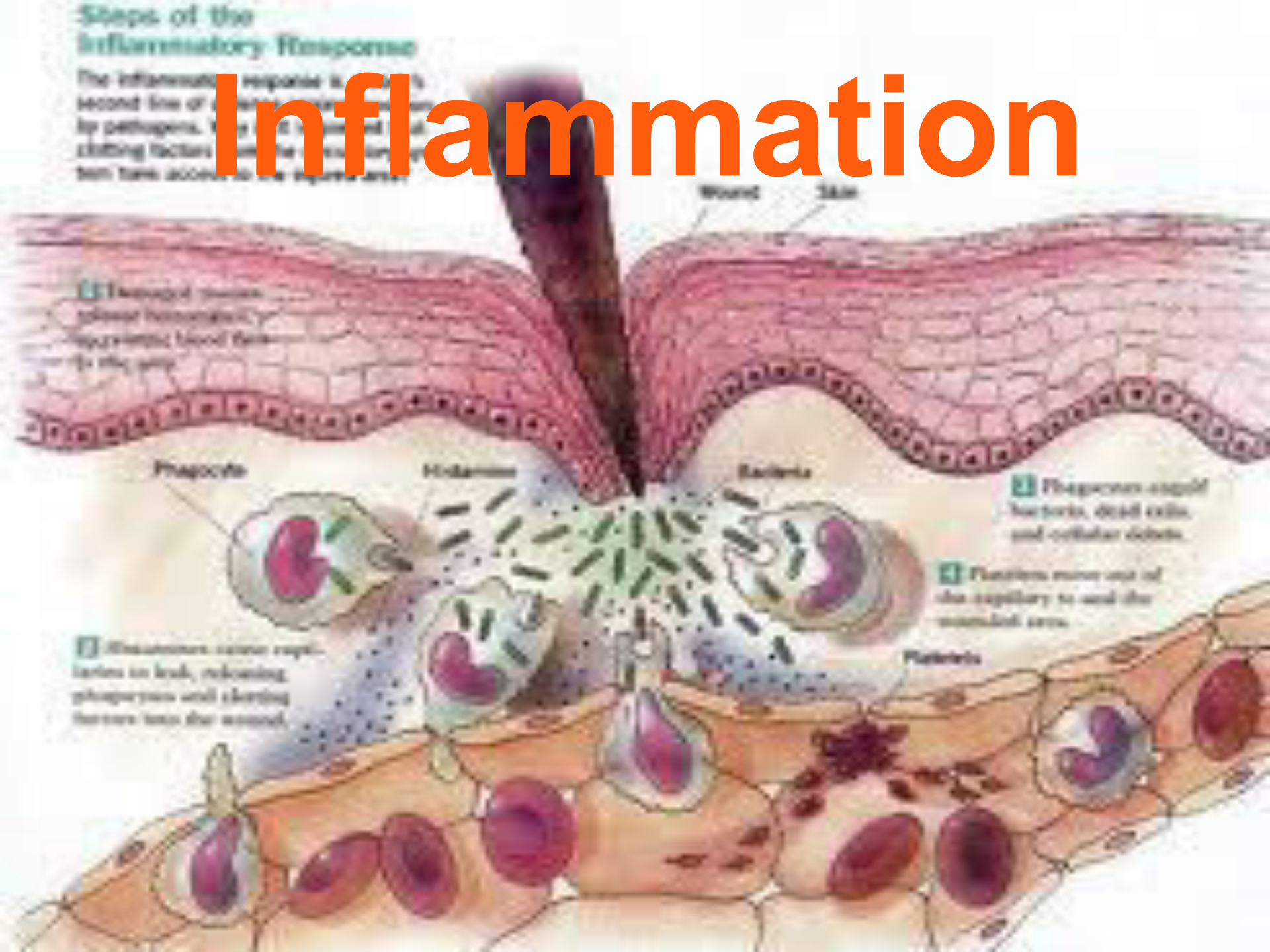
Inflammation



Inflammation

is a protective response intended to eliminate the initial cause of cell injury as well as the necrotic cells and tissues resulting from the original insult

A double edge sword?

Although inflammation helps clear infections and other noxious stimuli and initiates repair, the inflammatory reaction and the subsequent repair process can cause considerable harm.

Injurious stimuli cause a protective vascular connective tissue reaction called “inflammation”

-Dilute
-Destroy
-Isolate
-Initiate repair

Definition: is the response of living tissue to injurious agent.

Etiology:

1- Physical Agents: Mechanical trauma, extremes of temperature, radiation.

2- Chemical Agents and Drugs: Industrial and occupational hazards, such as asbestos.

3- Infectious Agents.

4- Tissue necrosis.

5- Immune reaction.

6- Foreign body.

Classification of inflammation:

1- Acute

2- Chronic

Acute inflammation:

Is a rapid host response that serves to deliver leukocytes and plasma proteins, such as antibodies, to sites of infection or tissue injury.

Etiology of Acute Inflammation:

Acute inflammatory reactions may be triggered by a variety of stimuli:

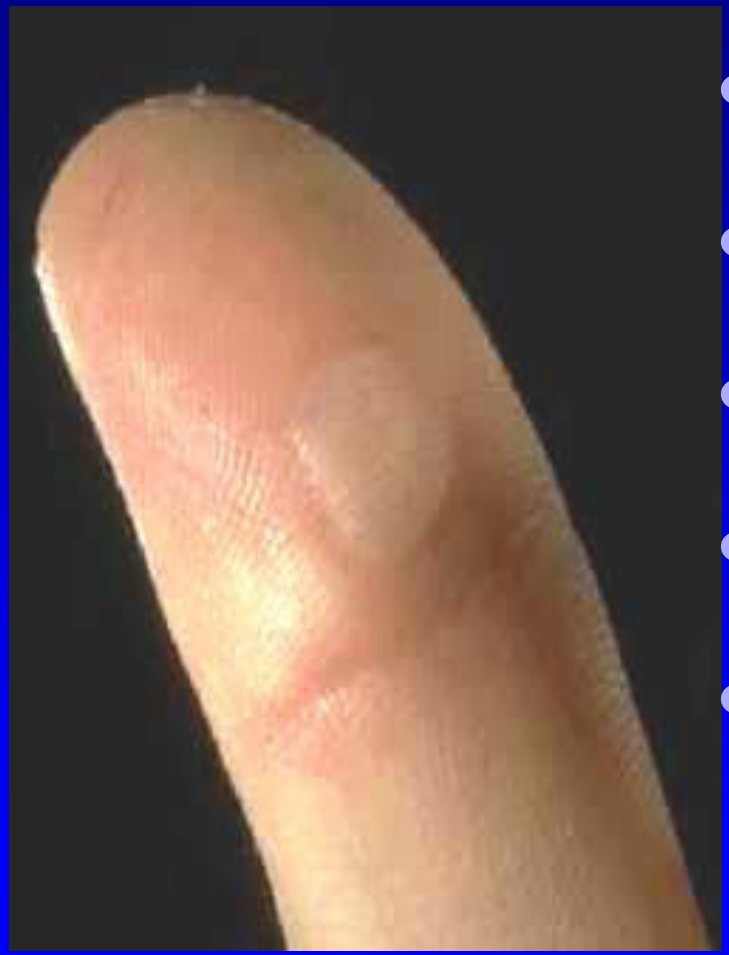
1• **Infections (bacterial, viral, fungal, parasitic) and microbial toxins.**

2• **Tissue necrosis from any cause, including ischemia (as in a myocardial infarct), trauma, and physical and chemical injury.**

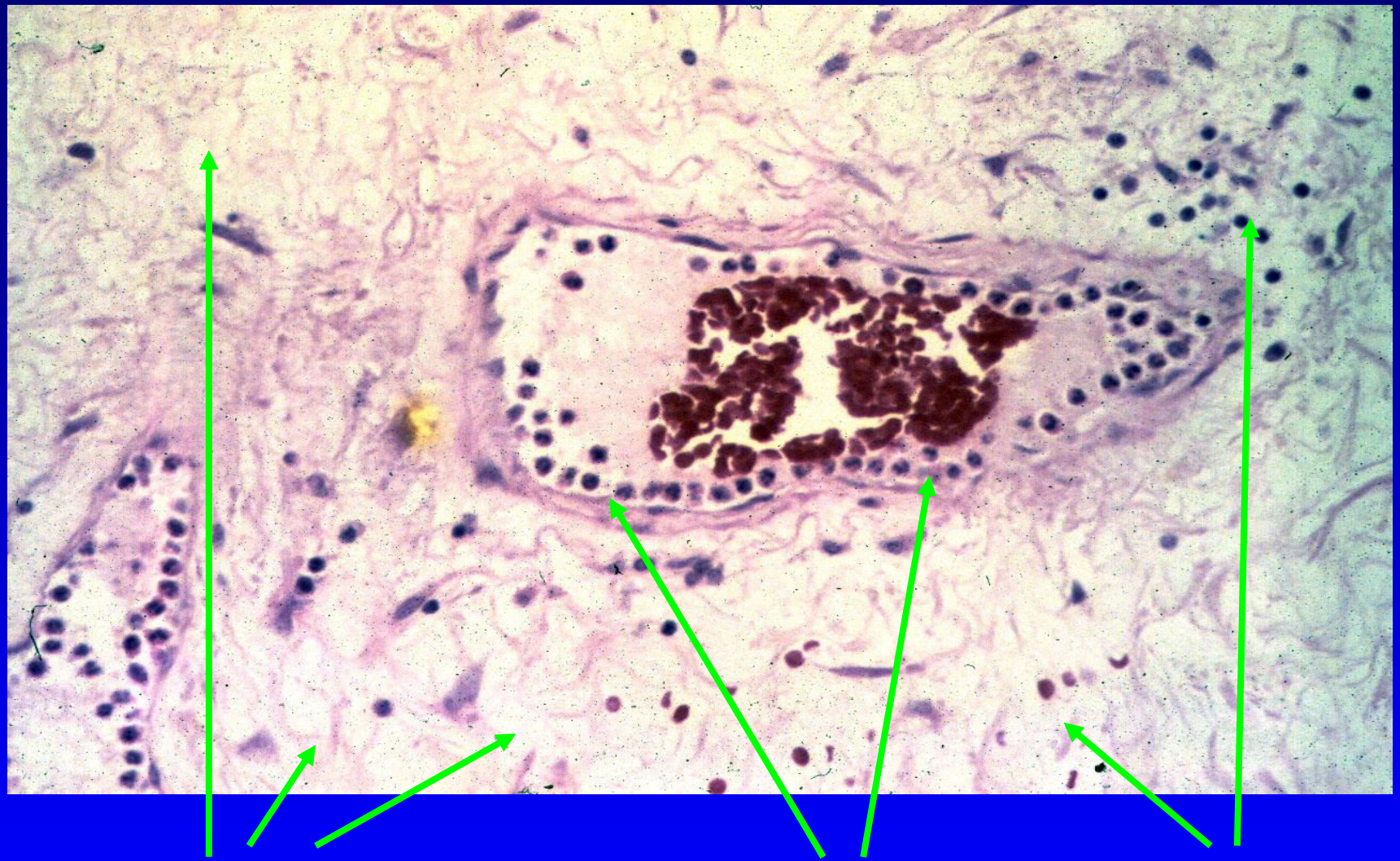
3• **Foreign bodies (splinters, dirt, sutures) typically elicit inflammation because they cause traumatic tissue injury or carry microbes.**

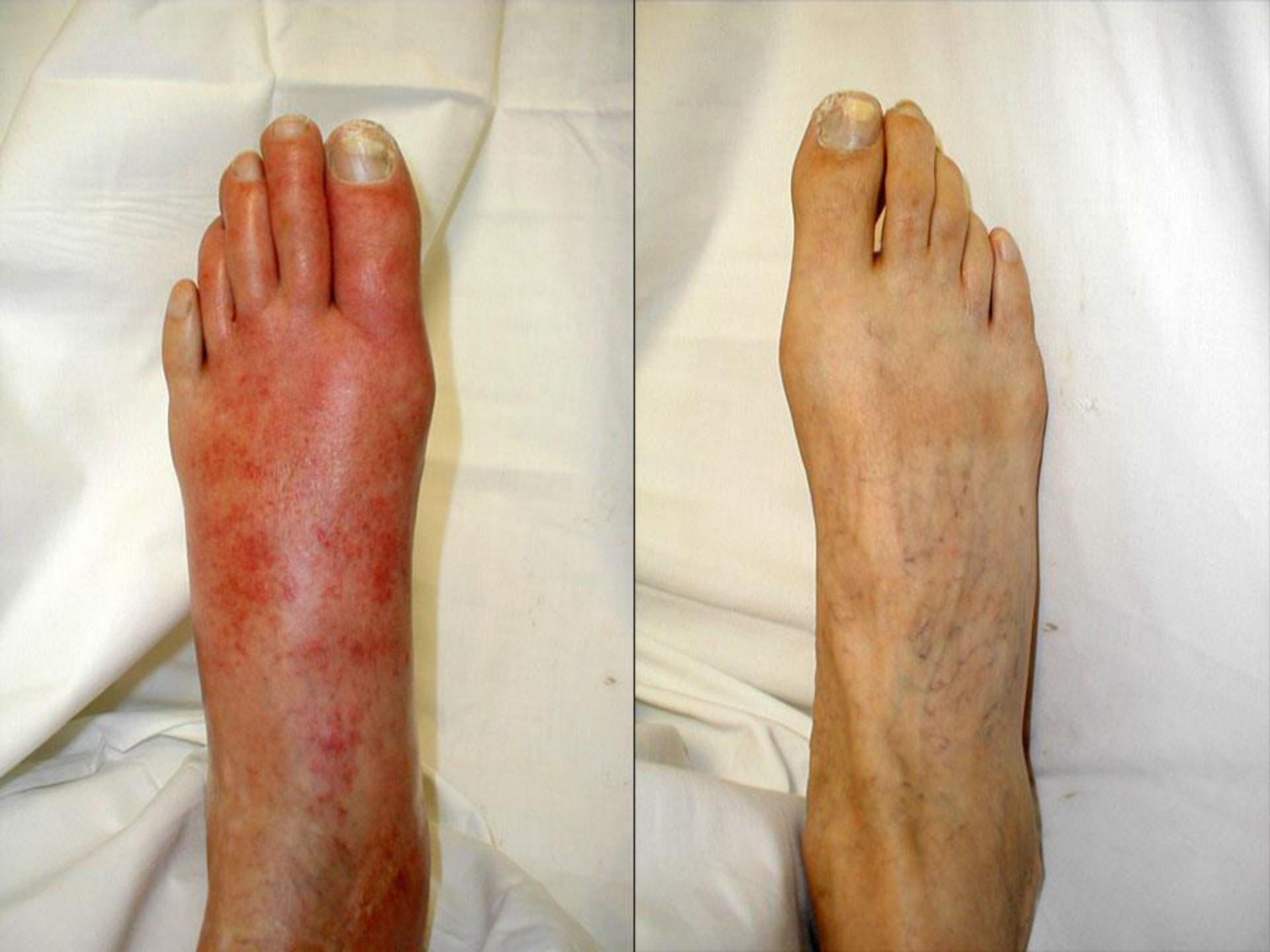
4• **Immune reactions (also called hypersensitivity reactions).**

