Acute and Chronic Inflammation

Dr Zuriel, Human Pathology.

2019

Learning objectives

- Definition
- Introduction
- Cellular events
- Vascular events
- Patterns including suppurative
- Outcomes

Definition

- Rapid host response that serves to deliver leucocytes and plasma proteins such as antibodies to sites of infection or tissue injury.

Inflammation is a war

- Coordinated response to eliminate the cause and consequence of injury or infection (noxious agent)
- Involves immune and vascular systems
- Acute inflammation is a stereotyped response to recent or ongoing injury
- Chronic inflammation is a response to prolonged problems, orchestrated by T-helper lymphocytes

Inflammatory process

- Inflammation
- Purpose is 3 d's:
  - Destroy
  - Dilute
  - Dam-off
- Desired result is healing
  - Regeneration (hyperplasia)
  - Fibrosis (scarring)
- Collateral damage may occur

Classical description

- Ancient Roman, Celsus, described inflammation
  - Calor—heat
  - Rubor—redness
  - Tumor—swelling
  - Dolor—pain
- Hunter described inflammation as good in 1790s
- Virchow added a fifth clinical sign in 1800s
  - Functio laesa—loss of function
- Metchnikoff discovered phagocytes 1883
- Ehrlich discovered mast cells, granulocytes 1878 as well as complement in 1899
  - Metchnikoff and Ehrlich shared Nobel Prize 1908

Inflammatory stimuli

- Physical injury
  - Cutaneous laceration, bone fracture, sunburn, toxins
- Necrosis
  - Resolution of regions of dead cells
- Infection
  - Innate response followed by adaptive response to microbial invader
- Immunological errors
  - Allergies—response to environmental substances
  - Autoimmunity—response to self

Foreign bodies.

Acute vascular changes

- Transient arteriolar constriction (seconds)
  - Nerve reflex, endothelin
  - Like the immediate first step of hemostasis
- Vasodilation of arterioles (until resolution)
  - Histamine, bradykinin mediate rapid response
  - Sustained by prostaglandins and NO
  - Hyperemia, erythema
  - Transudation increases blood viscosity, slows flow
  - Stasis and congestion in venules allows cells to contact endothelium
- Vascular leakage (minutes to hours to days)
  - Histamine, bradykinin mediate rapid response
  - Sustained by C3a, C5a, PAF, leukotrienes
  - Exudation results in local edema

Increased vascular permeability

- Contraction of vascular endothelium—rounding of cells and widening of intercellular spaces
  - Immediate, transient response (15-30 min)
    - Stimulated by histamine, bradykinin, substance P
    - venules of 20 – 60 um diameter respond
  - Delayed prolonged leakage (radiation burns)
    - begins after 2 – 12 h delay, lasts hours – days
    - stimulated by cytokines and apoptotsis of injured skin cells
    - venules and capillaries respond
  - Immediate, sustained response (days)
    - caused by direct damage to vasular endothelium
    - venules, capillaries, arterioles respond
    - ended by hemostasis, thrombosis, regeneration
  - Neutrophil-induced damage (days)
    - caused when neutrophils adhere and emigrate

Leukocyte extravasation

- Margination, rolling
  - Decreased flow rate and volume push WBCs toward vascular walls
  - Intermittent binding of selectins with glycoproteins causes rolling
- Adhesion, pavementing
  - mediated by integrins on leukocytes, activated by cytokines
  - integrin ligands VCAM-1, ICAM-1 on endothelial cells induced by TNF and IL-1
- Transmigration or *diapedesis*
  - chemokines stimulate adherent leukocytes to migrate through interendothelial spaces

Leukocyte transmigration

- Extension of leukocyte pseupodia between endothelial cells
- Binding to PECAM (CD31) expressed in endothelial junctions
- Focal digestion of basement membrane with elastase, collagenase and metalloproteinases from neutrophils
- Migration of leukocytes towards chemotactic gradient
- Adhere to ECM with integrins and CD44

