inflammation
- ❑ Trauma and various physical and chemical agents
- ❑ Tissue necrosis
- ❑ Foreign bodies
- ❑ Immune reaction--- hypersensitivity reaction

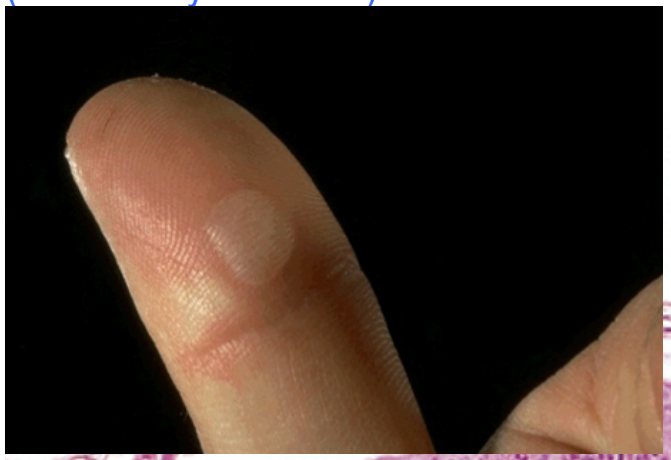
Morphological patterns of acute inflammation

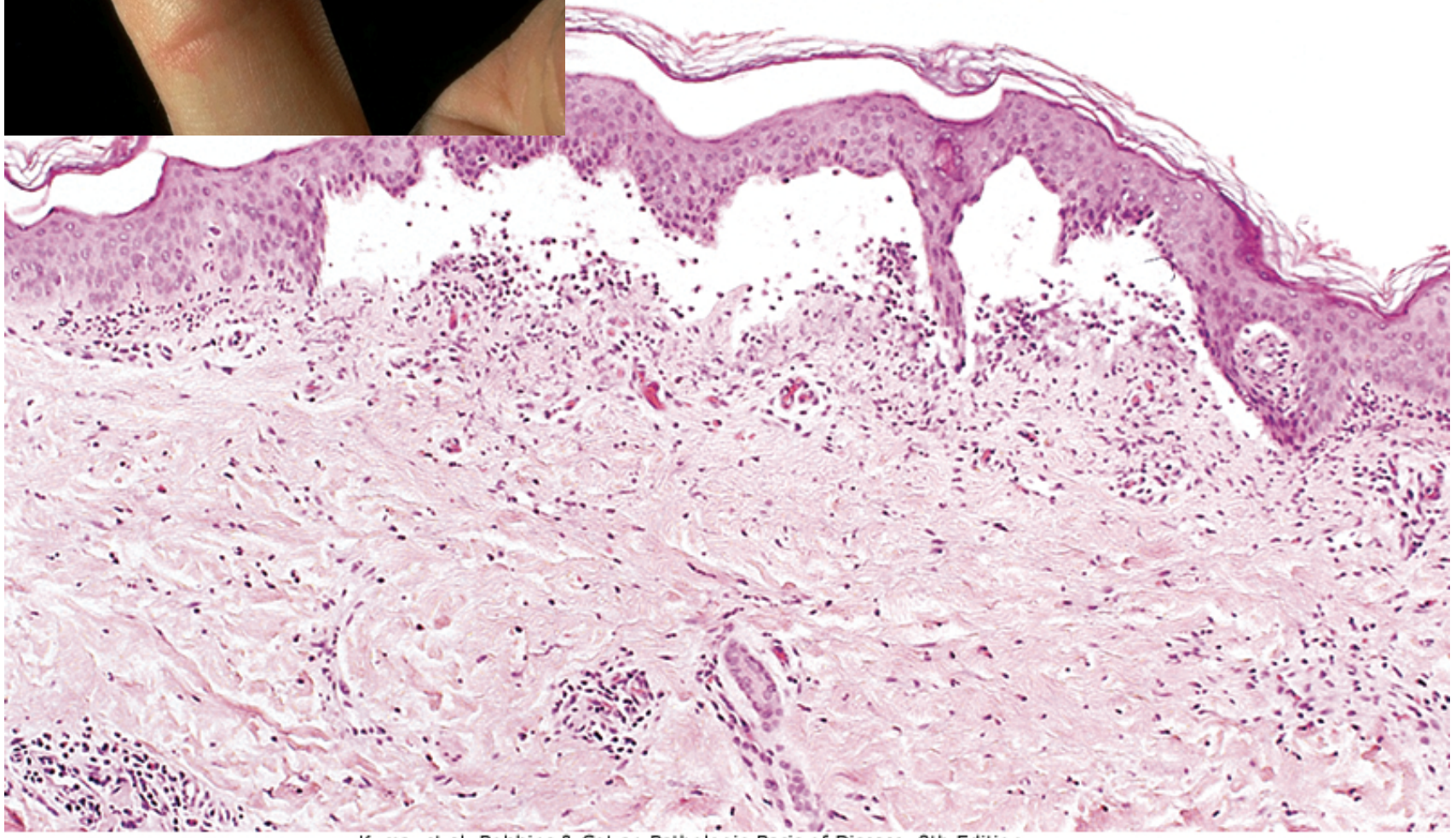
- Serous inflammation
- Fibrinous inflammation
- Suppurative (purulent) inflammation & Abscess formation
- Ulcer

❖ Serous inflammation

- ❑ It is characterized by the outpouring of a water, relatively *protein-poor fluid* that, depending on the site of injury.
- ❑ Skin blister--- burn or viral infection
- ❑ Fluid in a serous cavity is called an *effusion.*

(www.studyblue.com)

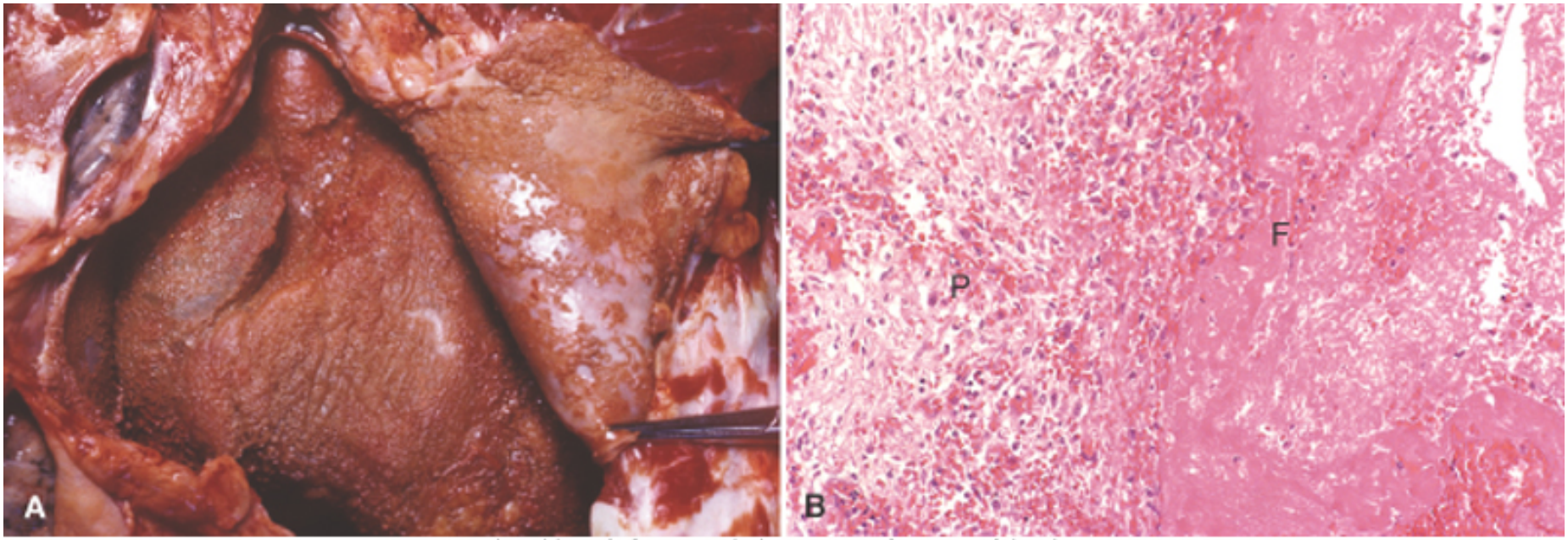




(Kumar et al, 2009)

❖ Fibrinous inflammation

- ❑ It occurs as a consequence of more severe injuries.--- greater vascular permeability that allows *large molecules* such as *fibrinogen* to pass the endothelial barrier.
- ❑ This reaction is characteristic of inflammation in the lining of body cavities.--- meninges, pericardium, and pleura

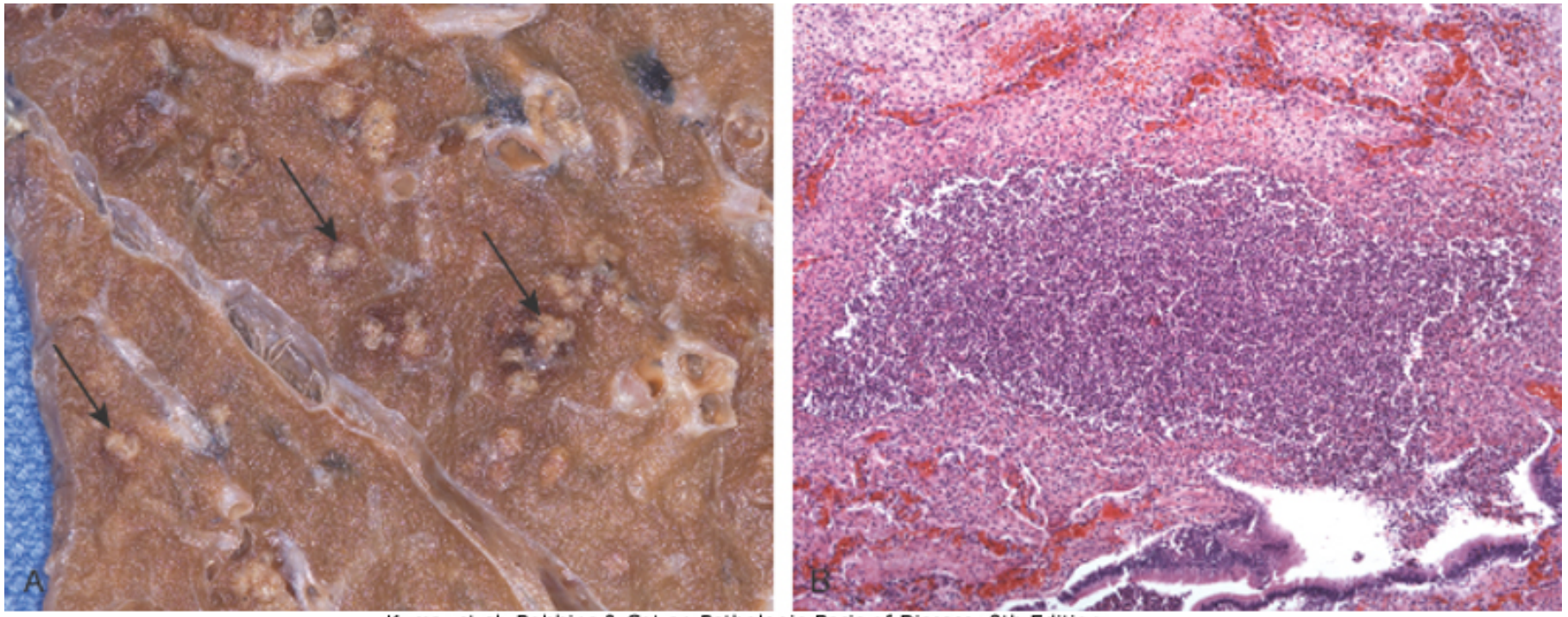


(Kumar et al, 2009)

Fibrinous pericarditis; fibrin exudate (F), pericardial surface (P)