Cardinal Signs of Inflammation



- Redness : Hyperaemia.
- Warm : Hyperaemia.
- Pain : Nerve, Chemical mediators
- Swelling : Exudation
- Loss of Function: Pain


Tissue oedema
Neutrophil margination …. And emigration



Changes of acute inflammation:

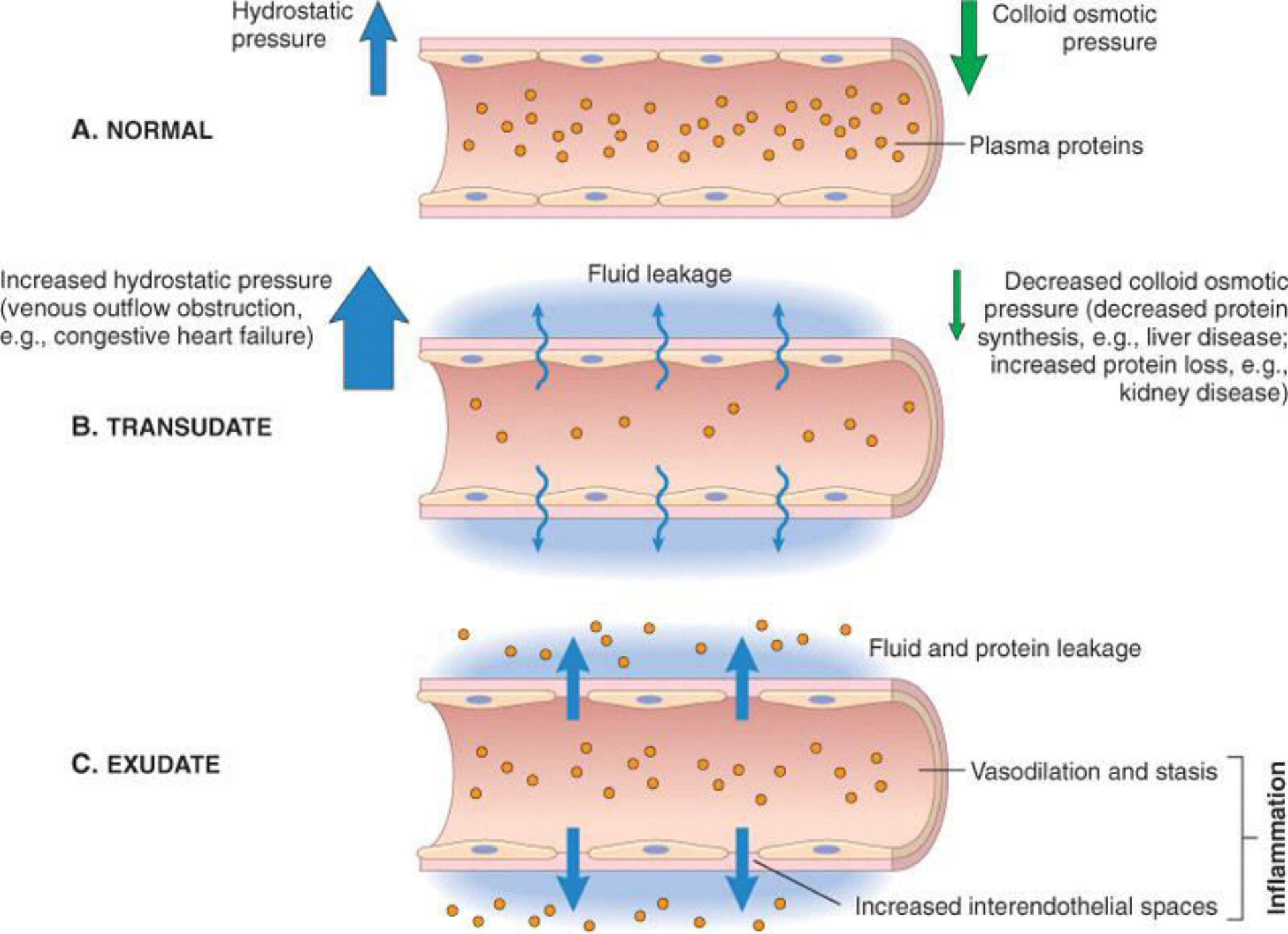
A- Vascular changes: which includes:

(1) Changes in vascular caliber and blood flow:

First: there is a transient constriction of arterioles, lasting a few seconds.

Second: vasodilation which involves the arterioles and then leads to opening of new capillary beds, the result is increased blood flow, which is the cause of heat and redness (erythema) at the site of inflammation, vasodilation is induced by the action of several mediators, notably histamine and nitric oxide (NO).

Third: slowing of blood flow (stasis) as a result of the loss of fluid, increased vessel diameter, concentration of red cells in small vessels, and increased viscosity of the blood.

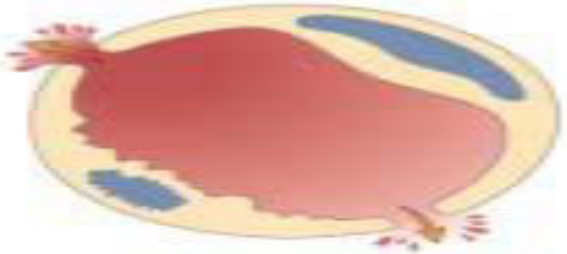


(2) Changes in the in vascular structure: (increased vascular permeability)

Increased vascular permeability leads to the escape of a protein-rich exudate into the extravascular tissue, causing edema. Several mechanisms are responsible for the increased vascular permeability:

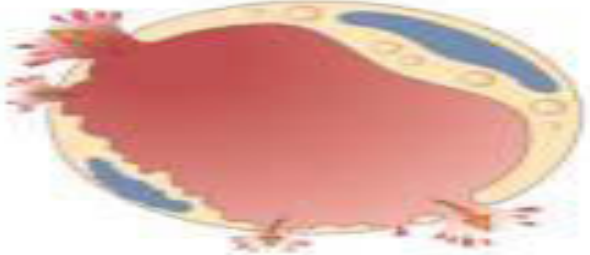
Gaps due to endothelial contraction

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



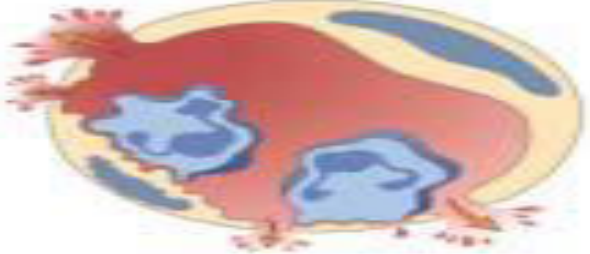
Direct injury

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



Leukocyte-dependent injury

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

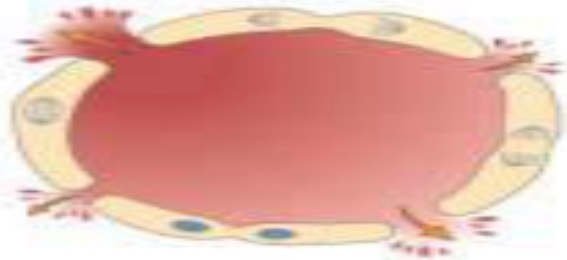


Increased transcytosis

- Venules
- Vascular endothelium–derived growth factor

New blood vessel formation

- Sites of angiogenesis
- Persists until intercellular junctions form



B- Cellular changes: which includes

(1) Emigration of the leukocytes from the microcirculation:

Leukocyte Adhesion to Endothelium.

Leukocyte Migration through Endothelium.

(2) Accumulation of the leukocytes in the focus of injury: Chemotaxis of Leukocytes.

(3) Activation of the leukocytes to eliminate the offending agent:

Recognition of Microbes and Dead Tissues

Removal of the Microbes and Dead Tissues

(1) Emigration of the leukocytes from the microcirculation.

Leukocyte Adhesion to Endothelium.

Margination: is the process of leukocyte redistribution, because blood flow slows early in inflammation (stasis), more white cells assume a peripheral position along the endothelial surface.

Rolling: is the process of leukocytes adhesion transiently to the endothelium, detach and bind again, thus rolling on the vessel wall.
Rolling is mediated by a family of proteins called selectins (adhesion molecules). There are three types of selectins: one expressed on leukocytes (L-selectin), one on endothelium (E-selectin), and one on platelets and on endothelium (P-selectin).

Adhesion: is the process of leukocytes adhesion firmly to the endothelium, firm adhesion is mediated by a family of proteins called integrins (VLA-4, LFA-1 and Mac-1)

Leukocyte Migration through Endothelium.

The next step is migration of the leukocytes through the endothelium, called transmigration or diapedesis. Transmigration of leukocytes occurs mainly in postcapillary venules. Chemokines act on the adherent leukocytes and stimulate the cells to migrate through interendothelial spaces toward the chemical concentration gradient, (toward the site of injury or infection where the chemokines are being produced), after traversing the endothelium, leukocytes penetrate the basement membrane, by secreting collagenases, and enter the extravascular tissue.

(2) **Accumulation of the leukocytes in the focus of injury. Chemotaxis of Leukocytes.**
After exiting the circulation, leukocytes emigrate in tissues toward the site of injury by a process called chemotaxis, which is defined as locomotion oriented along a chemical gradient.

Both exogenous and endogenous substances can act as chemoattractants.

The most common exogenous agents are bacterial products.

Endogenous chemoattractants include several chemical mediators:

(1) Cytokines (e.g., IL-8).

(2) Components of the complement system, particularly C5a

(3) Arachidonic acid (AA) metabolites, mainly leukotriene B4 (LTB4).

All these chemotactic agents bind to specific receptors on the surface of leukocytes result in increased cytosolic calcium, with actin and myosin changes at the leading edge of the cell. The leukocyte moves by extending filopodia that pull the back of the cell in the direction of extension, the net result is that leukocytes migrate toward the inflammatory stimulus in the direction of the gradient of locally produced chemoattractants.

The nature of the leukocyte infiltrate varies with the:

1- Age of the inflammatory response.

In most forms of acute inflammation neutrophils predominate in the inflammatory infiltrate during the first 6 to 24 hours and are replaced by monocytes in 24 to 48 hours. After entering tissues, neutrophils are short-lived; they undergo apoptosis and disappear after 24 to 48 hours.

Monocytes survive longer and proliferate in the tissues, and thus become the dominant population in chronic inflammatory reactions.

2- **Type of stimulus.**

In certain infections—for example, those produced by Pseudomonas bacteria— the cellular infiltrate is dominated by continuously recruited neutrophils for several days.

In viral infections, lymphocytes may be the first cells to arrive.