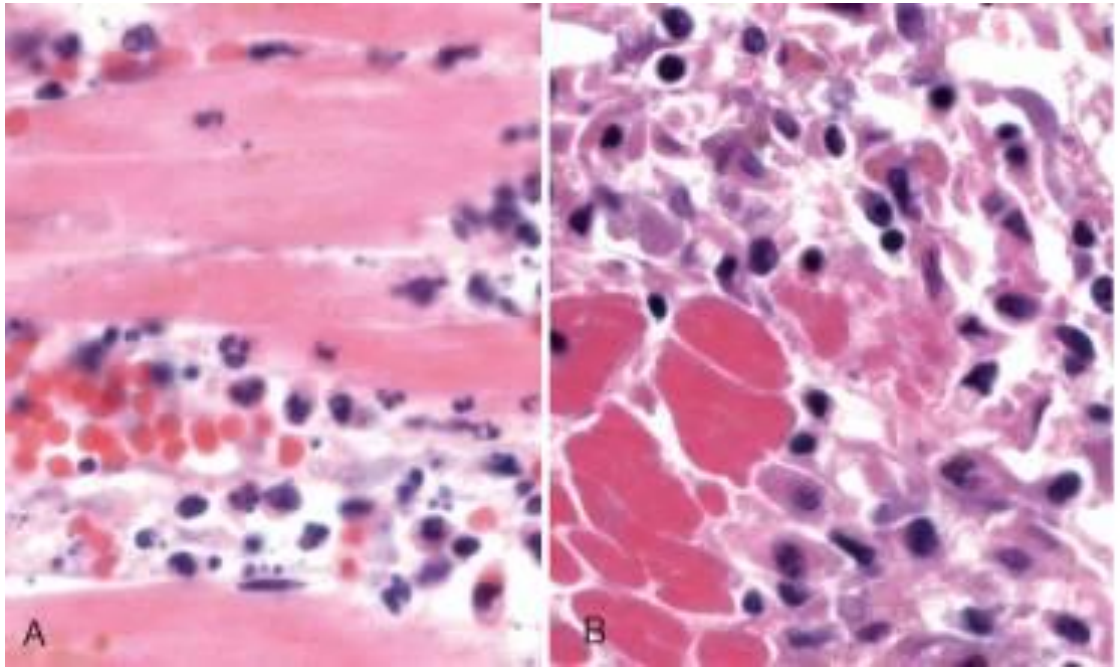
Chemotaxis of leukocytes

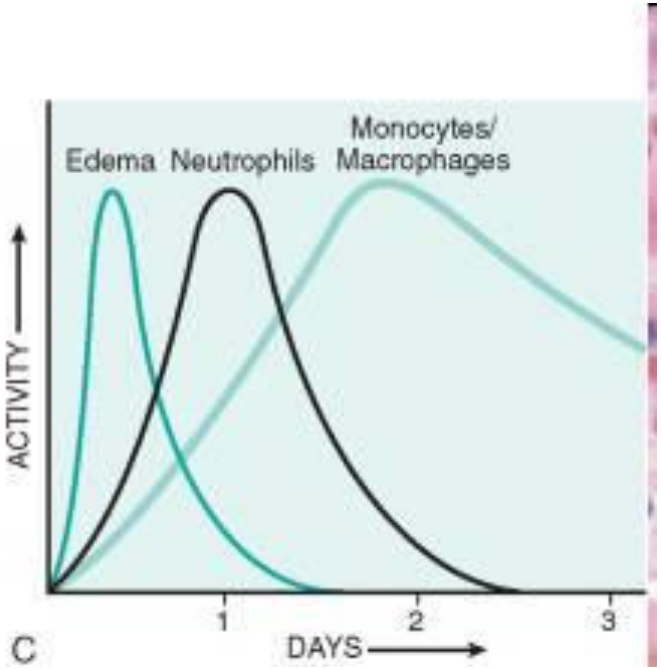
- Locomotion oriented along a gradient of
  - Bacterial products
    - N-formyl peptides, lipoproteins, lipopolysaccharides
  - Chemokines
    - IL-8, aka CXCL8 or granulocyte chemotactic protein 1
  - Complement proteins
    - Especially C5a
  - arachidonic acid (AA) metabolites
    - Leukotriene B4