❖ Suppurative (purulent) inflammation & Abscess formation

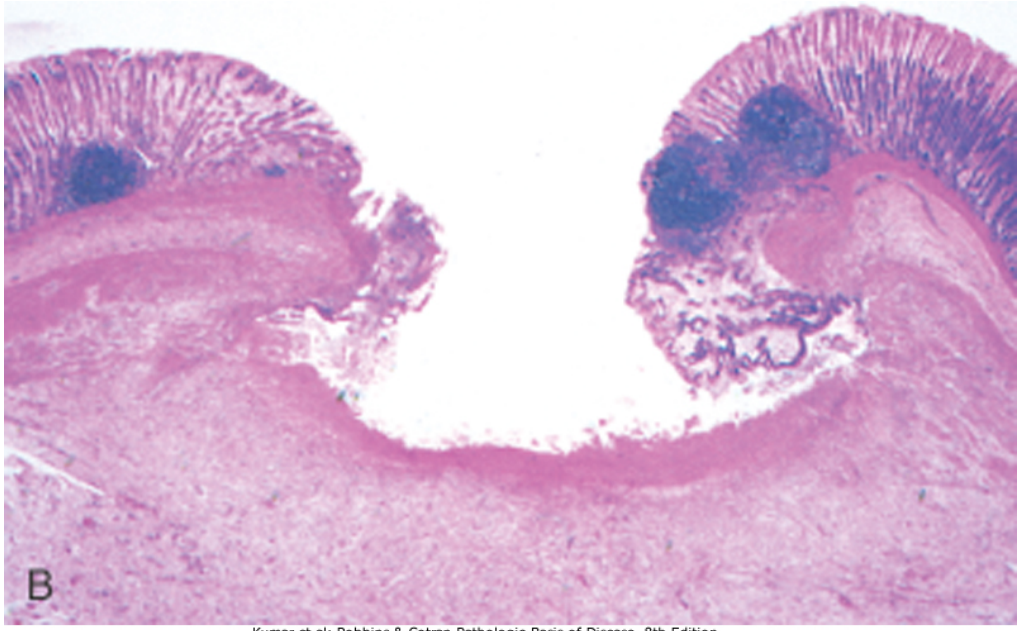
- ❑ The collection of amount of purulent exudate (pus)---*neutrophils, necrotic cells,* and *edema fluid*
- ❑ Abscesses are focal *collections of pus*.
- ❑ Abscesses typically have a central, largely necrotic region rimmed by a layer of preserved neutrophils with a surrounding zone of dilated vessels and fibroblast proliferation.



(Kumar et al, 2009)

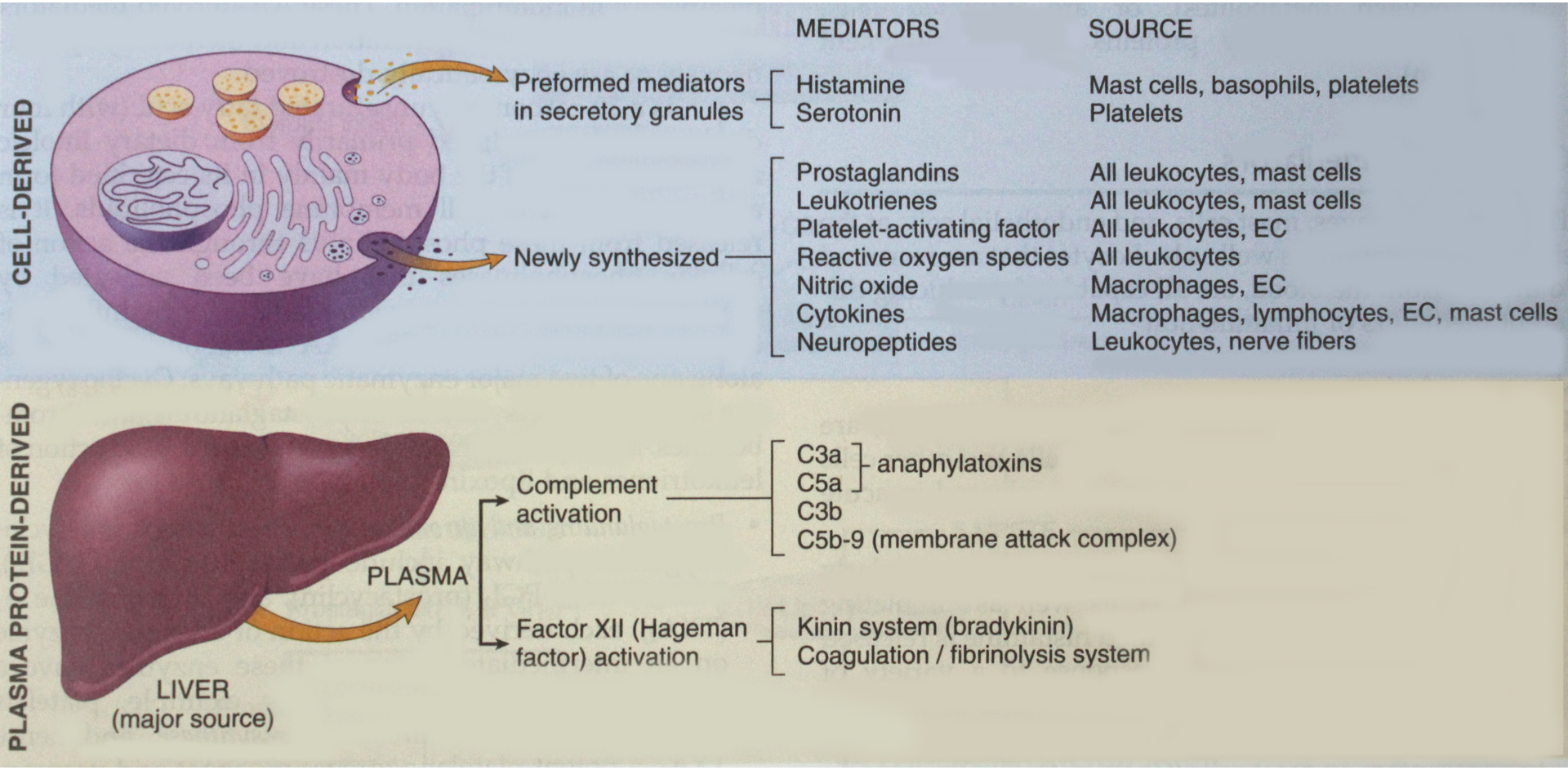
❖ Ulcer

- ❑ It is a local defect, or excavation of the surface of an organ or tissue that produced by necrosis of cells and sloughing (shedding) of necrotic and inflammatory tissue.
- ❑ Ulcerations are best exemplified by peptic ulcer of the stomach or duodenum.
- ❑ *Neutrophils and exudates* present in an acute stage.



(Kumar et al, 2009)

Chemical mediators and regulators of inflammation



(Kumar et al, 2015)

❑ Actions of the mediators of inflammation

Table 2–5 Actions of the Principal Mediators of Inflammation

Mediator	Source(s)	Actions
Cell-Derived		
Histamine	Mast cells, basophils, platelets	Vasodilation, increased vascular permeability, endothelial activation
Serotonin	Platelets	Vasoconstriction
Prostaglandins	Mast cells, leukocytes	Vasodilation, pain, fever
Leukotrienes	Mast cells, leukocytes	Increased vascular permeability, chemotaxis, leukocyte adhesion and activation
Platelet-activating factor	Leukocytes, mast cells	Vasodilation, increased vascular permeability, leukocyte adhesion, chemotaxis, degranulation, oxidative burst
Reactive oxygen species	Leukocytes	Killing of microbes, tissue damage
Nitric oxide	Endothelium, macrophages	Vascular smooth muscle relaxation; killing of microbes
Cytokines (TNF, IL-1, IL-6)	Macrophages, endothelial cells, mast cells	*Local*: endothelial activation (expression of adhesion molecules). *Systemic*: fever, metabolic abnormalities, hypotension (shock)
Chemokines	Leukocytes, activated macrophages	Chemotaxis, leukocyte activation
Plasma Protein–Derived		
Complement	Plasma (produced in liver)	Leukocyte chemotaxis and activation, direct target killing (MAC), vasodilation (mast cell stimulation)
Kinins	Plasma (produced in liver)	Increased vascular permeability, smooth muscle contraction, vasodilation, pain
Proteases activated during coagulation	Plasma (produced in liver)	Endothelial activation, leukocyte recruitment

IL-1, IL-6, interleukin-1 and -6; MAC, membrane attack complex; TNF, tumor necrosis factor.

(Kumar et al, 2015)