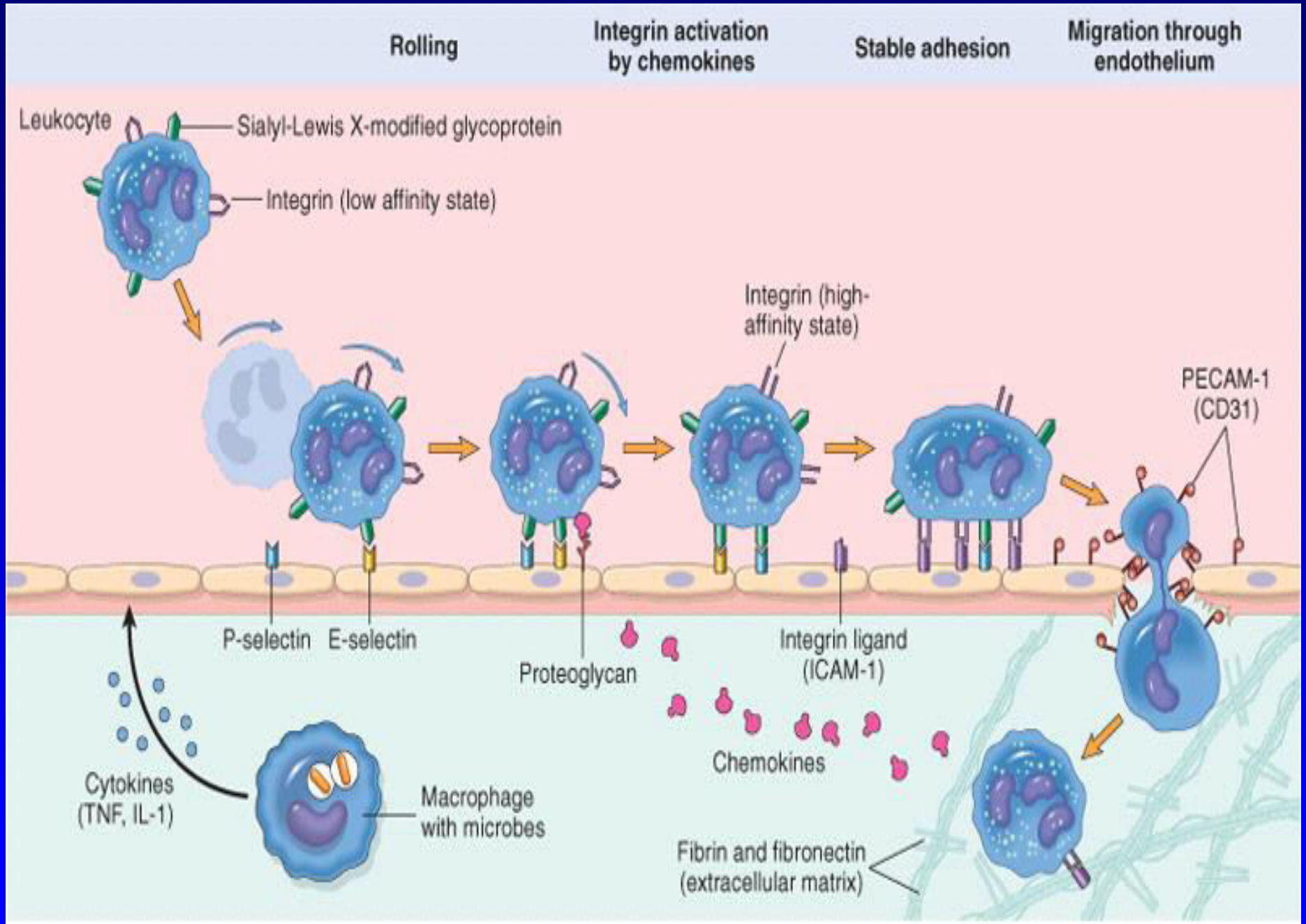
In some hypersensitivity reactions, eosinophils may be the main cell type.

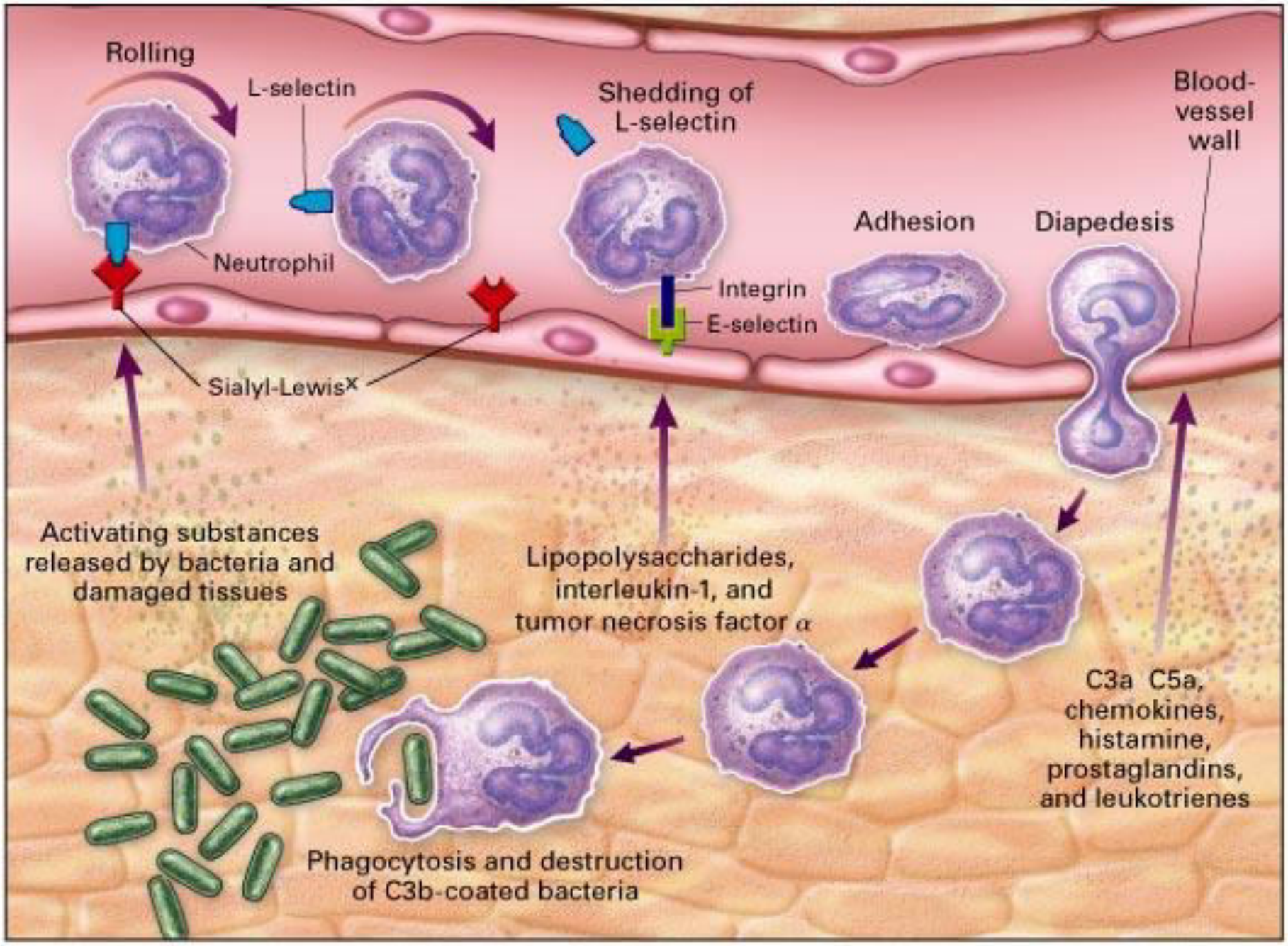
(3) Activation of the leukocytes to eliminate the offending agent.

Recognition of Microbes and Dead Tissues

Leukocytes express several receptors that recognize external stimuli:

- **Receptors for microbial products.**
- **G protein–coupled receptors.**
- **Receptors for opsonins: Leukocytes express receptors for proteins that coat microbes. The process of coating a microbe, to target it for ingestion (phagocytosis) is called opsonization, and substances that do this are opsonins. These substances include antibodies, complement proteins.**




Rolling
L-selectin
Shedding of L-selectin
Blood-vessel wall
Adhesion
Diapedesis
Neutrophil
Integrin
E-selectin
Sialyl-Lewis^x
Activating substances released by bacteria and damaged tissues
Lipopolysaccharides, interleukin-1, and tumor necrosis factor α
C3a C5a, chemokines, histamine, prostaglandins, and leukotrienes
Phagocytosis and destruction of C3b-coated bacteria

Removal of the Microbes and Dead Tissues

Recognition of microbes or dead cells by the receptors induces leukocytes for destruction of microbes by phagocytosis and intracellular killing.

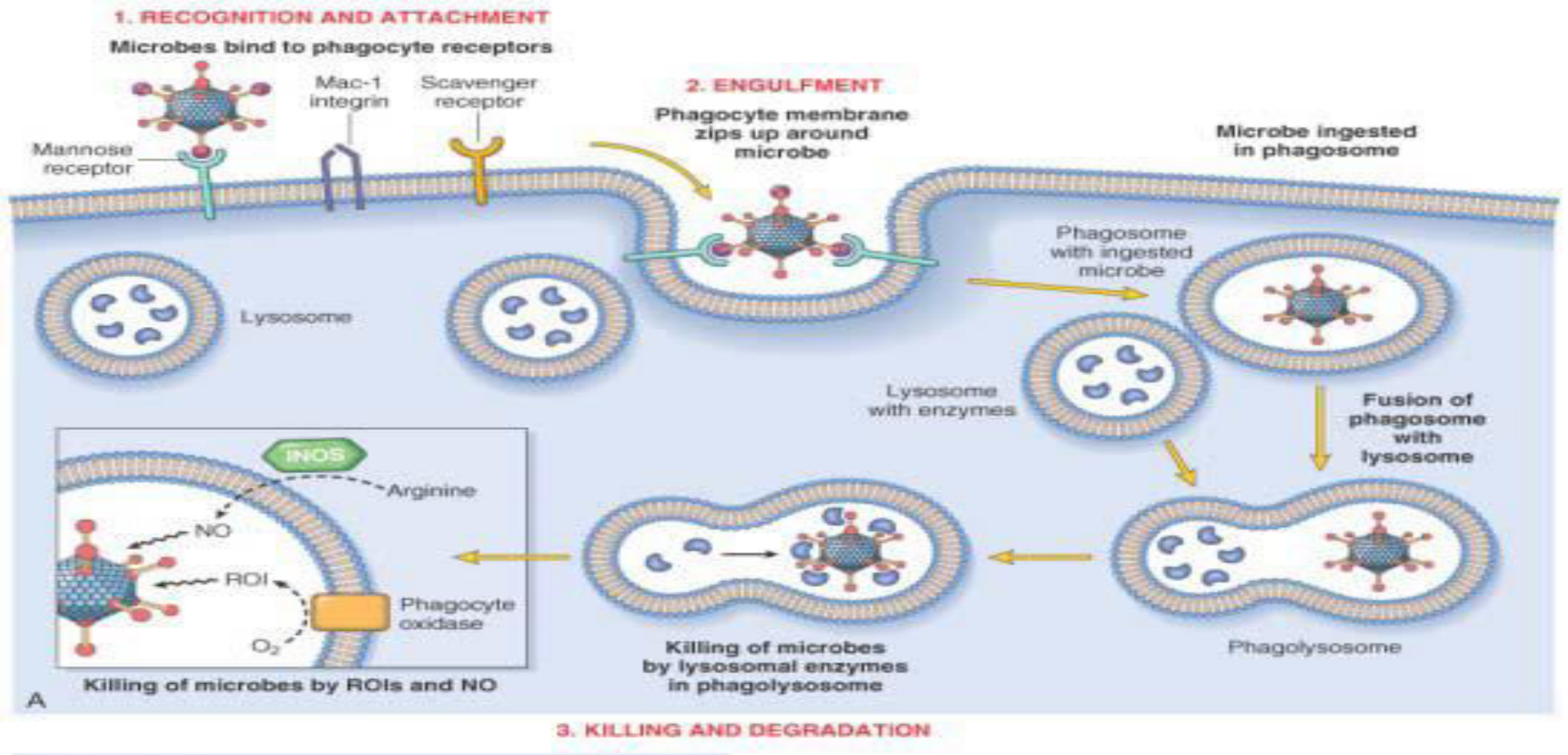
Phagocytosis and intracellular killing, involves three sequential steps:

(1) Attachment of the particle to be ingested by the leukocyte

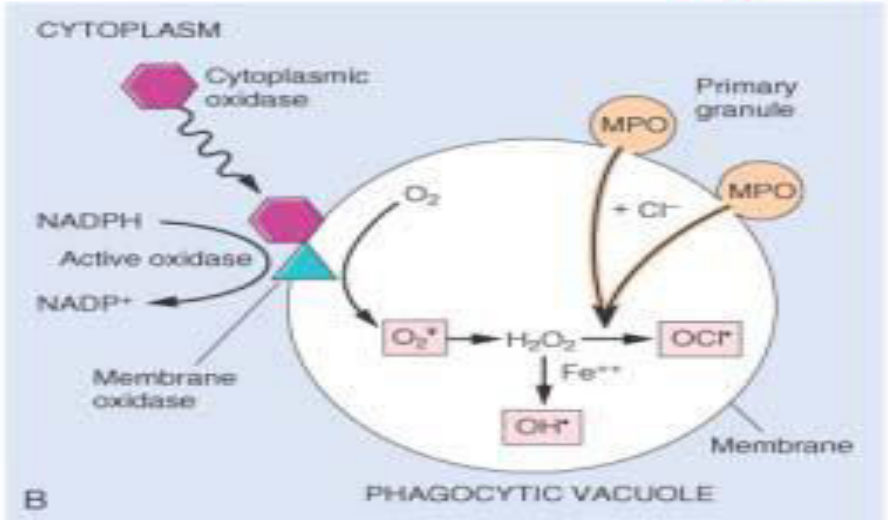
(2) Engulfment, with subsequent formation of a phagocytic vacuole; by extensions of the cytoplasm (pseudopods) around the microbe, and the formation of a vesicle (phagosome) that encloses the particle. The phagosome then fuses with a lysosomal granule, resulting in discharge of the granule's contents into the phagolysosome

(3) Killing or degradation of the ingested material within neutrophils and macrophages,

microbial killing is accomplished largely by reactive oxygen species (ROS, also called reactive oxygen intermediates) and reactive nitrogen species and action of other substances in leukocyte granules such as enzymes (elastase) , lysozyme, which hydrolyzes the bond found in the coat of all bacteria.