Which types of leukocytes respond

- Neutrophils are generally the first types of leukocytes to respond in acute (non-viral) inflammation or to necrosis
- Lymphocytes are usually the first cells to respond to viral infections or autoimmune diseases
  - lymphocytes and plasma cells also participate in most chronic inflammation, regardless of the inciting cause
- Macrophages begin to appear a few days after the onset of inflammation from almost any cause, and increase in numbers over time
  - *activated* macrophages may develop *abundant cytoplasm*, called epithelioid macrophage
  - macrophages merge to create *giant cells* with multiple nuclei
- Eosinophilic inflammation is highly suggestive of a response to helminths, arthropods, or allergens

Progression of infiltration





Acute inflammation

- Immediate, early response
  - Vasodilation
  - Vascular permeability
  - Emigration of leukocytes into tissues
- Reactions of leukocytes in inflammation
  - Recognition of microbes and dead tissues
  - Removal of the offending agents
  - Macrophage activation
  - Leukocyte-mediated tissue injury

Activation of neutrophils

- Stimulated by chemokines such as IL-8 and chemical mediators such as LTB4
  - conformational change of integrin (LFA-1) to increase avidity for receptor (ICAM-1)
  - activation of Arachidonic Acid metabolic cascades
    - produces vasoactive prostaglandins and leukotrienes
  - activation of the *oxidative burst* to produce reactive oxygen species
    - NADPH oxidase enzyme system produces superoxide anion radical, which is converted to H2O2, which leads to production of hydroxyl radical
    - myeloperoxidase produces HOCl, which halogenates microbes
  - secretion of lysosomal enzymes (degranulation)

Actions of activated neutrophils

- Phagocytosis has three steps
  - *recognition* and attachment of the particle to be ingested
  - *engulfment*, with subsequent formation of a phagocytic vacuole
  - *killing* or degradation of the ingested material
- Initiation of repair
  - stimulate the proliferation of endothelial cells and fibroblasts
  - stimulate synthesis of collagen and enzymes that remodel connective tissues

Phagocytosis—Recognition

- Mannose receptor
  - binds terminal mannose and fucose residues of glycoproteins and glycolipids (bacterial and fungal)
- Scavenger receptors
  - oxidized or acetylated low-density lipoprotein (exogenous and endogenous lipid toxins)
- High-affinity opsonin receptors
  - IgG antibodies—Fc receptor
  - C3b breakdown product of complement—C1R
  - mannan-binding lectin—C1R, CD14

Phagocytosis—Engulfment

- Extensions of the cytoplasm (pseudopods) flow around bound receptors
- Plasma membrane pinches off creating phagosome
- Phagosome then fuses with a lysosomal granule
- During this process the phagocyte may also release granule contents into the extracellular space
- Engulfment is dependent on polymerization of actin filaments