❑ The roles of cytokines in acute inflammation

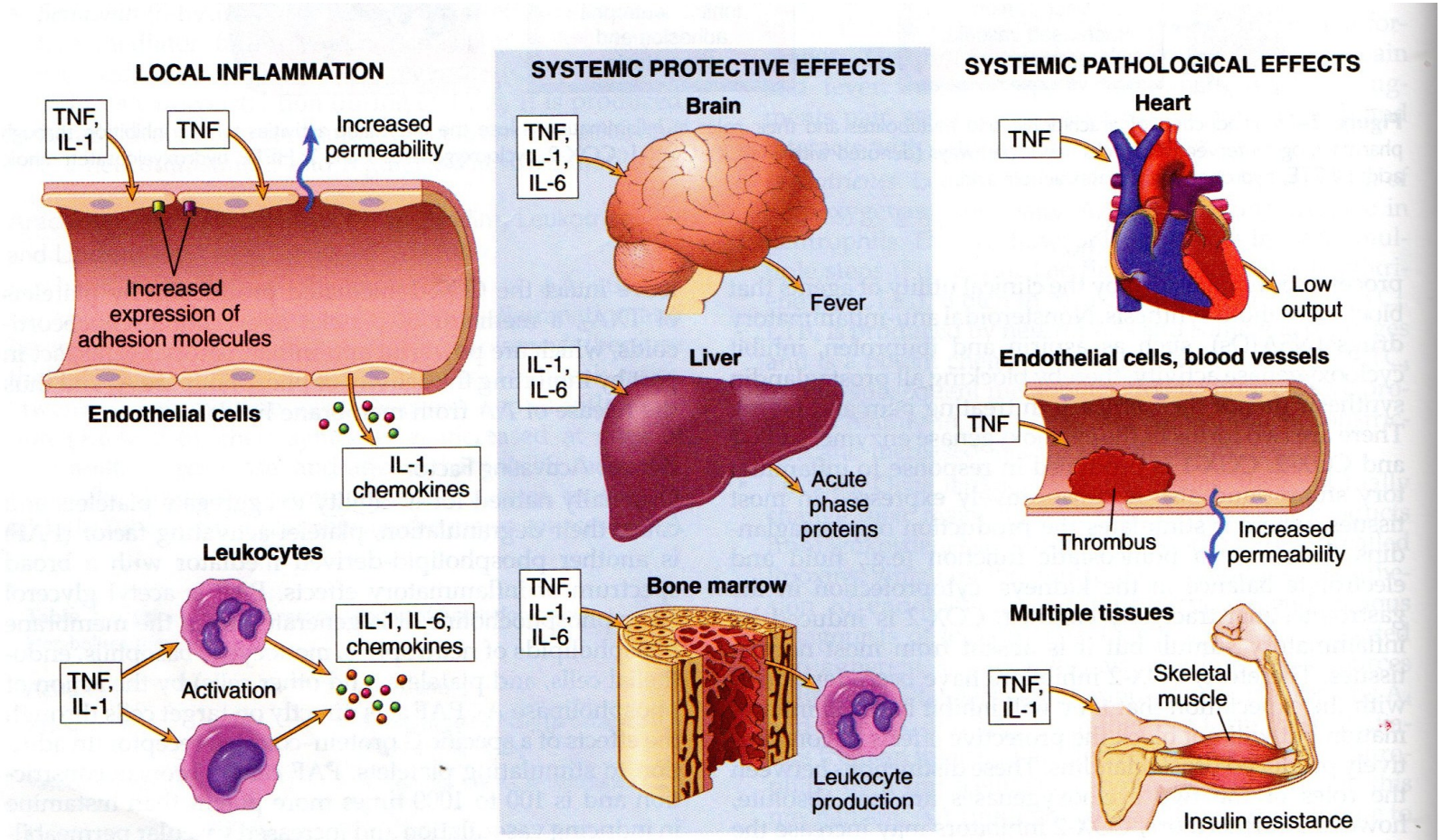


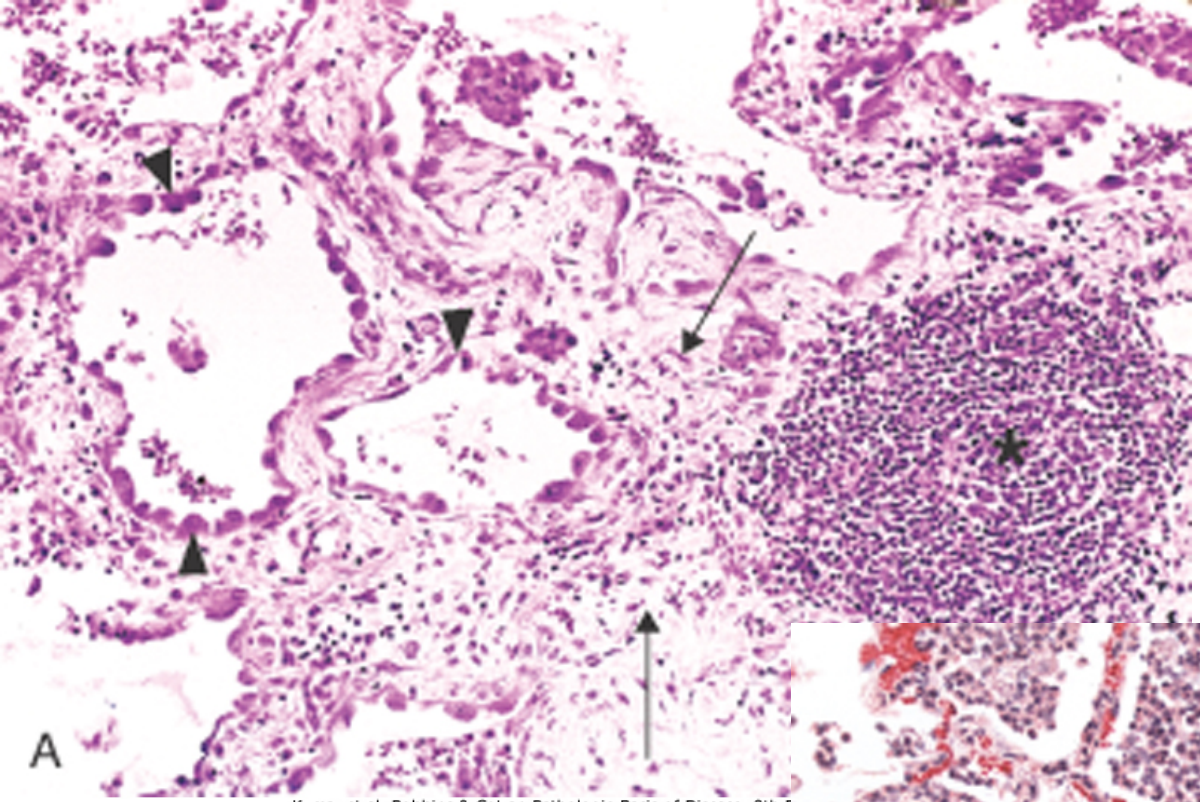
Figure 2–17 The roles of cytokines in acute inflammation. The cytokines TNF, IL-1, and IL-6 are key mediators of leukocyte recruitment in local inflammatory responses and also play important roles in the systemic reactions of inflammation.

(Kumar et al, 2015)

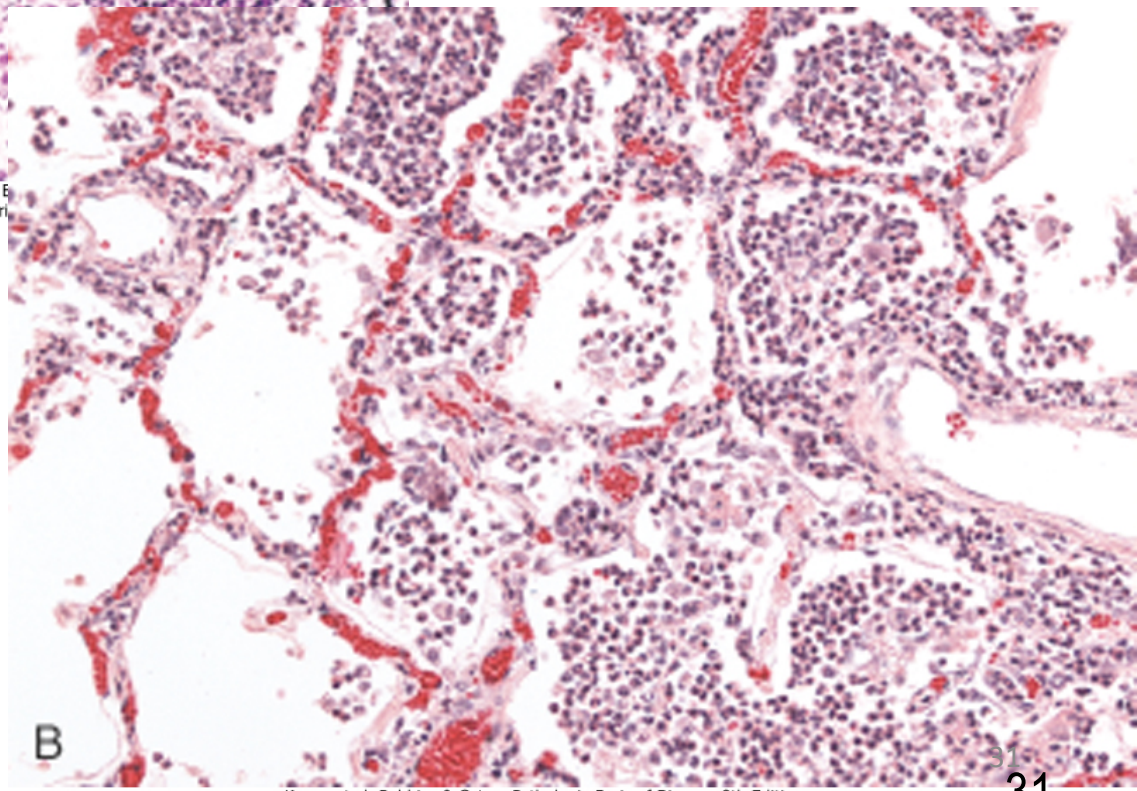
Chronic inflammation

- Chronic inflammation is inflammation of *prolonged duration* (weeks to years).
- Infiltration with mononuclear cells--- *macrophages lymphocytes, plasma cells*
- Tissue destruction--- largely induced by the products of the inflammatory cells
- Repair process--- new vessel proliferation (angiogenesis) and *fibrosis*

Chronic inflammation



(Kumar et al, 2009)



Acute inflammation

31

❖ The stimuli for chronic inflammation

- ❑ Persistent infections by microbes--- *Mycobacterium tuberculosis*, *Treponema pallidum*, Virus, and Fungi
- ❑ Immune-mediated inflammatory diseases--- autoimmune diseases, allergic diseases
- ❑ Prolonged exposure to potentially toxic agents

❖ Chronic inflammation cells and mediators

- ❑ The combination of prolonged and repeated inflammation, tissue destruction, and *fibrosis*
- ❑ Chronic inflammation involved complex interaction between several cell populations and their secreted mediators.

❑ Macrophage-lymphocyte interactions in chronic inflammation

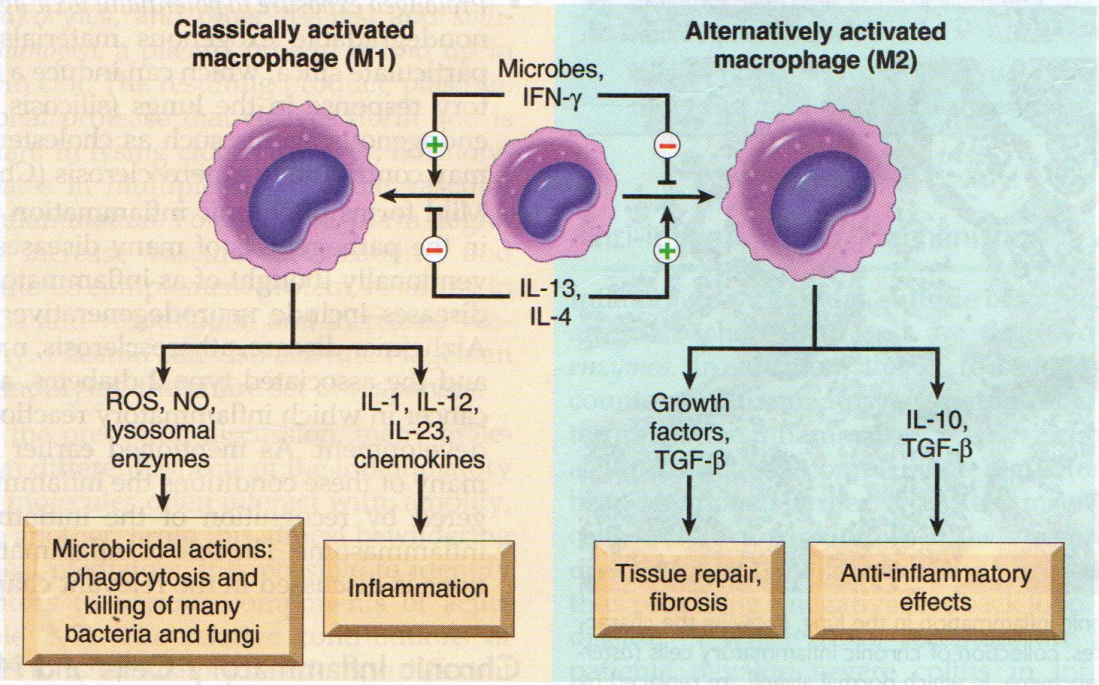


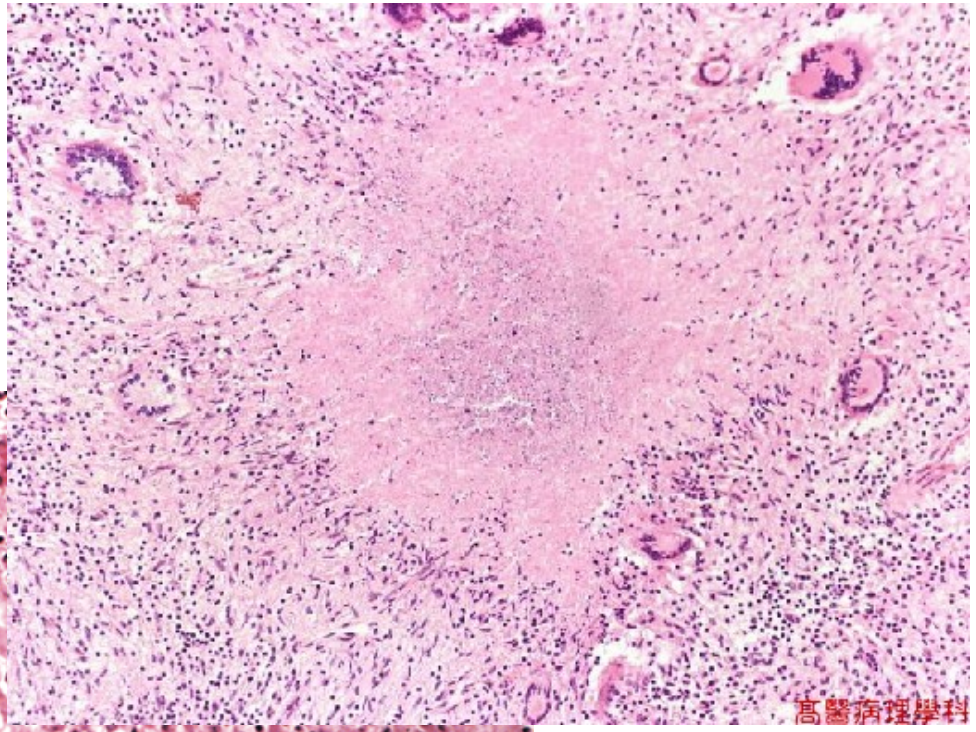
Figure 2–21 Pathways of macrophage activation. Different stimuli activate monocytes/macrophages to develop into functionally distinct populations. Classically activated macrophages are induced by microbial products and cytokines, particularly IFN-γ, and are microbicidal and involved in potentially harmful inflammation. Alternatively activated macrophages are induced by IL-4 and IL-13, produced by T_H2 cells (a helper T cell subset) and other leukocytes, and are important in tissue repair and fibrosis. IFN-γ, interferon-γ; IL-4, IL-13, interkeukin-4, -13.