3. KILLING AND DEGRADATION



Termination (Control) of the Acute Inflammatory Response

Acute inflammation, needs tight controls to minimize the damage.

1- Inflammation declines simply because the mediators of inflammation have short half-lives, and are degraded after their release.
2- Neutrophils also have short half-lives in tissues and die by apoptosis within a few hours after leaving the blood.
3- There are a variety of stop signals that serve to terminate the inflammation, including transforming growth factor-β (TGF-β) and IL-10.

Sequelae of Acute Inflammation

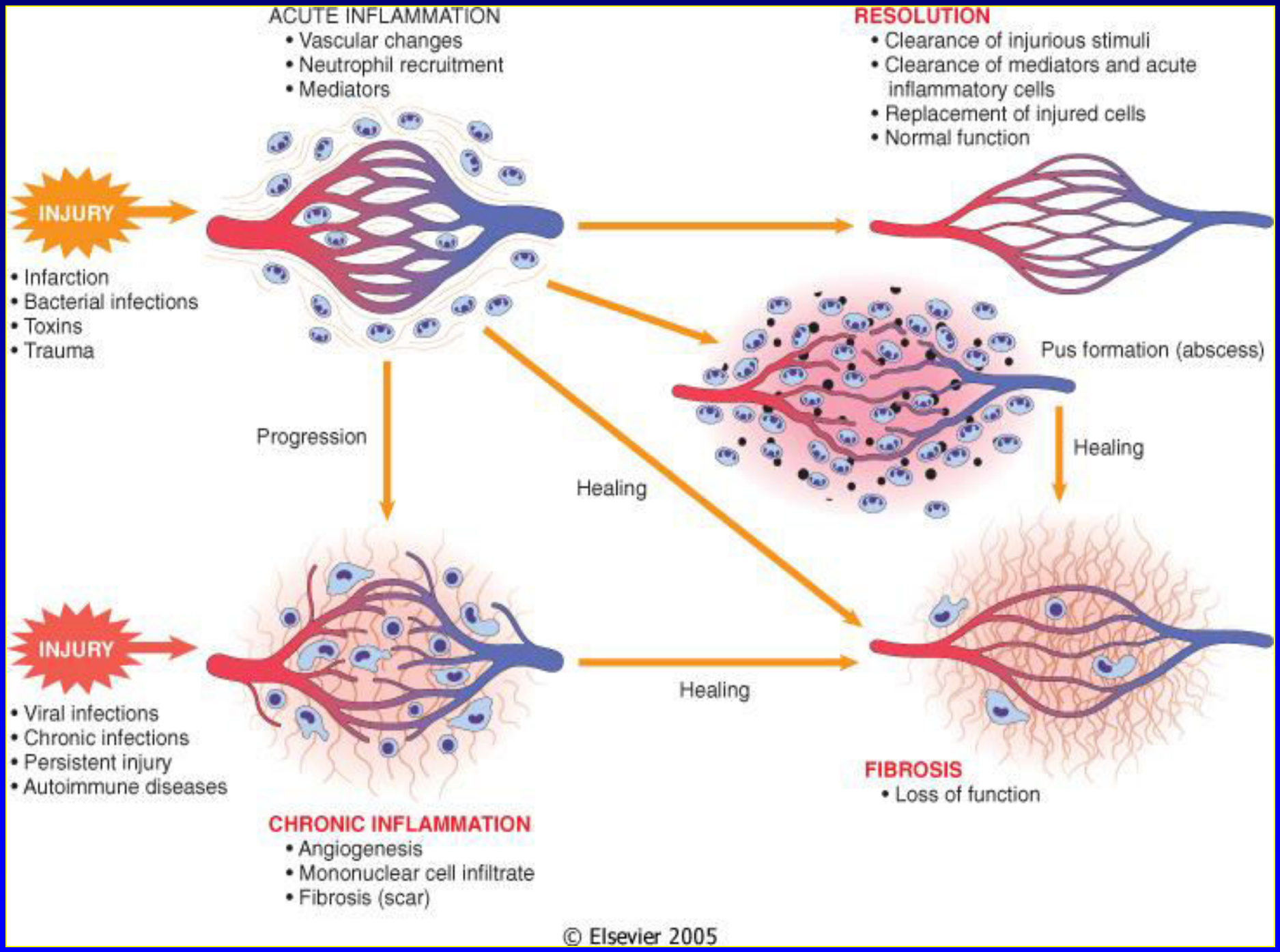
there are four main possible sequelae of acute inflammation:

- **Resolution:** complete resolution occurs following short-lived tissue injury in which there has been little tissue damage. The bacterium may be neutralized, killed and cleared by the acute inflammatory response and the affected tissues return entirely to normal. This occurs in some acute bacterial infections and is the ideal outcome.
- **Abscess formation:** This is characteristically seen with certain pyogenic organisms such as staphylococci. An abscess may discharge spontaneously or require drainage by surgical intervention.

Healing by fibrosis and scar formation:

Healing by fibrosis and scar formation occurs when substantial tissue destruction is seen during the acute inflammation. The damaged tissues are unable to regenerate and are replaced by fibrous tissue.

- **Progression to chronic inflammation**

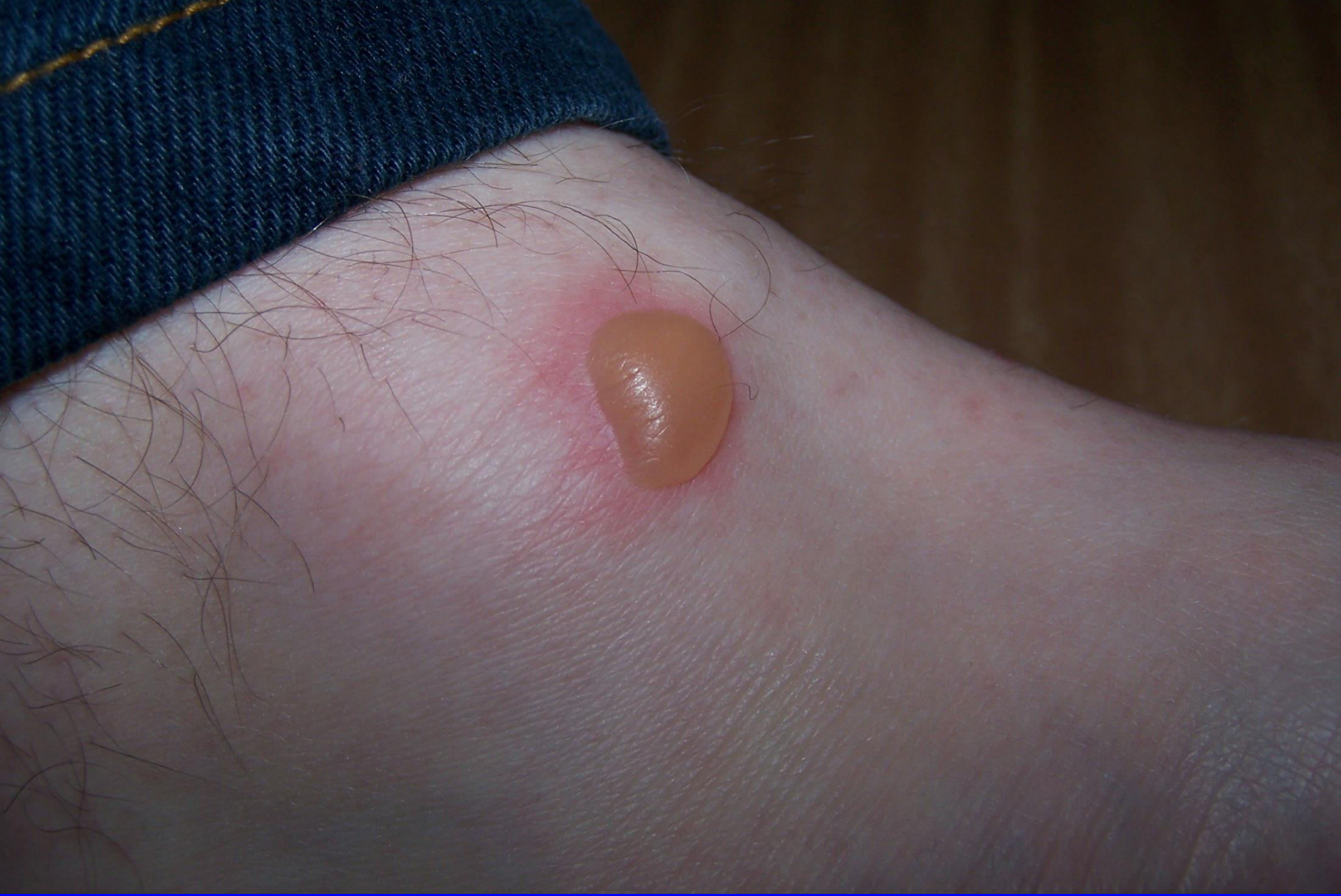


Factors affecting outcome of acute inflammation

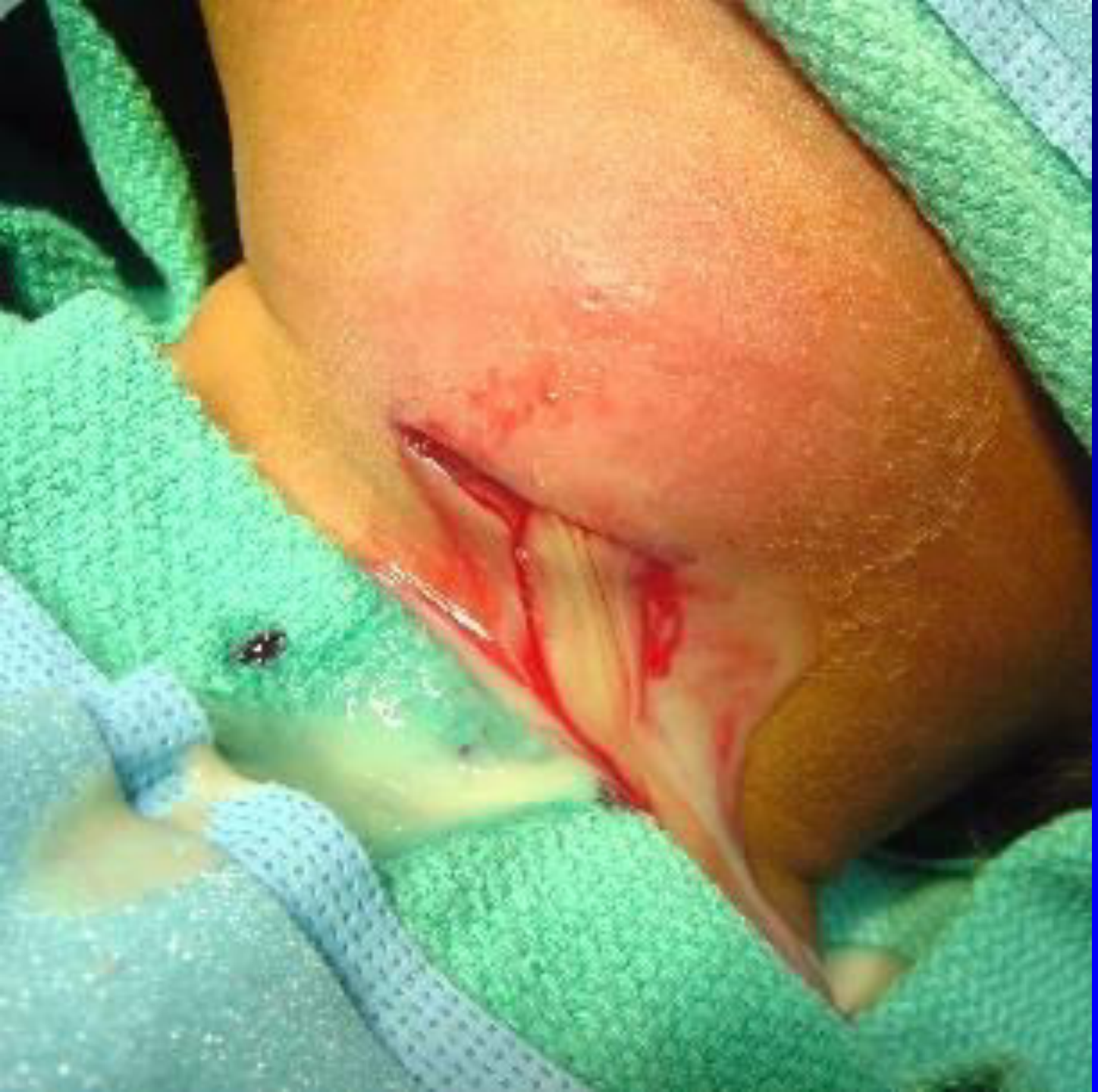
1. Severity of tissue damage
2. Capacity of cells to divide
3. Type of agent causing damage
4. The responsiveness of the host
5. Site involved