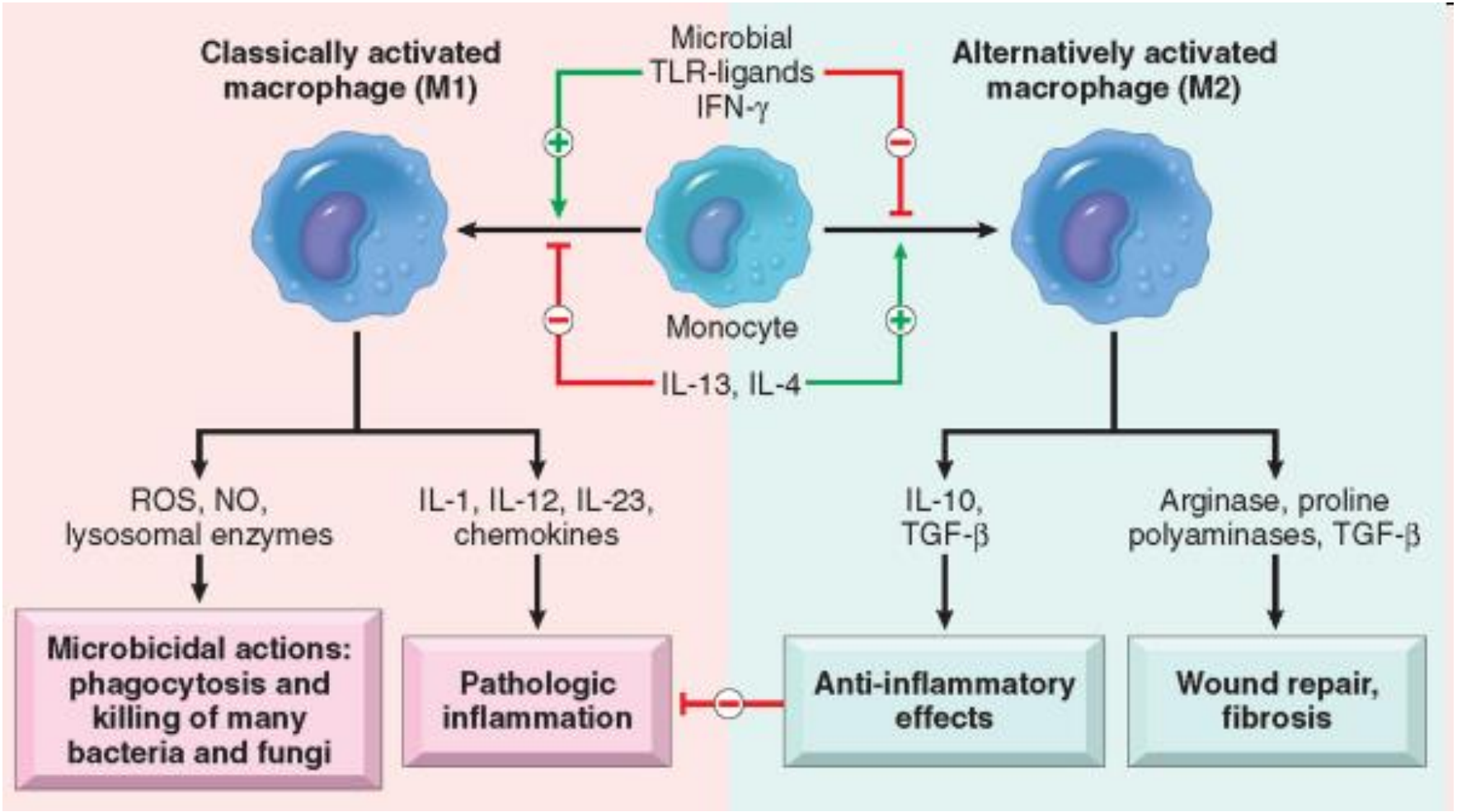
Phagocytosis—Oxygen dependent killing

- ROS generation is due to the rapid assembly and activation of NADPH oxidase (phagocyte oxidase), which reduces oxygen to superoxide anion
  - At least seven protein subunits located in the plasma membrane and the cytoplasm of resting neutrophils translocate to the phagosomal membrane to form the functional enzyme complex
  - Respiratory burst of G6PDH activity generates NADPH
  - Superoxide is converted to hydrogen peroxide (H_2O_2), mostly by spontaneous dismutation
  - Myeloperoxidase (MPO) from azurophilic granules converts H_2O_2 to hypochlorite (OCl•) with Cl-
- NO generated by inducible nitric oxide synthase iNOS, aka NOS2
  - NO reacts with superoxide to generate the highly reactive free radical peroxynitrite (ONOO•)

Phagocytosis—Oxygen independent killing

- proteases, such as elastase and collagenase
- defensins, cationic arginine-rich granule peptides that are toxic to microbes
- lysozyme, which hydrolyzes the muramic acid–N-acetylglucosamine bond, found in the glycopeptide coat of bacteria
- cathelicidins, antimicrobial proteins
- lactoferrin, an iron-binding protein
- major basic protein, a cationic protein of eosinophils, which is cytotoxic to many parasites
- bactericidal/permeability increasing protein, which binds bacterial endotoxin

Other functional responses of activated leukocytes



Damaging effects of phagocytes

- Tissue damage occurs from
  - *digestion of basement membranes* during transmigration; caused by elastase and metalloproteinases
    - counteracted by α1-antitrypsin, C-reactive protein, and other circulating antiproteases
  - *lysosomal leakage during phagocytosis* (regurgitation or frustrated phagocytosis)
    - leaks acid hydrolases, free radicals, and hypochlorous acid
  - *inflammatory mediators* produced by phagocytes, such as prostaglandins and leukotrienes
  - *necrosis of phagocytes* in situ