(Kumar et al, 2015)

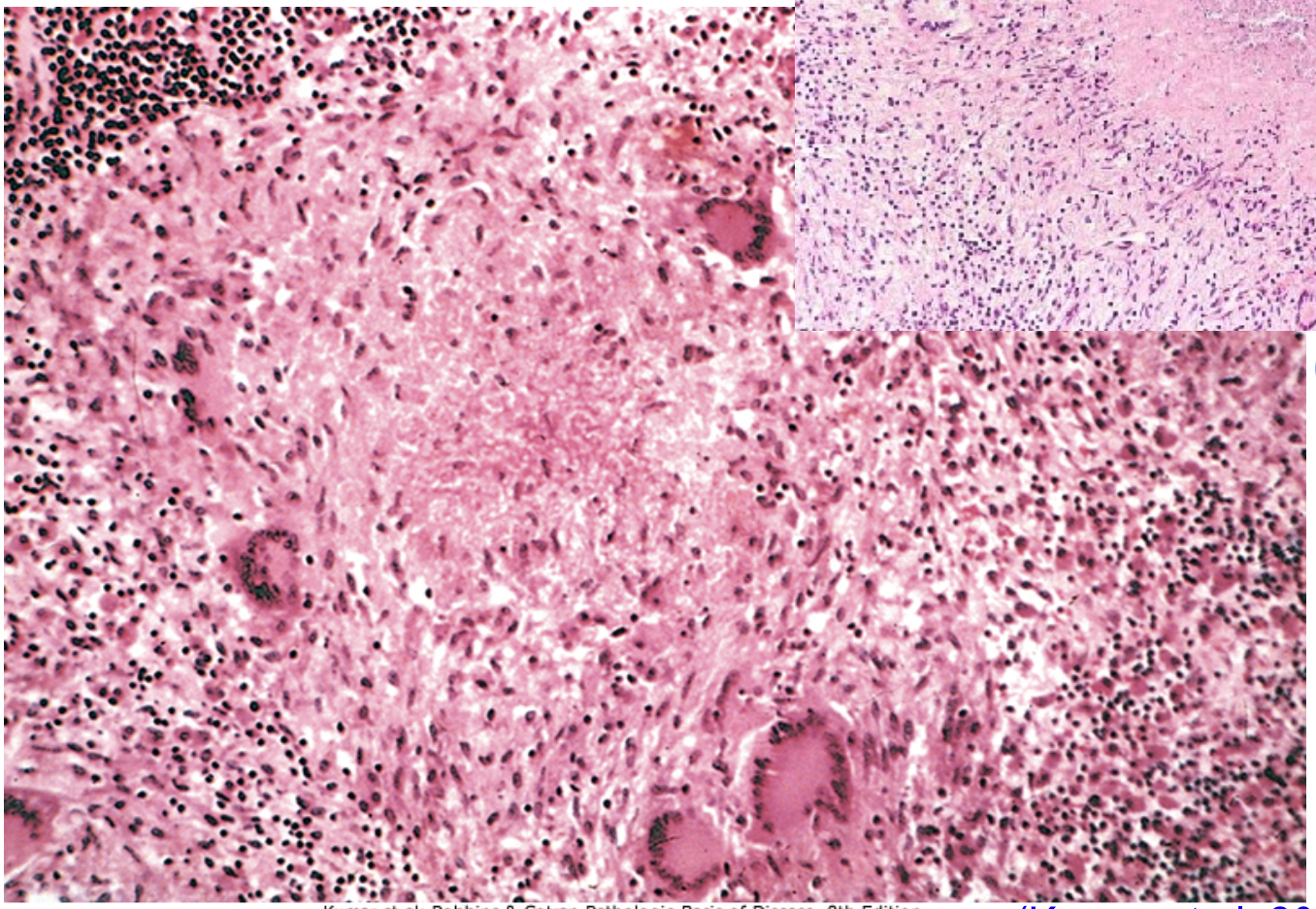
❖ Granulomatous inflammation

- It is a distinctive pattern of *chronic inflammation* characterized by aggregates of activated macrophages with scattered lymphocytes.
- Granulomas can form under three settings:
  - Persistent T-cell responses to certain microbes--- M. tuberculosis, T. pallidum, or fungi
  - Some immune-mediated inflammatory diseases--- Crohn disease
  - Sarcoidosis--- unknown etiology

- Caseous necrosis
- Activated epithelioid macrophage
- Giant cells--- Langhans giant cell
- A peripheral accumulation of lymphocytes



(theartofmed.wordpress.com)



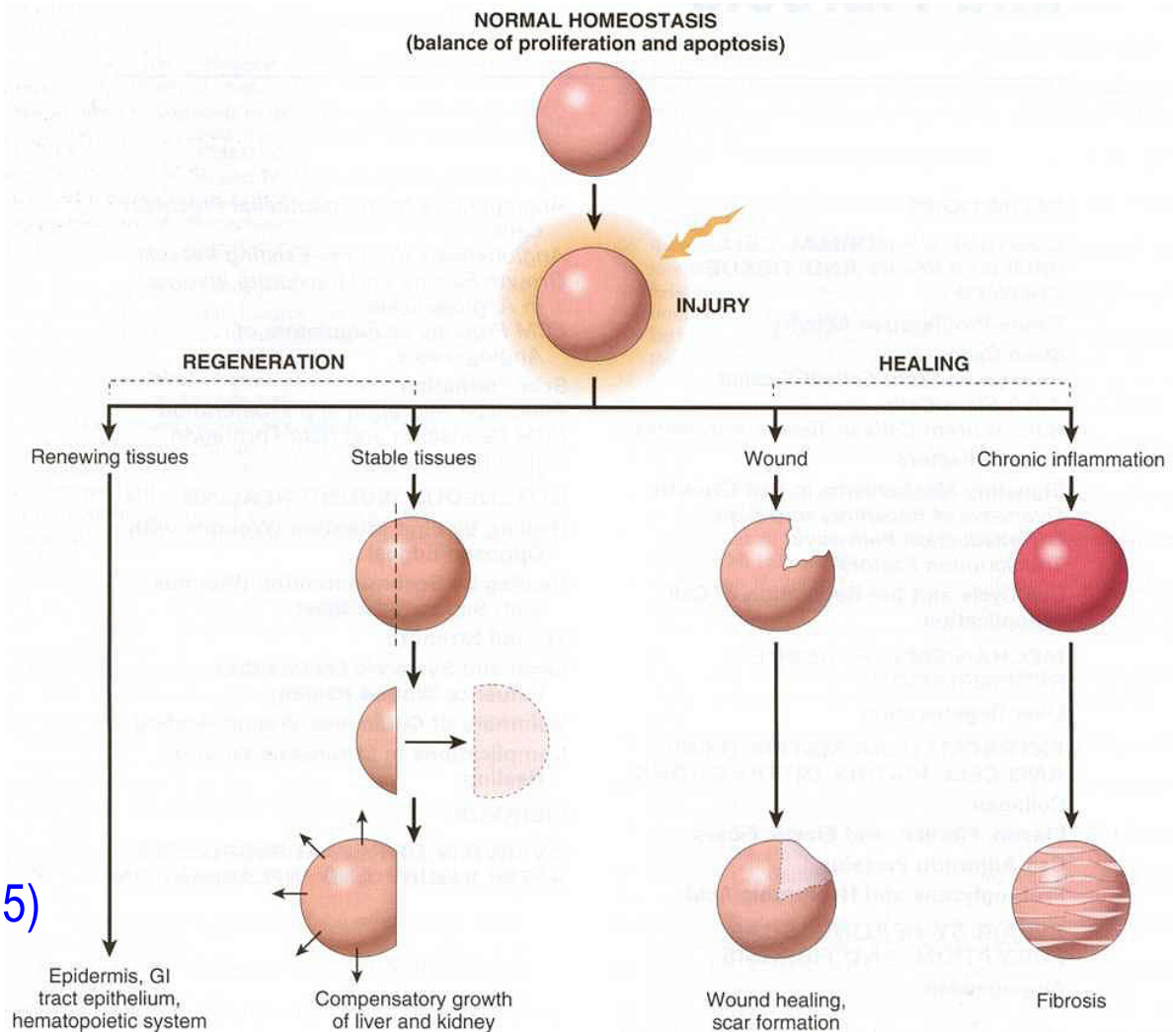
(Kumar et al, 2009)

Systemic effects of inflammation

- Acute-phase reaction or the systemic inflammatory response syndrome
- *TNF, IL-1, and IL-6* are the most important mediator.
- Clinical and pathologic changes:

  - *Fever*--- the most prominent manifestations
  - Elevated plasma levels of acute-phase proteins--- C-reactive protein, fibrinogen, and SAA protein
  - Leukocytosis
  - Others manifestations--- increased heart rate and blood pressure
  - In severe bacterial infection--- *sepsis*