Morphologic PATTERNS of Acute INFLAMMATION

- **Serous** (watery)
- **Fibrinous** (hemorrhagic, rich in FIBRIN)
- **Suppurative** (PUS)
- **Ulcerative**



BLISTER, “Watery”, i.e., SEROUS



PUS

=

PURULENT

ABSCESS

=

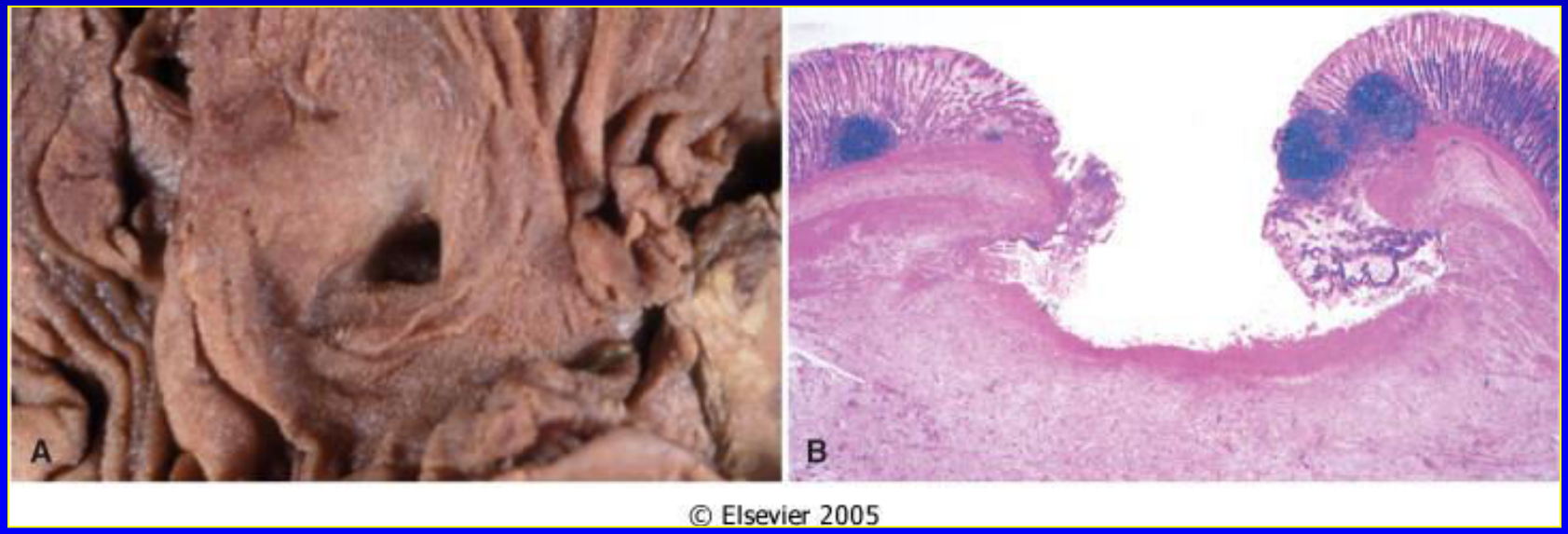
POCKET

OF

PUS

Ulcerative

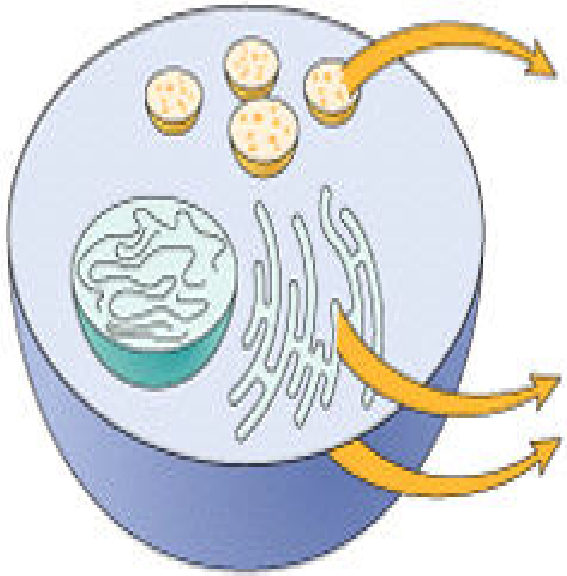
- Necrotic and eroded epithelial surface
- Underlying acute and chronic inflammation



Chemical mediators of inflammation

• Mediators may be produced **locally by** cells at the site of inflammation,

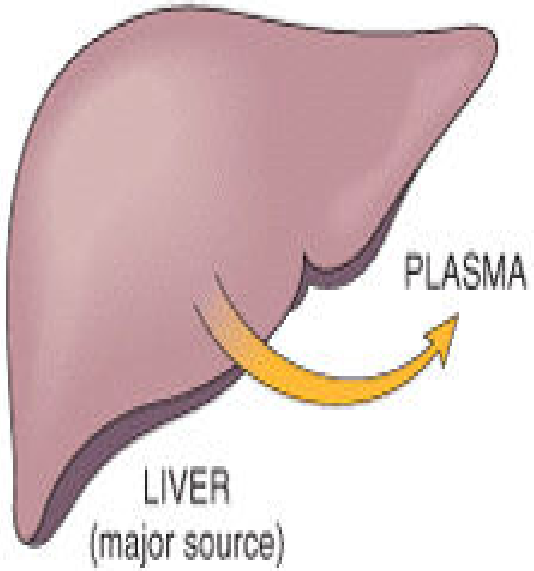
• or may be **circulating in the plasma as** inactive precursors that are activated at the site of inflammation



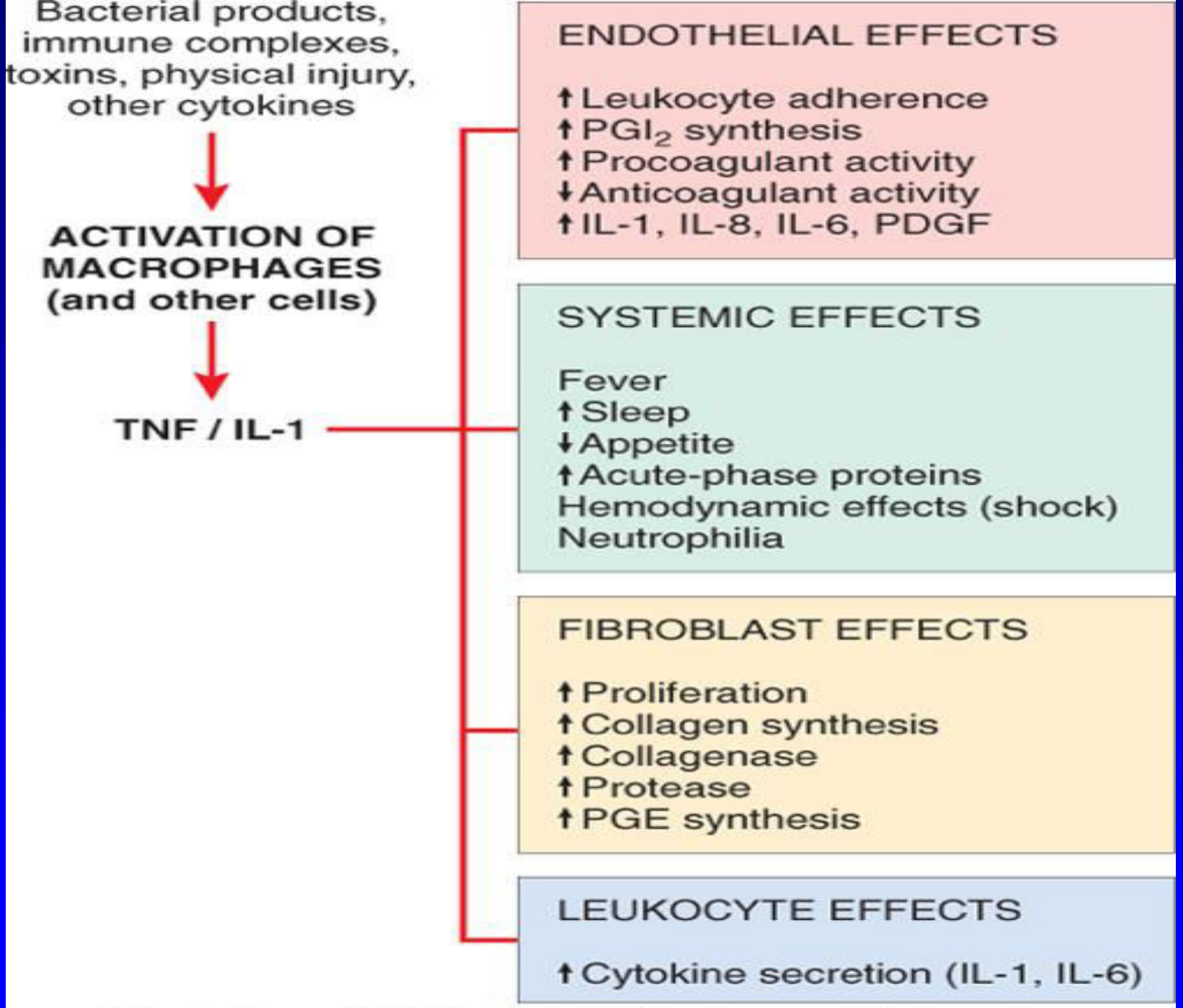
CELL-DERIVED

	MEDIATORS	SOURCE
Preformed mediators in secretory granules	Histamine	Mast cells, basophils, platelets
	Serotonin	Platelets
Newly synthesized	Prostaglandins	All leukocytes, mast cells
	Leukotrienes	All leukocytes, mast cells
	Platelet-activating factor	All leukocytes, EC
	Reactive oxygen species	All leukocytes
	Nitric oxide	Macrophages, EC
	Cytokines	Macrophages, lymphocytes, EC, mast cells
	Neuropeptides	Leukocytes, nerve fibers

PLASMA PROTEIN-DERIVED



Complement activation	C3a	anaphylotoxins
	C5a	anaphylotoxins
	C3b	
	C5b-9 (membrane attack complex)	
Factor XII (Hageman factor) activation	Kinin system (bradykinin)	
	Coagulation / fibrinolysis system	



Chronic Inflammation

Chronic inflammation is inflammation of prolonged duration (weeks or months)

in which

inflammation, tissue injury, and attempts at repair coexist, in varying combinations.

CAUSES OF CHRONIC INFLAMMATION

1. *Persistent Infection*
2. *Immune-mediated inflammatory diseases*
3. *Toxic Agents*

Causes of chronic inflammation

- **Acute inflammation**:
  - Progressive: osteomyelitis
  - Recurrent: cholycystitis, gastritis.
- **Primary: (abinitio**) abinitio means "from the beginning“
- Contents
  - TB, fungal inf.
  - HSR.
- **Persistent factor** : foreign bodies

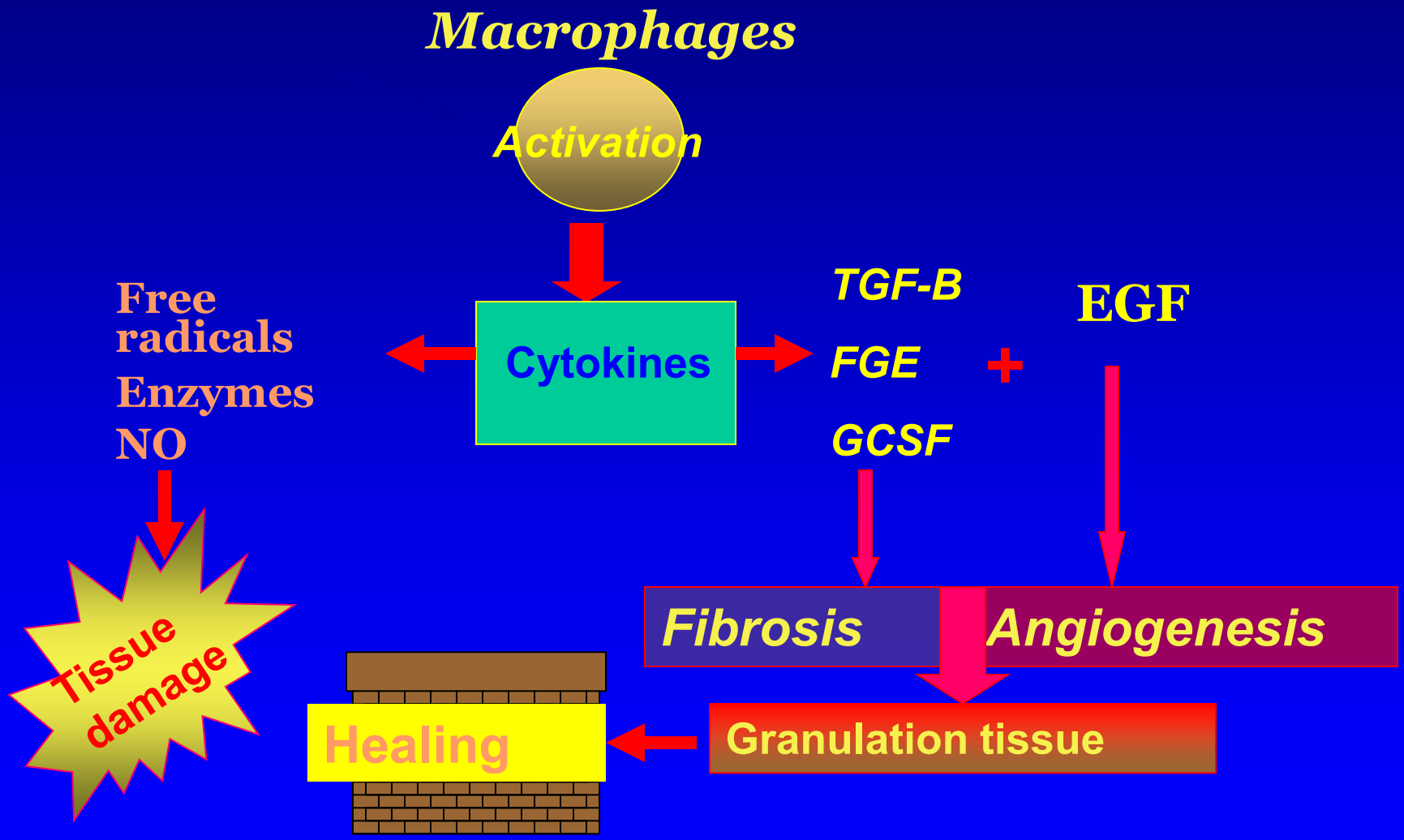
Primary Chronic Inflammation

It is the cause of tissue damage in some of the most common and disabling human diseases, such as

Rheumatoid arthritis, atherosclerosis, tuberculosis, and pulmonary fibrosis.