Morphologic Patterns of Acute Inflammation

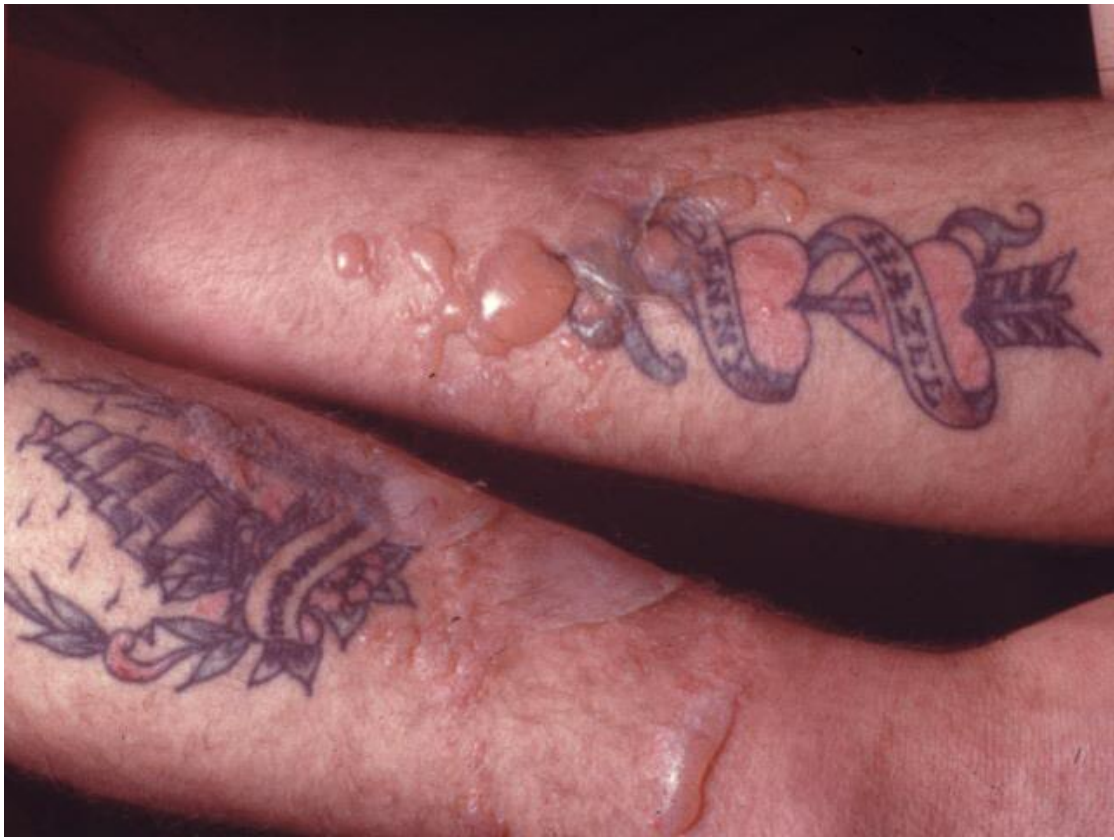
- Several types of inflammation vary in their morphology and clinical correlates.
- Why?
  - The severity of the reaction
  - specific cause
  - the particular tissue
  - site involved