Regenerative & Healing tissues

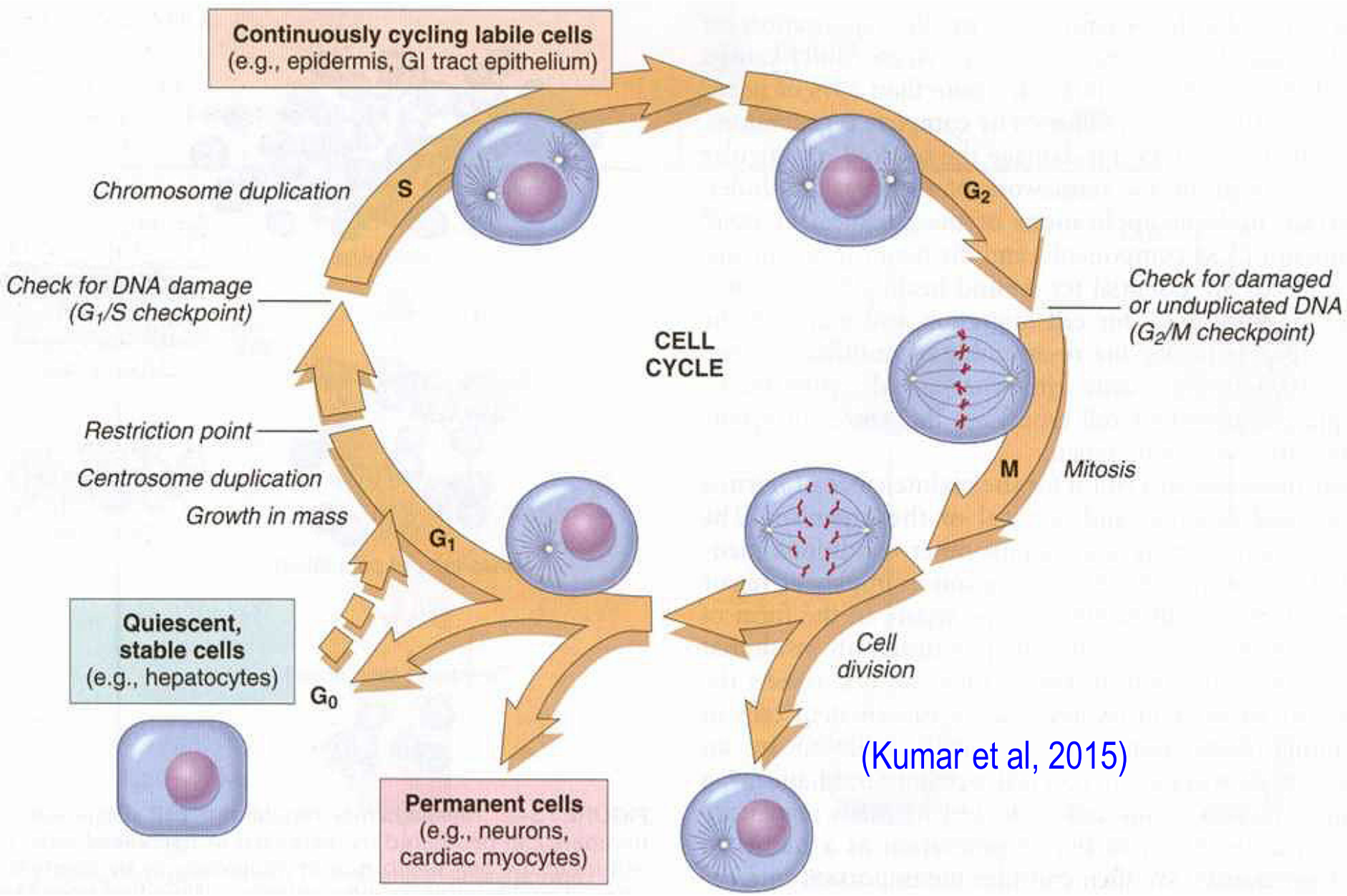


(Kumar et al, 2015)

❑ Regenerative tissue

- ❖ It refers to growth of cells and tissues to replace the lost.

- ❖ Tissues with regenerative capacity
  - Renewing tissue--- high proliferative tissue
  - Labile tissue

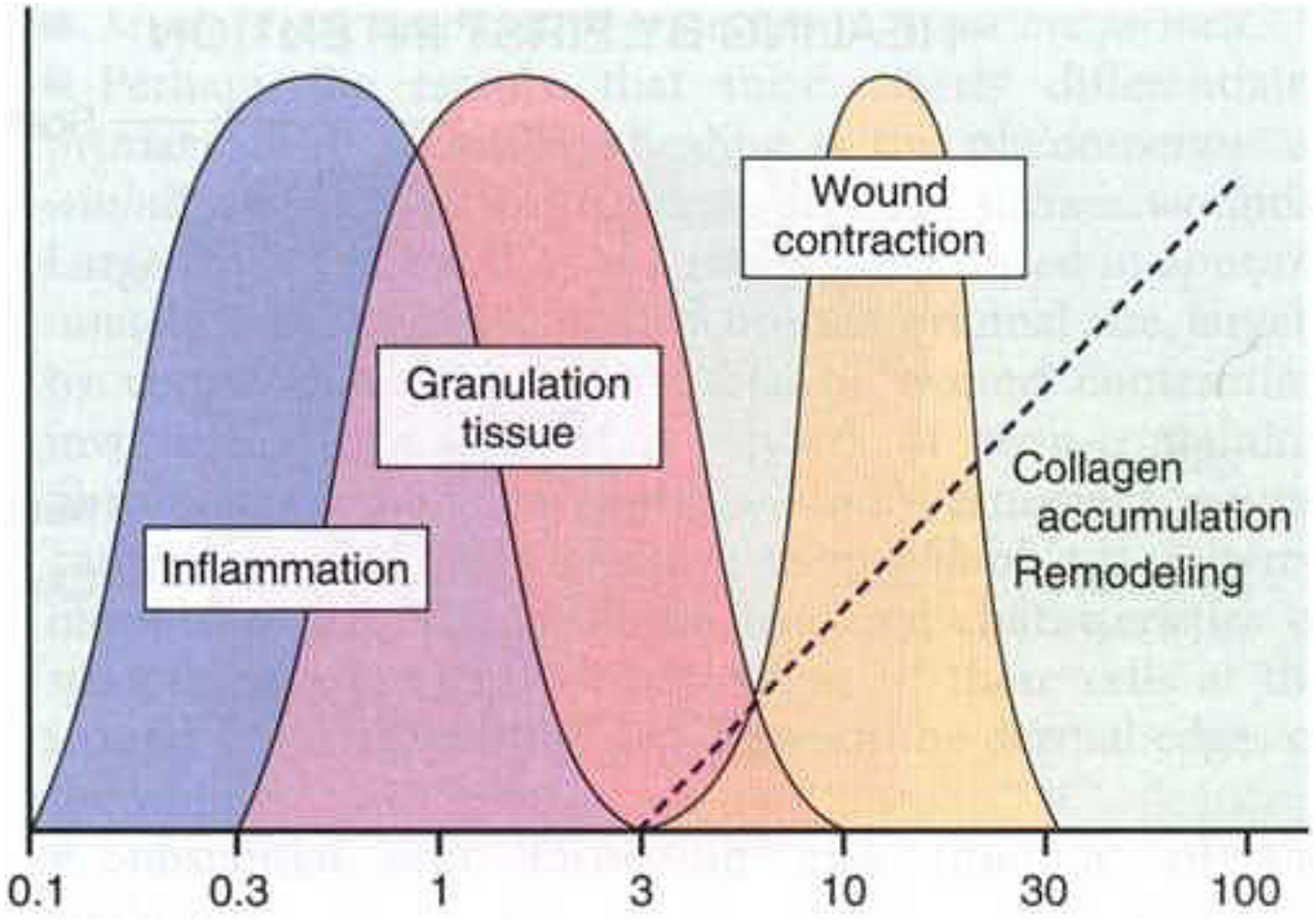


(Kumar et al, 2015)

❑ Healing tissue

- ❖ It is usually a tissue response to
  - Wound--- commonly in the skin inflammatory process
  - Cell necrosis in organs which incapable regeneration
- ❖ Scar formation, Fibrosis

❑ Healing process



(Kumar et al, 2015)

❑ Wound Healing is a complex of…

- ❖ Induction of acute inflammation process
- ❖ Formation of new blood vessels
- ❖ Synthesis of extracellular matrix (ECM)
- ❖ Tissue remodeling

❑ Phases of wound healing

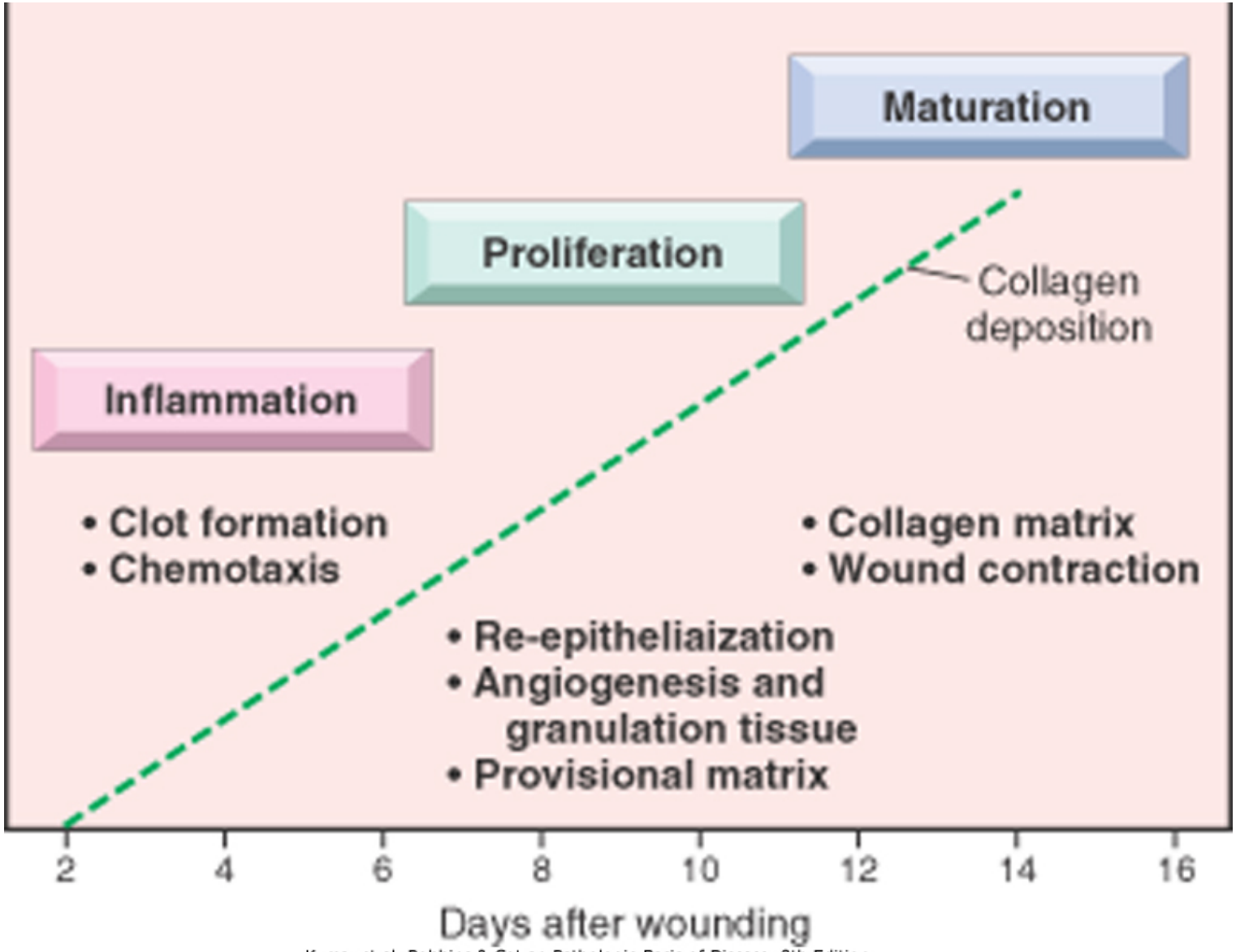


TABLE 3–4 Growth Factors and Cytokines Affecting Various Steps in Wound Healing	
Monocyte chemotaxis	PDGF, FGF, TGF-β
Fibroblast migration	PDGF, EGF, FGF, TGF-β, TNF, IL-1
Fibroblast proliferation	PDGF, EGF, FGF, TNF
Angiogenesis	VEGF, Ang, FGF
Collagen synthesis	TGF-β, PDGF
Collagenase secretion	PDGF, FGF, EGF, TNF, TGF-β inhibits

(Kumar et al, 2015)