It has also been implicated in the progression of cancer and in diseases once thought to be purely degenerative, such as Alzheimer disease.

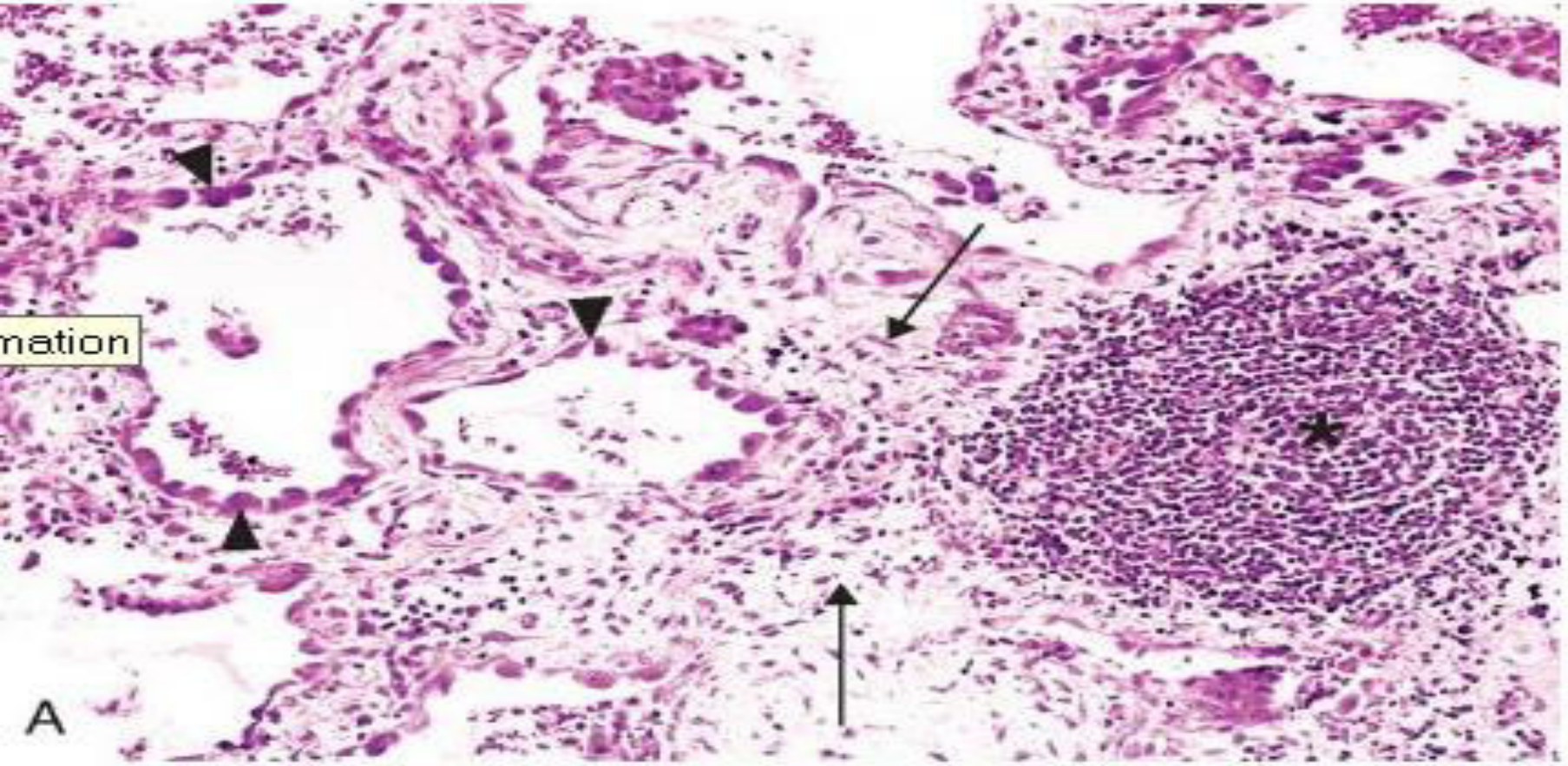
Mechanism of chronic inf



MORPHOLOGIC FEATURES

Chronic inflammation is characterized by:

1. ***Infiltration with mononuclear cells*, which include macrophages, lymphocytes, and plasma cells**
2. ***Tissue destruction*, induced by the persistent offending agent or by the inflammatory cells**
3. **Attempts at *healing by connective tissue replacement of damaged tissue*, accomplished by proliferation of small blood vessels (*angiogenesis*) and, in particular, *fibrosis*.**



A, Chronic inflammation in the lung, showing all three characteristic histologic features: (1) collection of chronic inflammatory cells (*), (2) destruction of parenchyma (normal alveoli are replaced by spaces lined by cuboidal epithelium, *arrowheads*), and (3) replacement by connective tissue (fibrosis, *arrows*).

Role of macrophages in inflammation

- Phagocytosis & pinocytosis
- Antigen processing & antigen presentation
- Constituent of granulomas
- Regulate lymphocyte response
- Secretion of biologically active substances

MONONUCLEAR PHAGOCYTE SYSTEM

- Closely related cells of bone marrow origin-
  - ~ Blood monocytes (t1/2- 1 day)
  - ~ Tissue macrophages (t1/2- several months)

- Kupffer cells (liver)
- Histiocytes
- Alveolar macrophages
- Microglia (CNS)
- Osteoclasts (bone)
- Langerhans' cells & Dendritic cells(skin)
- Macrophages of bone marrow
- Tingible body cells of germinal centres lymph node
- Littoral cells of splenic sinusoids
- Mesangial cells of glomerulus

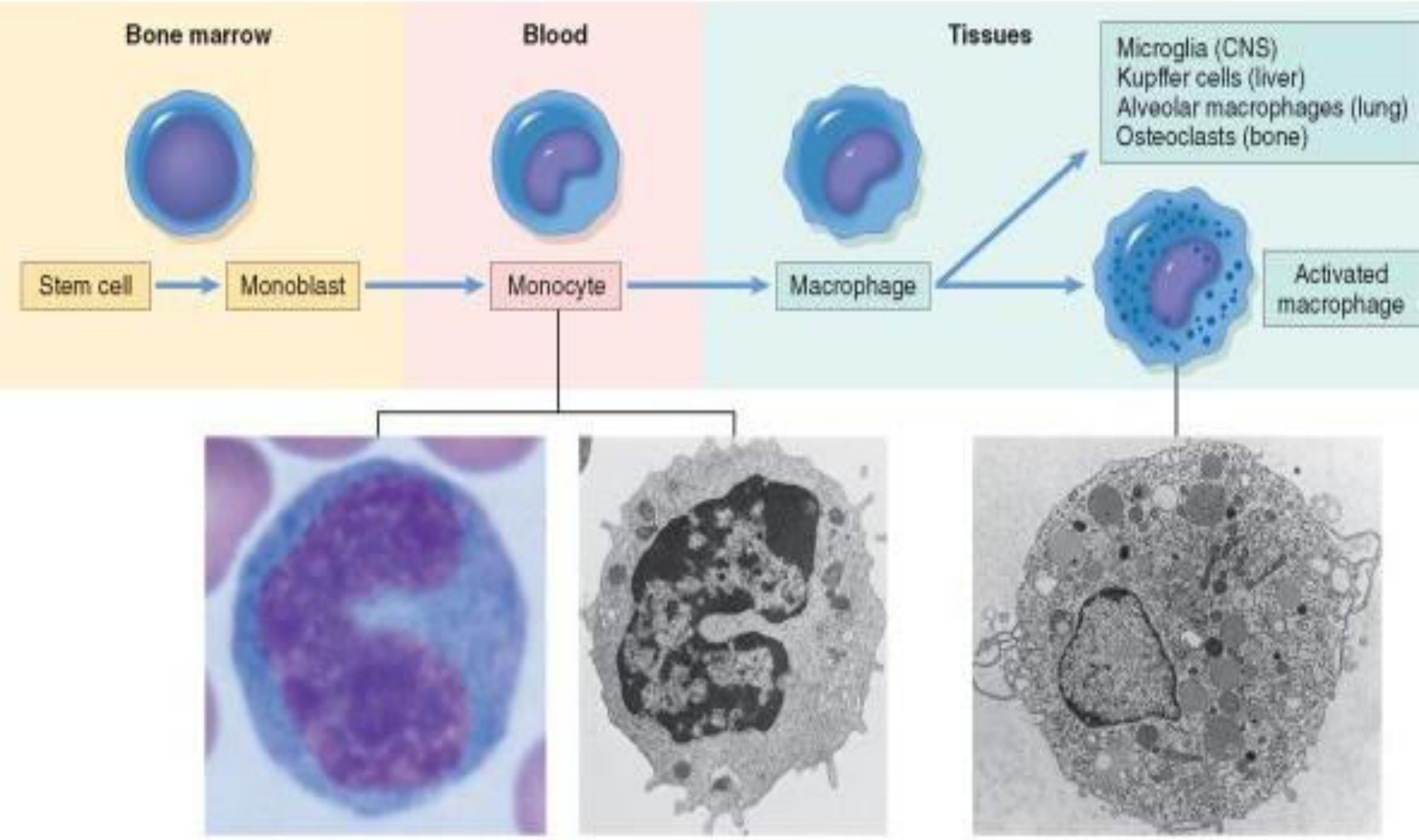
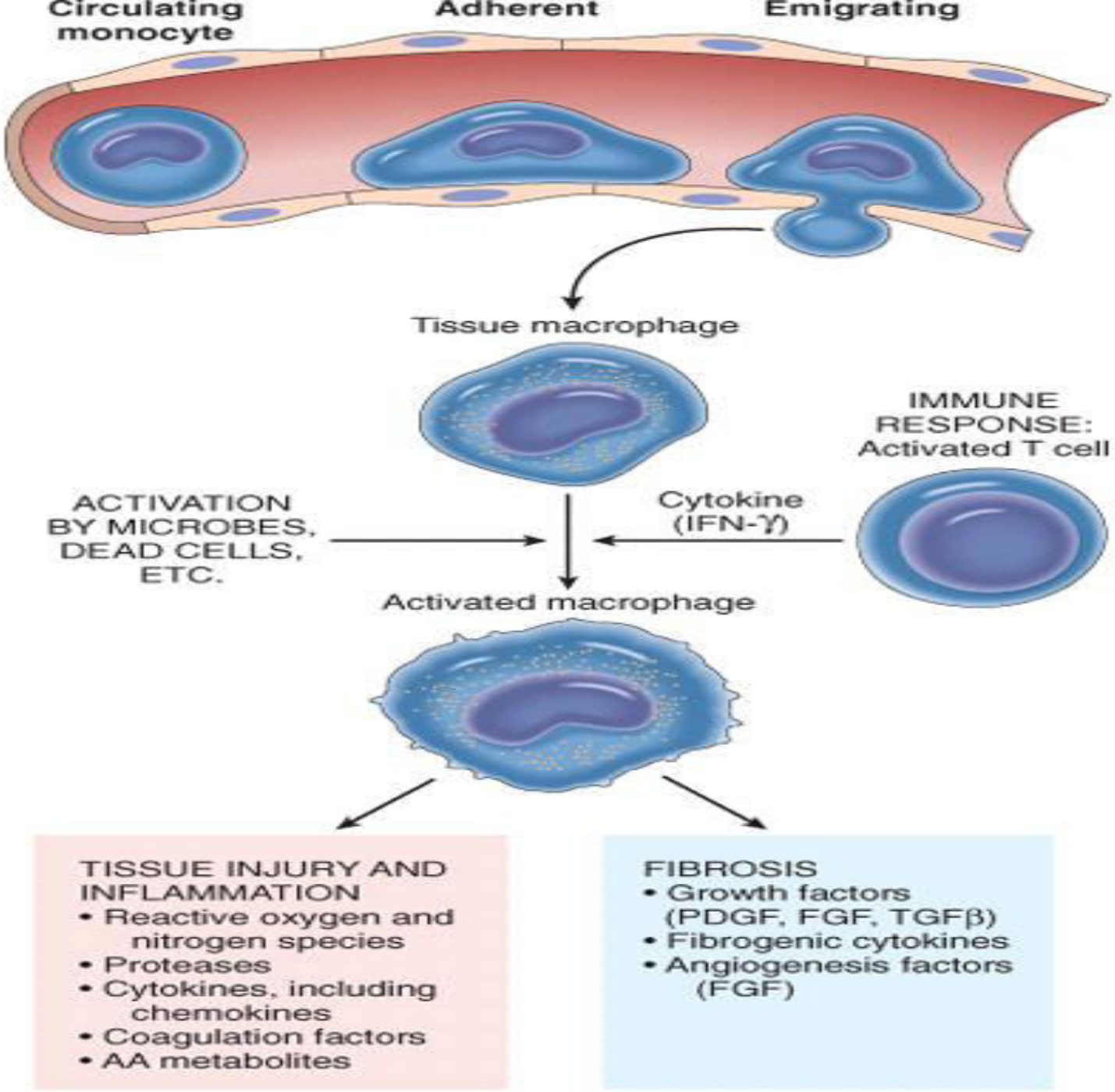