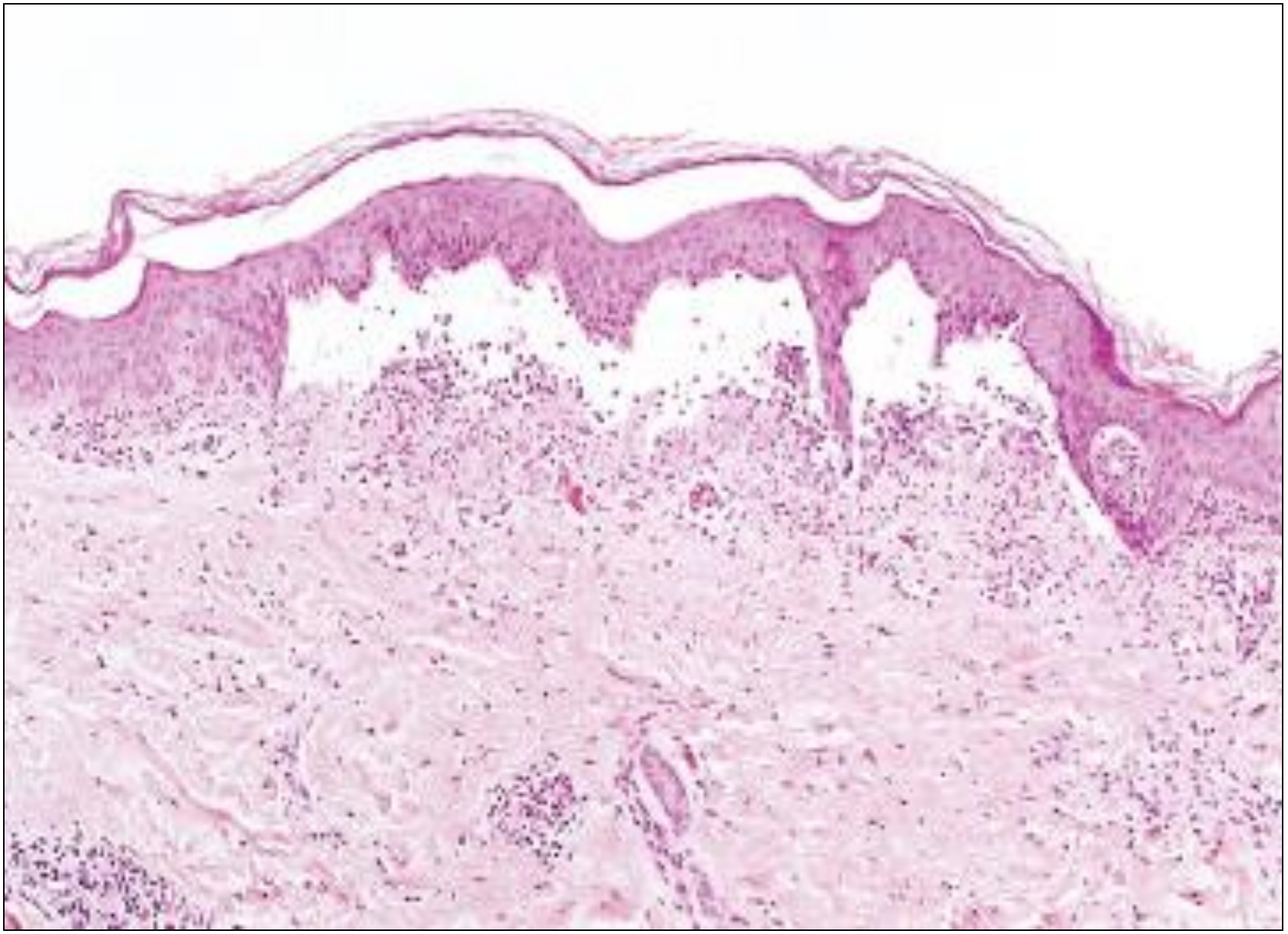
Morphologic Patterns of Acute Inflammation

- **serous inflammation**
- **fibrinous inflammation**
- **suppurative or purulent inflammation**
- **ulcers**

Patterns of Acute Inflammation

- **SEROUS INFLAMMATION:**
  - Serous inflammation is marked by the outpouring of a thin fluid
  - e.g. the skin blister resulting from a burn or viral infection represents a large accumulation of serous fluid