❑ Angiogenesis

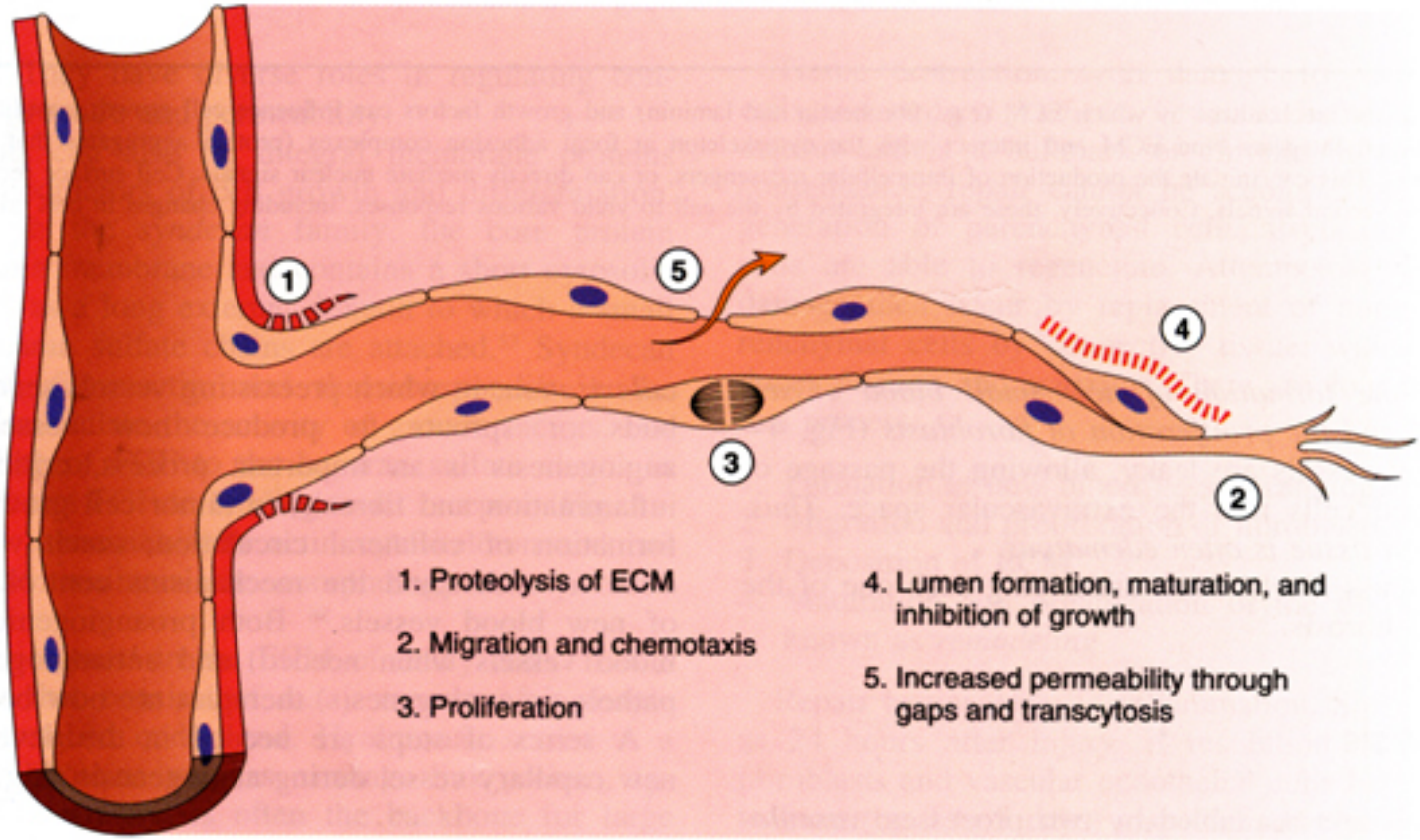


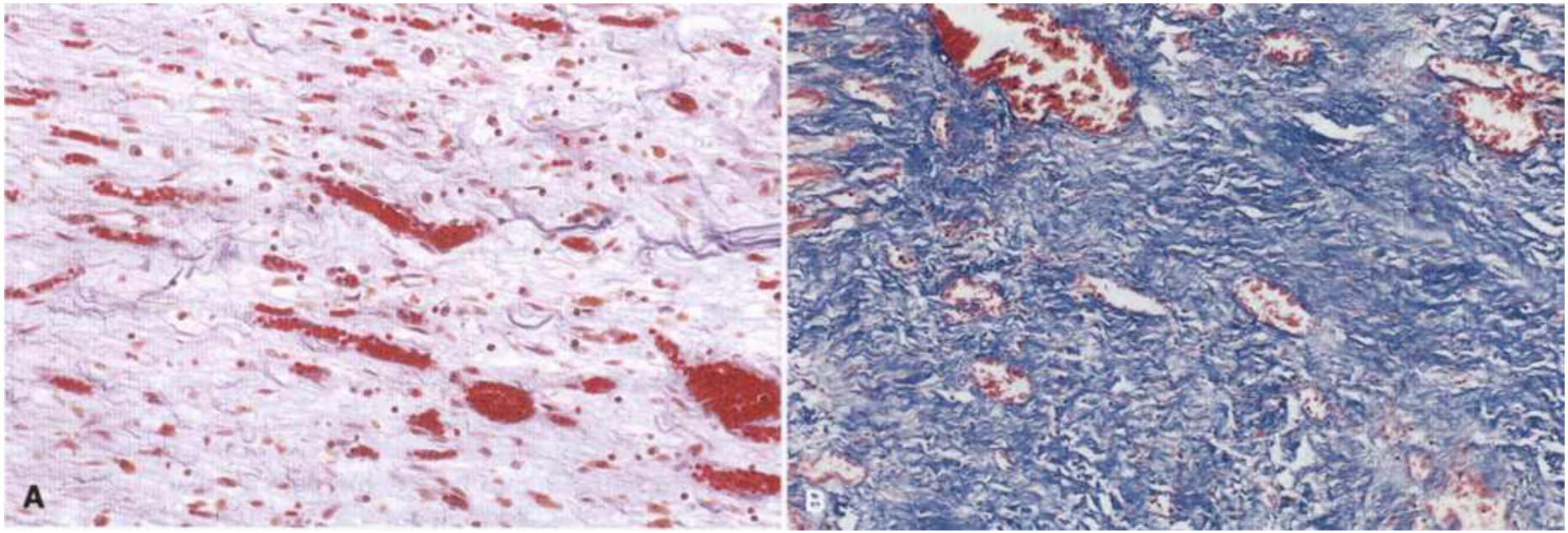
Figure 4–14

Steps in the process of angiogenesis (see text). (Modified from Motamed K, Sage EH: Regulation of vascular morphogenesis by SPARC. Kidney Int 51: 1383, 1997.)

(Kumar et al, 2015)

❑ Granulation tissue

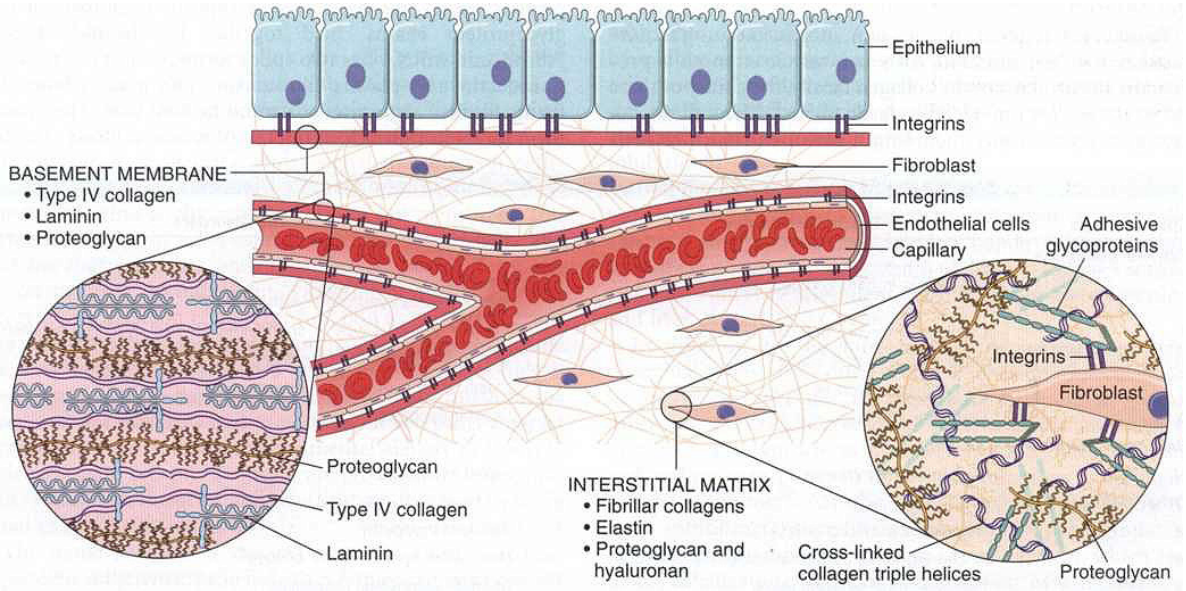
- ❖ Inflammatory cells
- ❖ Angiogenesis
- ❖ ECM



(Kumar et al, 2015)

❑ Extracellular matrix (ECM)

- ❖ Fibrous structural proteins--- Collagens, Elastins
- ❖ Adhesive glycoprotein--- Fibronectin, Laminin
- ❖ Water-hydrated gels--- Proteoglycans, Hyaluronan



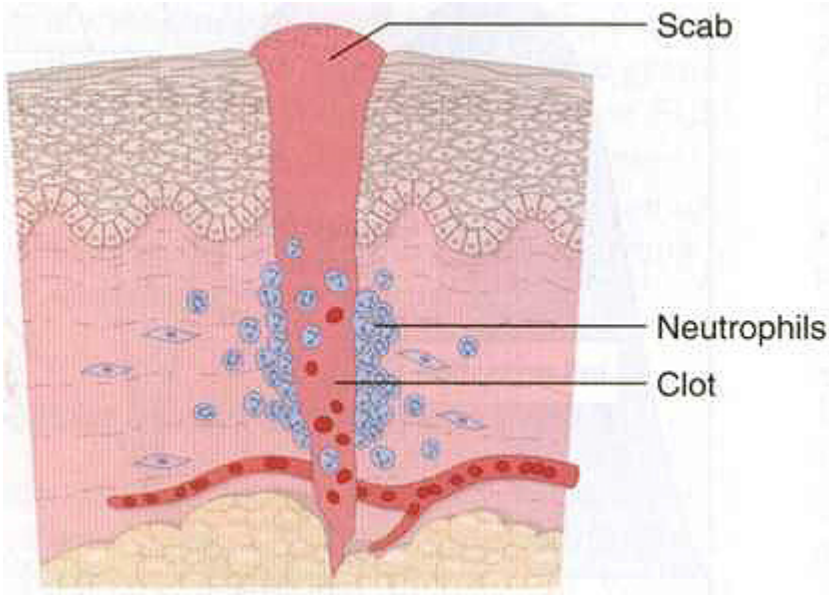
(Kumar et al, 2015)

❑ Tissue remodeling

- ❖ The replacement of granulation tissue with a scar
- ❖ The balance between ECM synthesis and degradation
  - Matrix metalloproteinases (MMPs)
  - Tissue inhibitor of metalloproteinases (TIMPs)

❑ Steps in wound healing

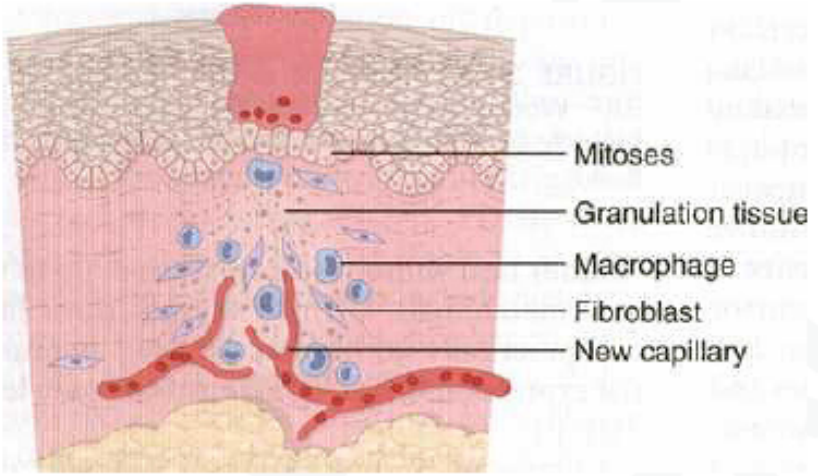
1st Intention



(Kumar et al, 2015)

- Neutrophils appear at the margins and move toward the fibrin clot.