FIGURE 2-23 Maturation of mononuclear phagocytes. *(From Abbas AK et al: Cellular and Molecular Immunology, 5th ed. Philadelphia, WB Saunders, 2003.)*

Products released by macrophages

- ENZYMES-
  ~ Neutral proteases
  (elastases, collagenases, PA)
  ~ Acid hydrolases
  (phosphatases, lipases)
- PLASMA PROTEINS-
  ~ Complement components
  (e.g. C1 to C5, properdin)
  ~ Coagulation factors
  (e.g. Factor V, VIII, tissue factor)
- Reactive metabolites of oxygen
- Nitric oxide
- Eicosanoids
- Cytokines (IL-1, TNF, IL-8)
- Growth factors (PDGF,EGF,FGF,TGF-β)



Cells involved in chronic inflammation

- Mononuclear–phagocyte system (MPS)
- Lymphocytes
- Plasma cells
- Eosinophils
- Mast cells
- Neutrophils (in some cases)

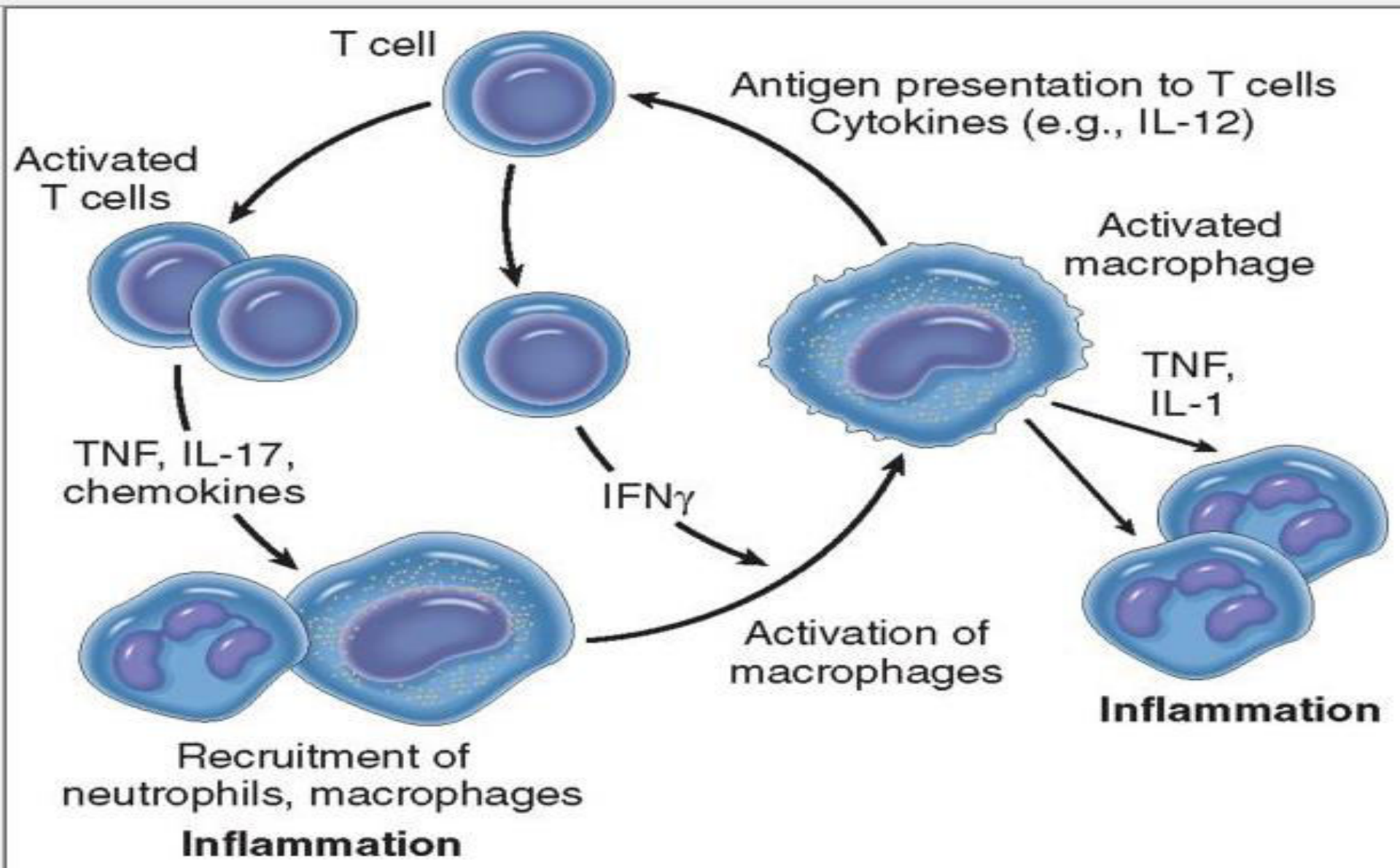


FIGURE 2-25 Macrophage-lymphocyte interactions in chronic inflammation. Activated T cells produce cytokines that recruit macrophages (TNF, IL-17, chemokines) and others that activate macrophages (IFNγ). Different subsets of T cells (called T_H1 and T_H17) may produce different sets of cytokines; these are described in Chapter 6 . Activated macrophages in turn stimulate T cells by presenting antigens and via cytokines (such as IL-12).

Mechanism of macrophage accumulation

- Recruitment of monocytes from circulation

~Chemotactic stimuli for monocytes

-chemokines (by macrophages & lymphocytes)
MCP-1(monocyte chemoattractant protein)

-C5a

-growth factors (PDGF,TGF-β)

-break down fragments of collagen & fibronectin

- Local proliferation of macrophages
- Immobilization of macrophages within site of inflammation (role of certain cytokines-MIF & oxidized lipids)

CELL INFILTRATION

Emigration of monocytes into extravascular space

↓

Transformation into larger tissue macrophage

↓

Endotoxin

IFN-gamma

Activation of macrophages

Non-immune activation

Activated T-cell

-increased size
-increased lysosomal enzymes
-more active metabolism,
-greater ability to phagocytose

↓

Secretion of biologically active substances

substances

-Toxic O2 metabolites
-Proteases
-Neutrophil chemotactic factors
-Coagulation factors
-AA metabolites
-Nitric oxide

↓

TISSUE INJURY

-Growth factors (PGDF,FGF,TGF-β)
-Fibrogenic cytokines
-Angiogenesis factors (FGF)
-"Remodelling collagenesis"

↓

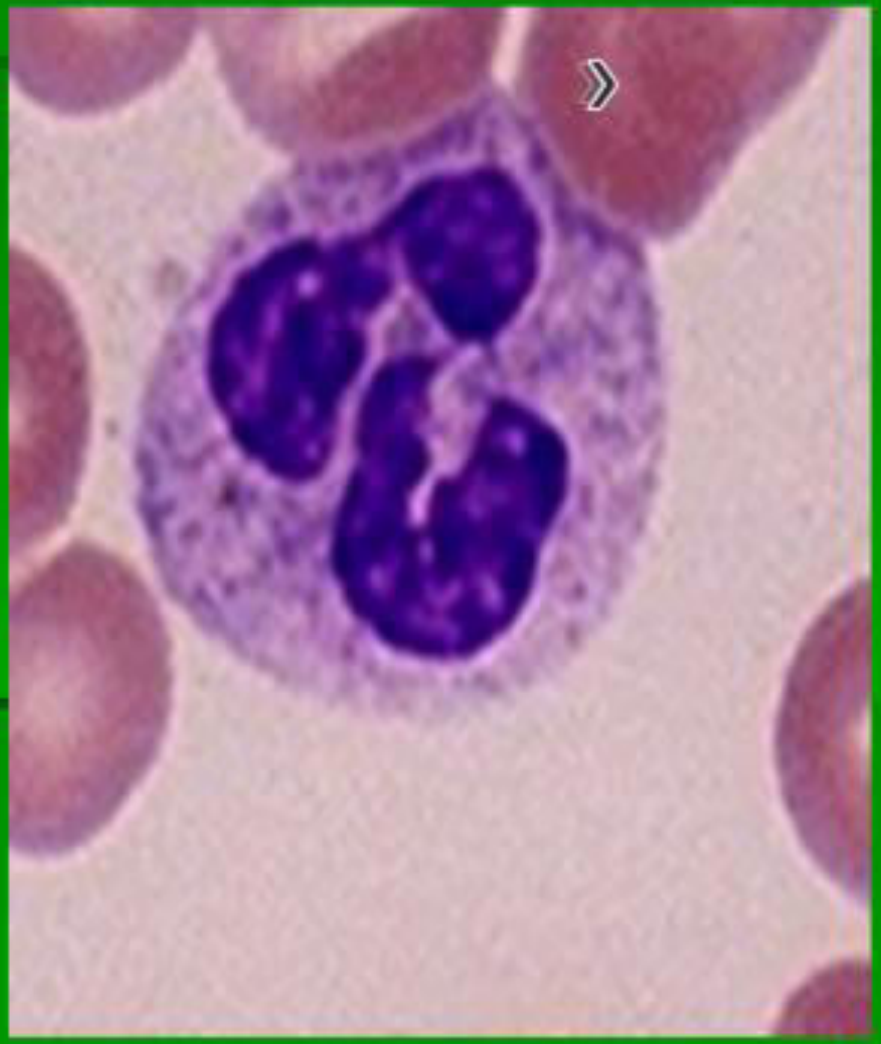
FIBROSIS

Role of neutrophils

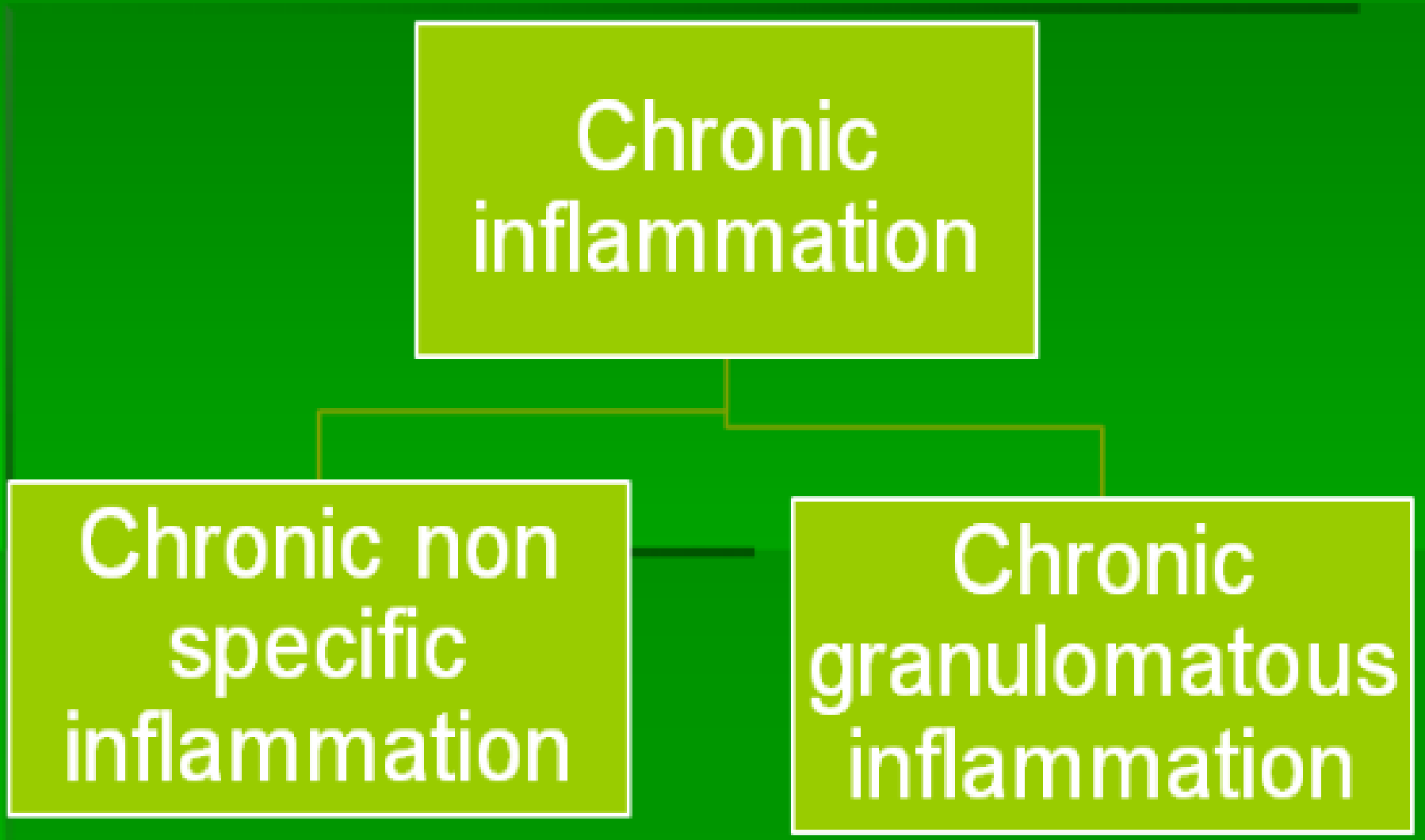
- Persist in some forms of chronic inflammation
- Induced by
  - persistent microbes

    or

  - mediators produced by macrophages & T-lymphocytes
- Example- chronic osteomyelitis, chronic damage in lungs (smokers)



Classification



GRANULOMATOUS INFLAMMATION

***Granulomatous inflammation** is a distinctive pattern of chronic inflammation* that is encountered in a limited number of infectious and some noninfectious conditions.