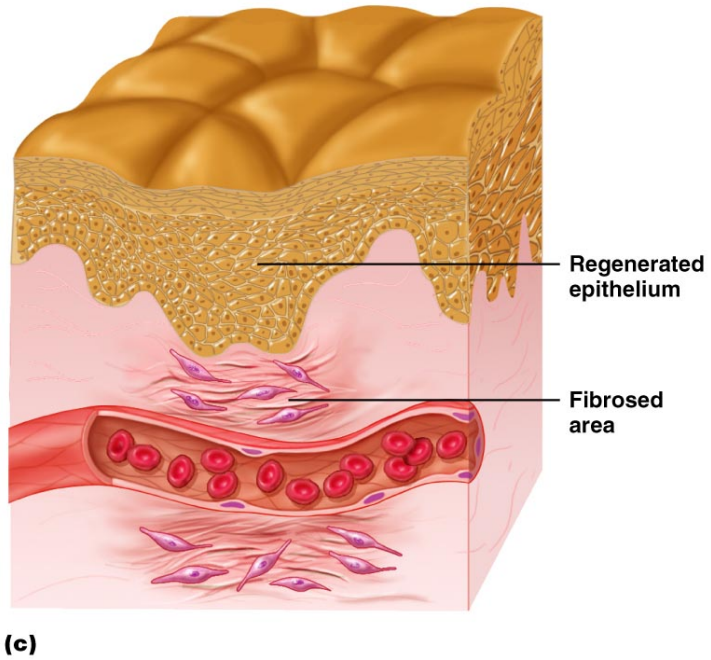
3 to 7 days



(Kumar et al, 2015)

- Neutrophils are replaced by MØ.
- Granulation beings to appear.

- The incisional space is filled with granulation tissue.
- Maximal neovascularization



- *2 weeks*, there is continued accumulation and proliferation of collagen and fibroblasts.

1 month:

- The scar is made up of a cellular connective tissue *devoid of inflammatory infiltrate.*
- Covered now by intact epidermis

2nd Intention

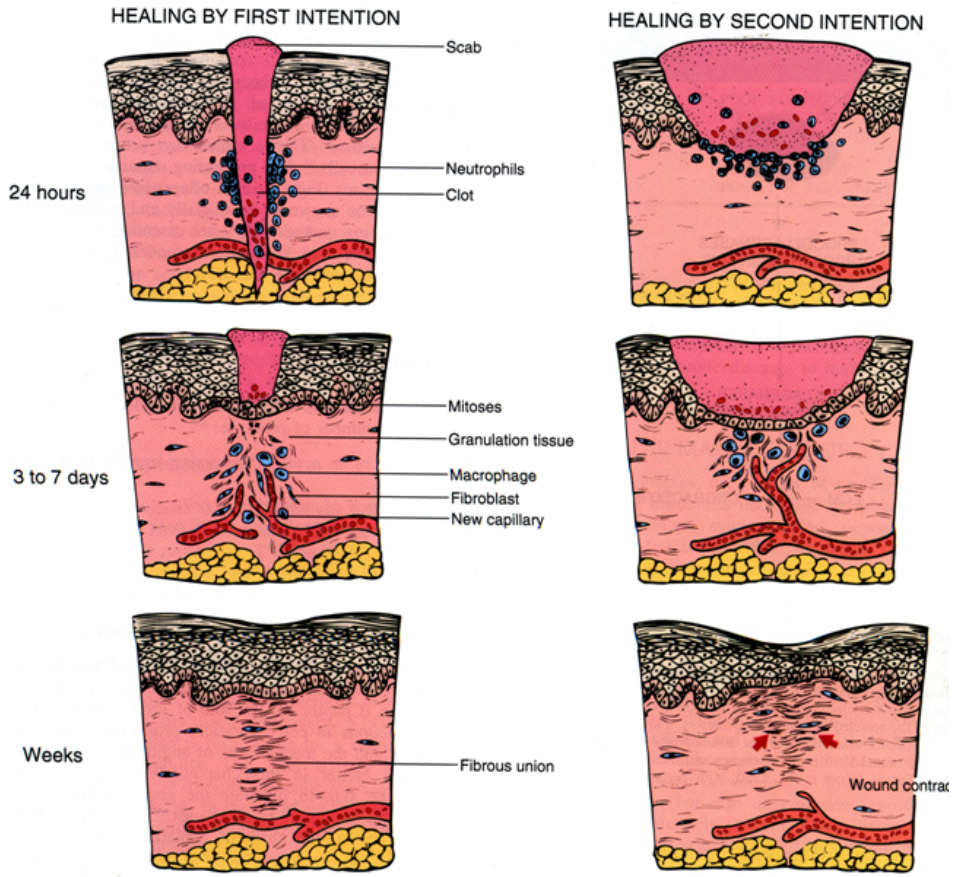


Figure 4–17

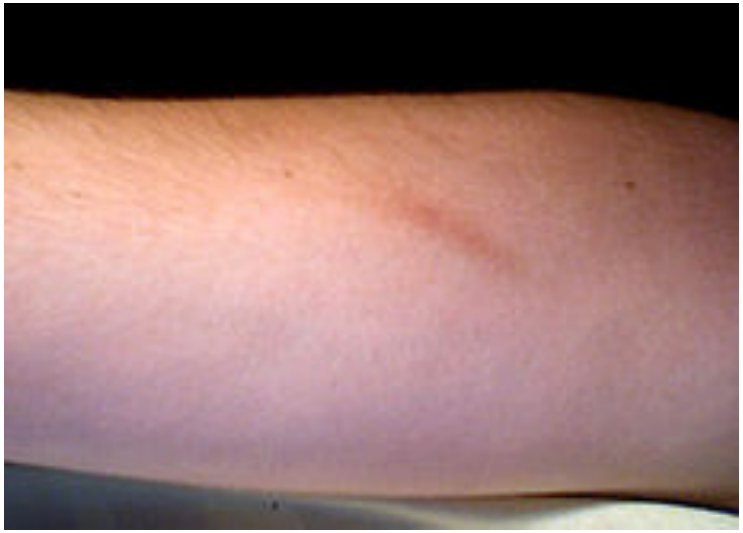
Steps in wound healing by first intention *(left)* and second intention *(right)*. In the latter, the resultant scar is much smaller than the original woun to wound contraction.

(Kumar et al, 2015)

- Large tissue defects generate a larger fibrin clot.
- Larger granulation tissue are formed.
- Substantial scar formation and thinning of the epidermis

❑ Scar

❖ It is areas of fibrous tissue that replace normal skin/tissue after injury.

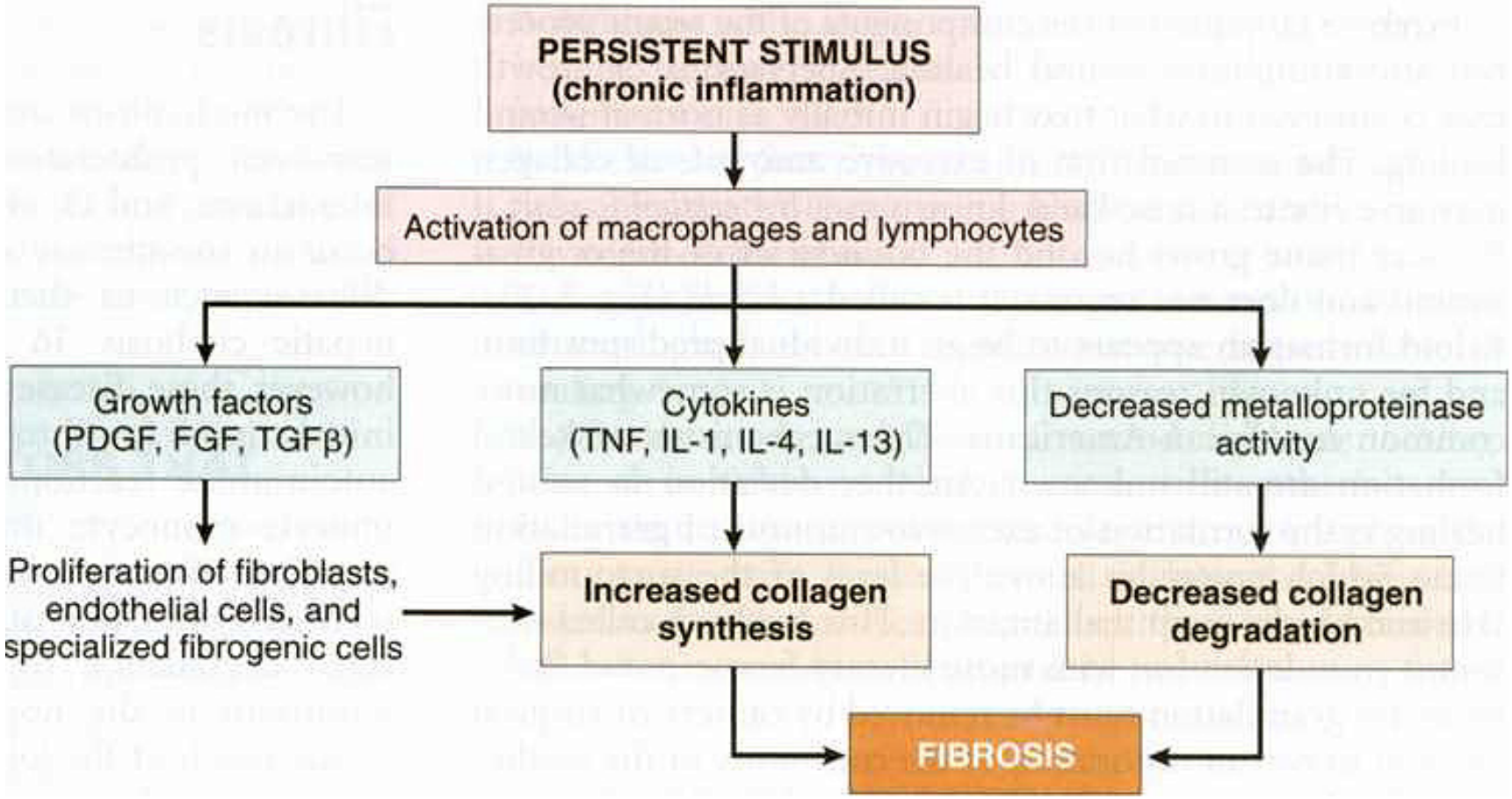


(http://en.wikipedia.org/wiki/Scar)

❖ It is a composed of mainly either type III (early) or type I (late) collagen.

❖ Natural part of the healing process

❑ Development of fibrosis in chronic inflammation



(Kumar et al, 2015)

❑ Wound strength

- ❖ Wound strength is approximately 10% in 1 week.
- ❖ The strength increases rapidly within 4 weeks.
- ❖ The recovery of tensile strength results from the excess of collagen synthesis (2 months).
- ❖ 70% to 80% the tensile strength of unwounded skin (3 months)

❑ The factors that influence wound healing

TABLE 3–5 Factors That Retard Wound Healing

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

(Kumar et al, 2015)

❖ Complications in cutaneous wound healing

They can arise from abnormalities in any of the basic components of the repair process.

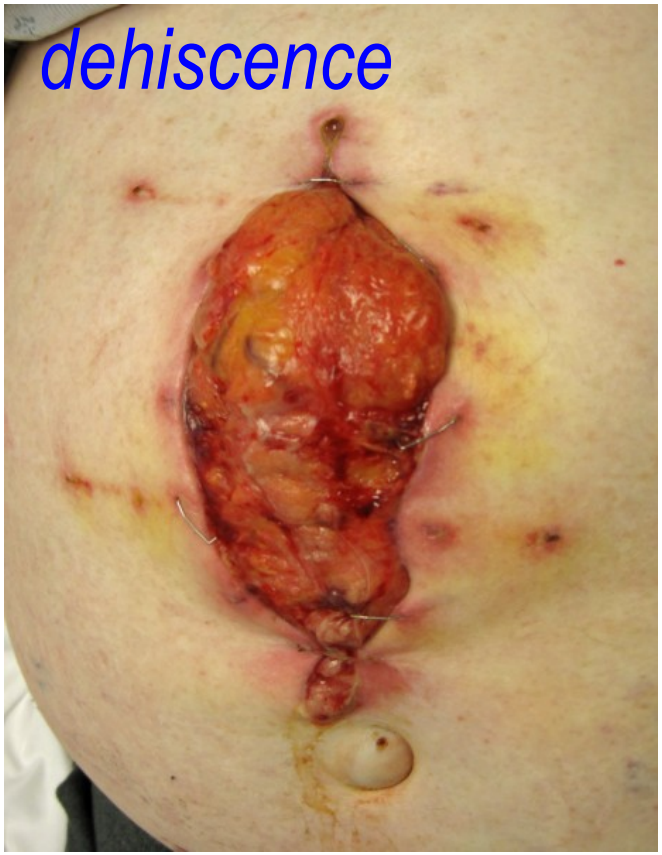
(1) Deficient scar formation

(2) Excessive formation of the repair components

(3) Formation of contractures

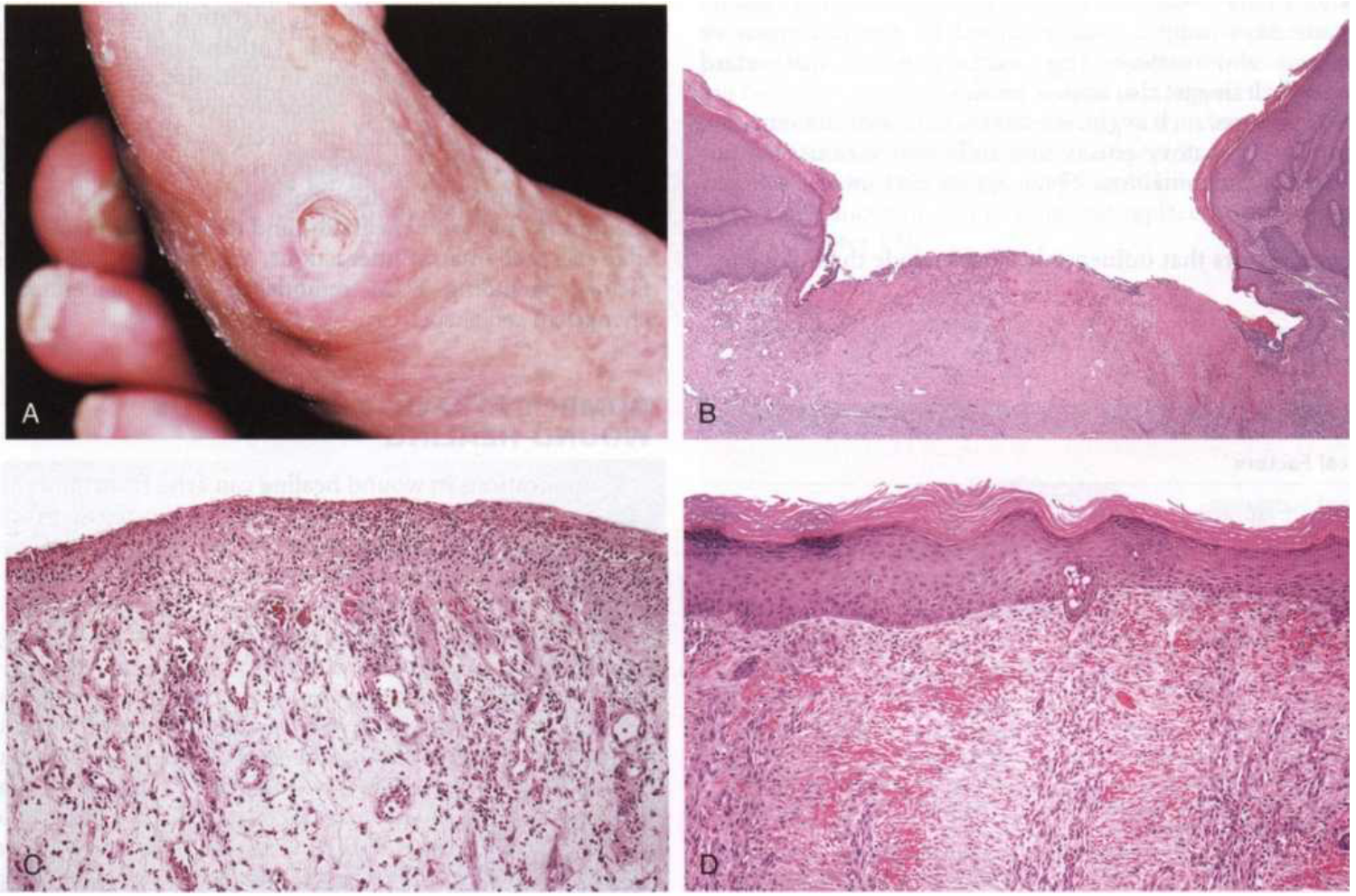
1. Deficient scar formation

- Inadequate formation of granulation tissue or assembly of a scar
- Wound dehiscence
- Ulceration



(www.epmonthly.com)

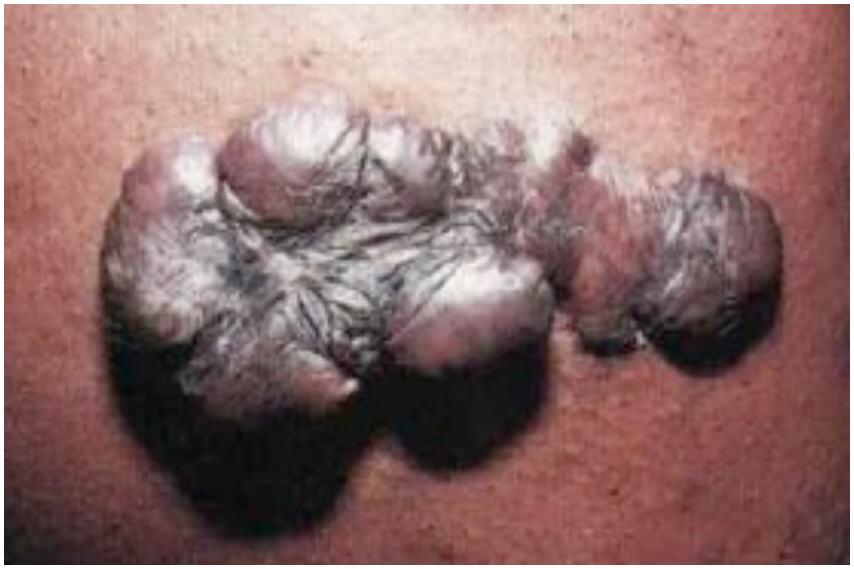
❖ Healing of skin ulcers

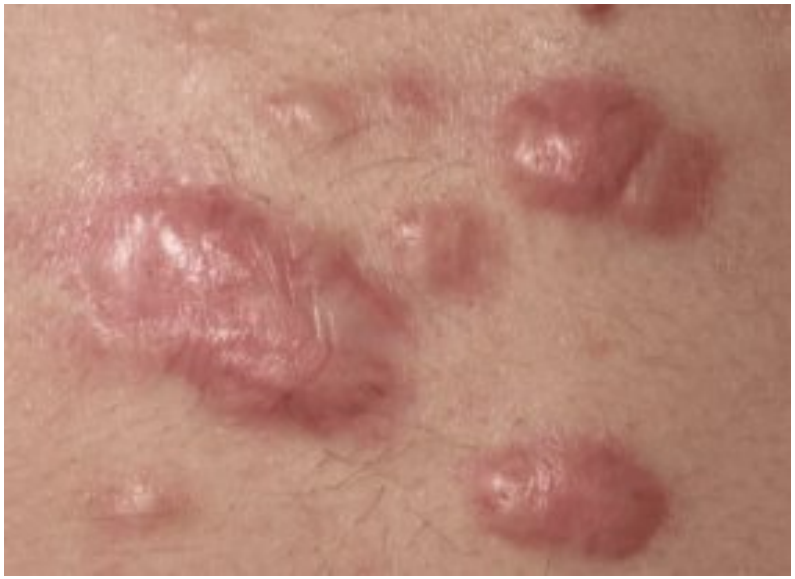


(Kumar et al, 2015)

2. Excessive scar formation

- Keloid (immature type III collagen)
- Hypertrophic scar (in black people)

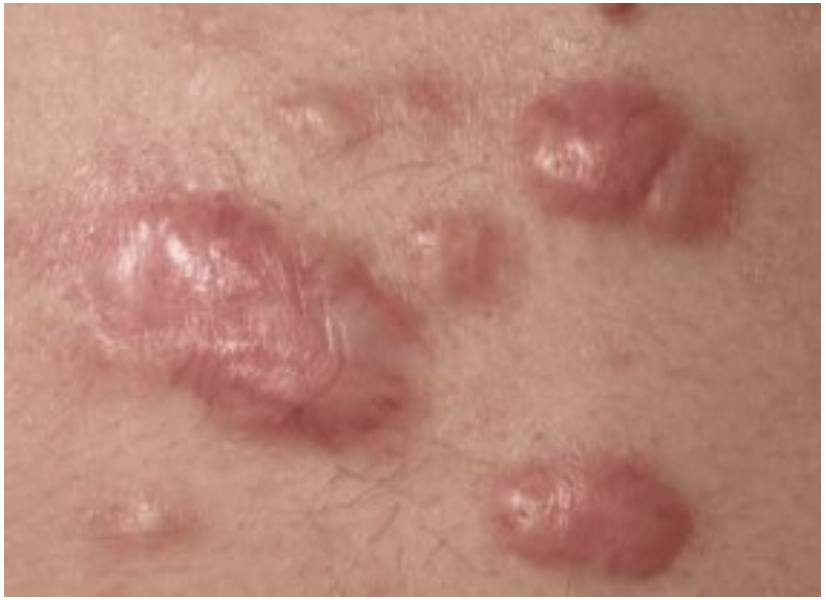


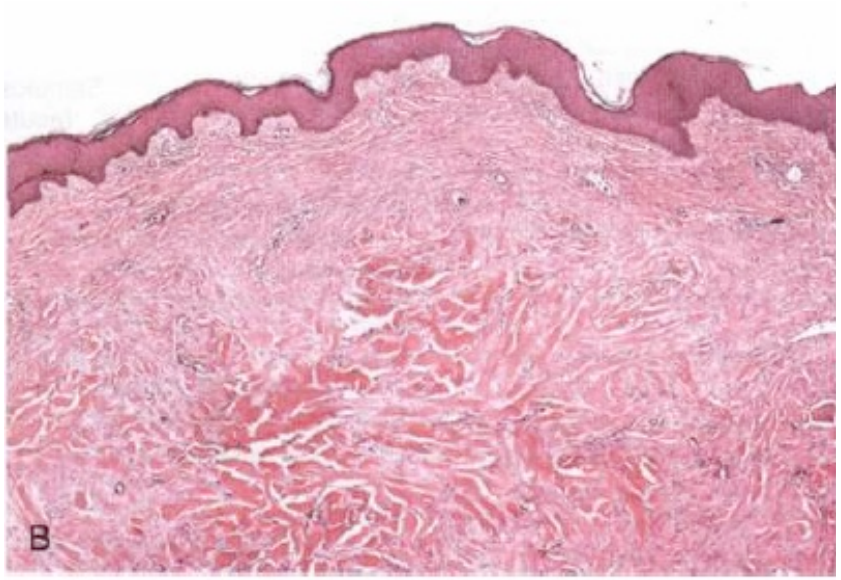


(Kumar et al, 2015)

❑ Keloid

- ❖ It is a result of an overgrowth of granulation tissue (collagen type 3) at the site of a healed skin injury.
- ❖ It is then slowly replaced by collagen type 1.





(Kumar et al, 2015)

3. Formation of contractures

- The size of a wound is an important part of the normal healing process.
- The excess of wound contraction leads to physical deformity that characterized by skin constriction and functional limitations.

References

- Vinay Kumar, Abul K. Abbas, Nelson Fausto, Jon C Aster. Robbins and Cotran, Pathologic Basis of Disease; 2015
- J.C.E Underwood and S.S. Cross. General and Systemic Pathology; 2009.