Immune reactions are usually involved in the development of granulomas.

A granuloma is a cellular attempt to contain an offending agent that is difficult to eradicate.

In this attempt there is often strong activation of T lymphocytes leading to macrophage activation, which can cause injury to normal tissues.

TABLE 2-8 -- Examples of Diseases with Granulomatous Inflammation

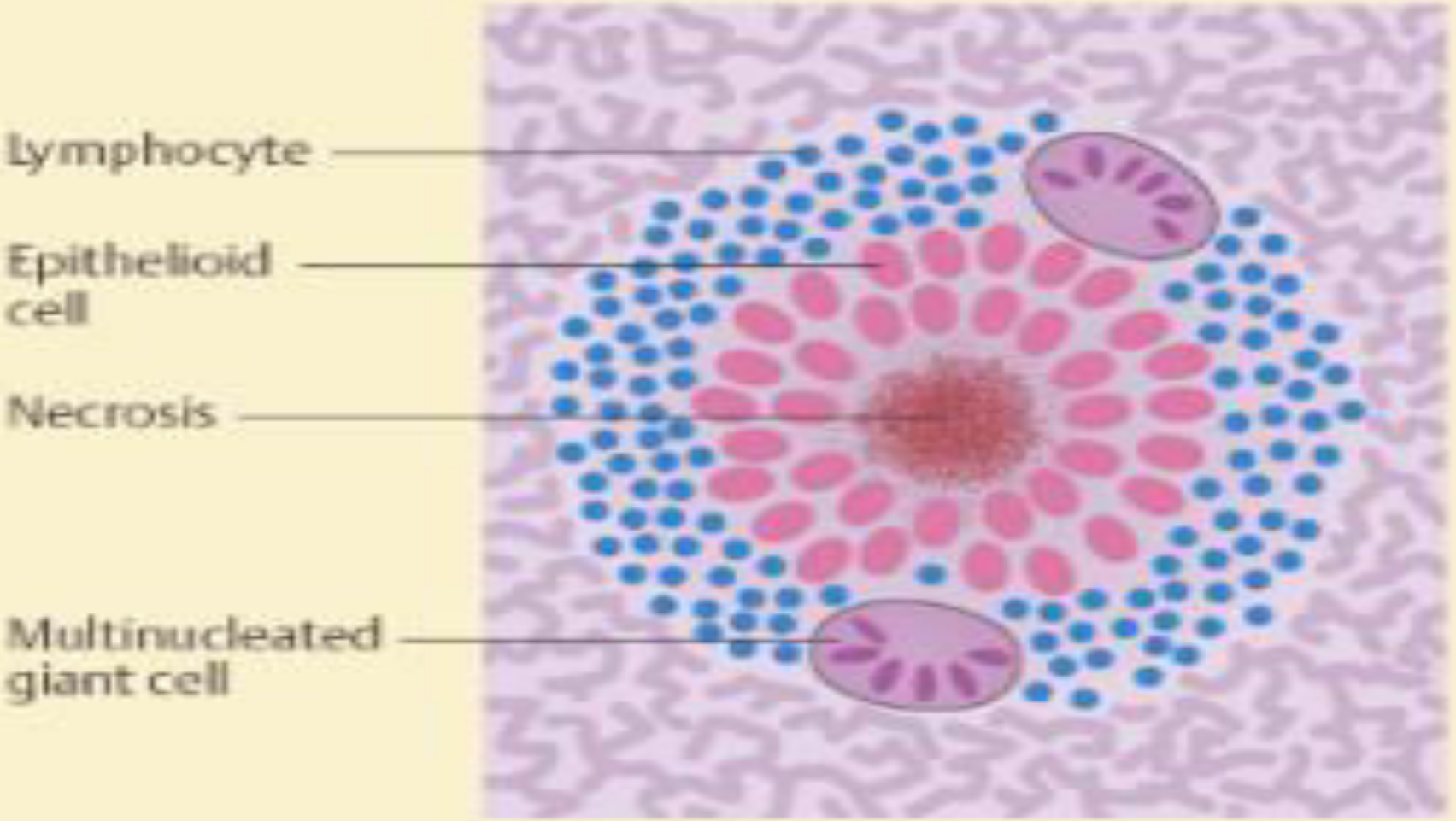
Disease	Cause	Tissue Reaction
Tuberculosis	*Mycobacterium tuberculosis*	Caseating granuloma (tubercle): focus of activated macrophages (epithelioid cells), rimmed by fibroblasts, lymphocytes, histiocytes, occasional Langhans giant cells; central necrosis with amorphous granular debris; acid-fast bacilli
Leprosy	*Mycobacterium leprae*	Acid-fast bacilli in macrophages; noncaseating granulomas
Syphilis	*Treponema pallidum*	Gumma: microscopic to grossly visible lesion, enclosing wall of histiocytes; plasma cell infiltrate; central cells necrotic without loss of cellular outline
Cat-scratch disease	Gram-negative bacillus	Rounded or stellate granuloma containing central granular debris and recognizable neutrophils; giant cells uncommon
Sarcoidosis	Unknown etiology	Noncaseating granulomas with abundant activated macrophages
Crohn disease (inflammatory bowel disease)	Immune reaction against intestinal bacteria, self-antigens	Occasional noncaseating granulomas in the wall of the intestine, with dense chronic inflammatory infiltrate

A granuloma is a focus of chronic inflammation **consisting of**

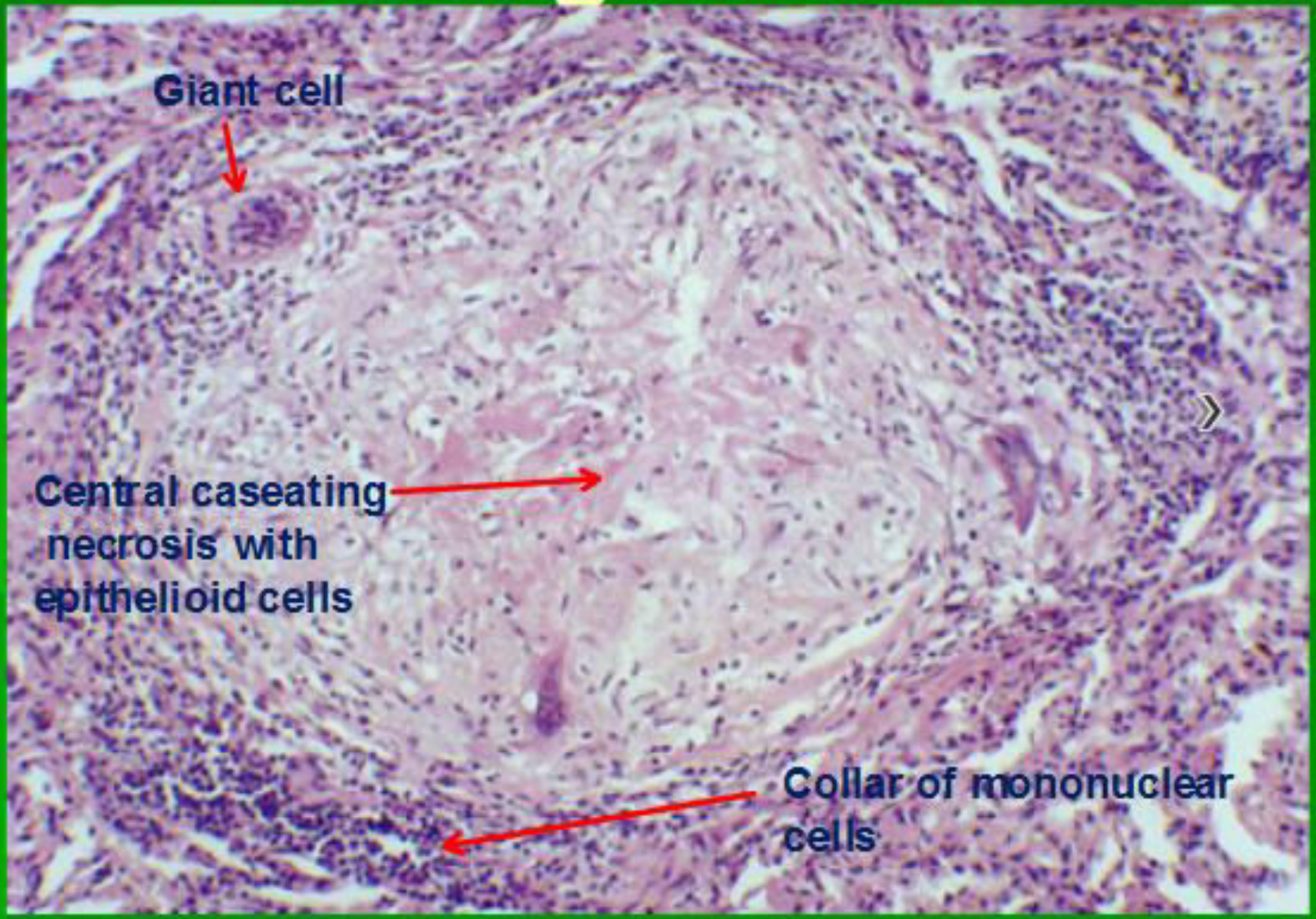
a microscopic aggregation of macrophages

that are transformed into epithelium-like cells, surrounded by a collar of mononuclear leukocytes, principally lymphocytes .

A **Tuberculous granuloma**



Tubercular granuloma



Giant Cells

Older granulomas develop an enclosing rim of fibroblasts and connective tissue.

Frequently, epithelioid cells fuse to form *giant cells* in the periphery or sometimes in the center of granulomas.

These giant cells may attain diameters of 40 to 50 µm. They have a large mass of cytoplasm containing 20 or more small nuclei arranged either peripherally (Langhans-type giant cell) or haphazardly (foreign body–type giant cell).

Types of Granulomas

I. Foreign body granulomas

II. Immune granulomas

Foreign body granulomas

Incited by relatively inert foreign bodies.

Typically, foreign body granulomas form around material that are large enough to preclude phagocytosis by a single macrophage and do not incite any specific inflammatory or immune response.

The foreign material can usually be identified in the center of the granuloma, particularly if viewed with polarized light, in which it appears refractile.

Immune granulomas

Caused by agents that are capable of inducing an immune response which produces granulomas usually when the inciting agent is poorly degradable or particulate.

Epithelioid cells

- These are activated macrophages with epithelial (squamous) cell like appearance
- Cells with indistinct cell boundaries

-abundant pale staining granular cytoplasm

-elongated/oval, slipper shaped nuclei

- Weakly phagocytic

Methods of identification of Specific etiologic agent in Granulomatous diseases

1. Special stains for organisms

(e.g., acid-fast stains for tubercle bacilli),

2. Culture methods

(e.g., in tuberculosis and fungal diseases),

3. Molecular techniques

(e.g., the polymerase chain reaction in tuberculosis),

4. Serologic studies

(e.g., in syphilis).

Differences between Acute and Chronic Inflammation

	Acute	Chronic
Duration	Short (days)	Long (weeks to months)
Onset	Acute	Insidious
Specificity	Nonspecific	Specific (where immune response is activated)
Inflammatory cells	Neutrophils, macrophages	Lymphocytes, plasma cells, macrophages, fibroblasts
Vascular changes	Active vasodilation, increased permeability	New vessel formation (granulation tissue)
Fluid exudation and edema	+	–
Cardinal clinical signs (redness, heat, swelling, pain)	+	–
Tissue necrosis	– (Usually) + (Suppurative and necrotizing inflammation)	+ (ongoing)
Fibrosis (collagen deposition)	–	+
Operative host responses	Plasma factors: complement, immunoglobulins, properdin, etc; neutrophils, nonimmune phagocytosis	Immune response, phagocytosis, repair
Systemic manifestations	Fever, often high	Low–grade fever, weight loss, anemia
Changes in peripheral blood	Neutrophil leukocytosis; lymphocytosis (in viral infections)	Frequently none; variable leukocyte changes, increased plasma immunoglobulin