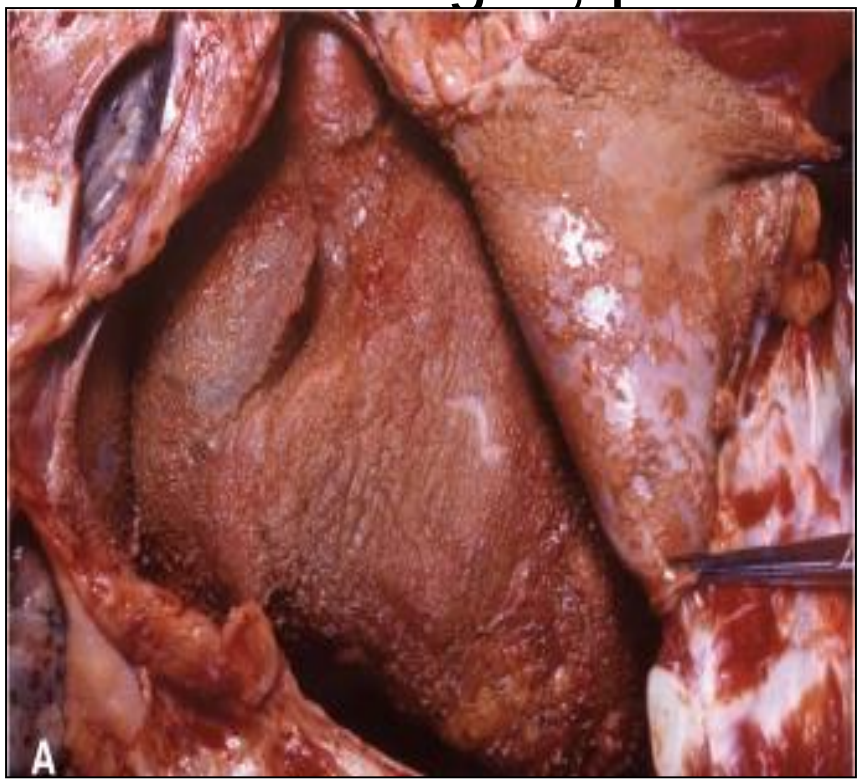
Morphologic Patterns of Acute Inflammation

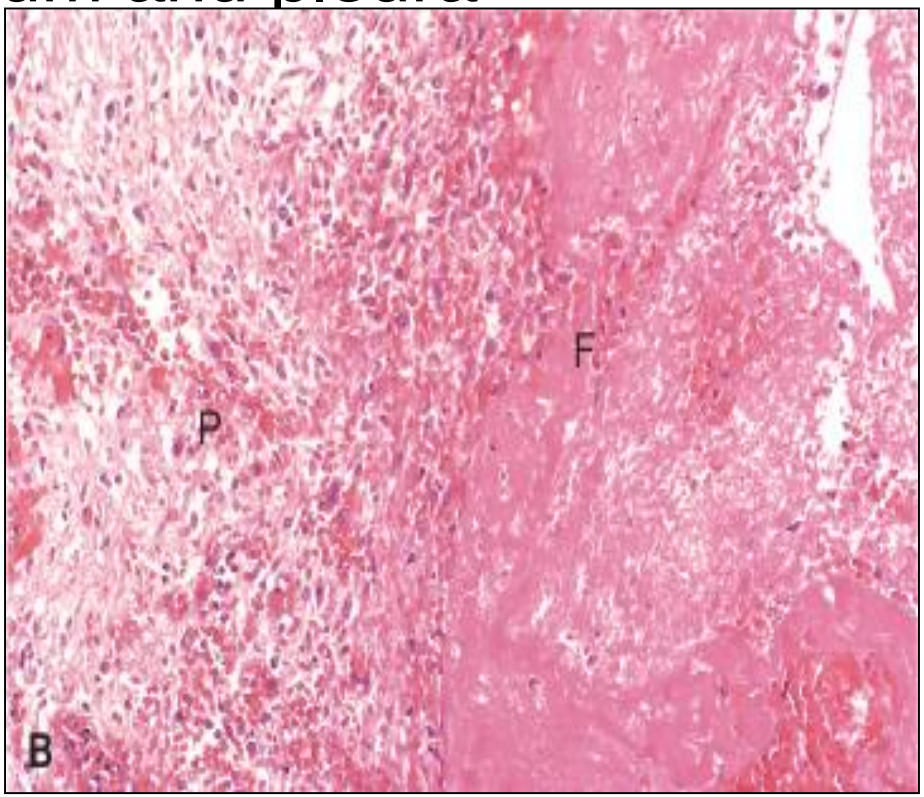
- **FIBRINOUS INFLAMMATION**
  - more severe injuries and more greater vascular permeability, larger molecules such as fibrinogen pass the vascular barrier, and fibrin is formed and deposited

Morphologic Patterns of Acute Inflammation

FIBRINOUS INFLAMMATION

- A fibrinous exudate is characteristic of inflammation in the lining of body cavities, such as the meninges, pericardium and pleura





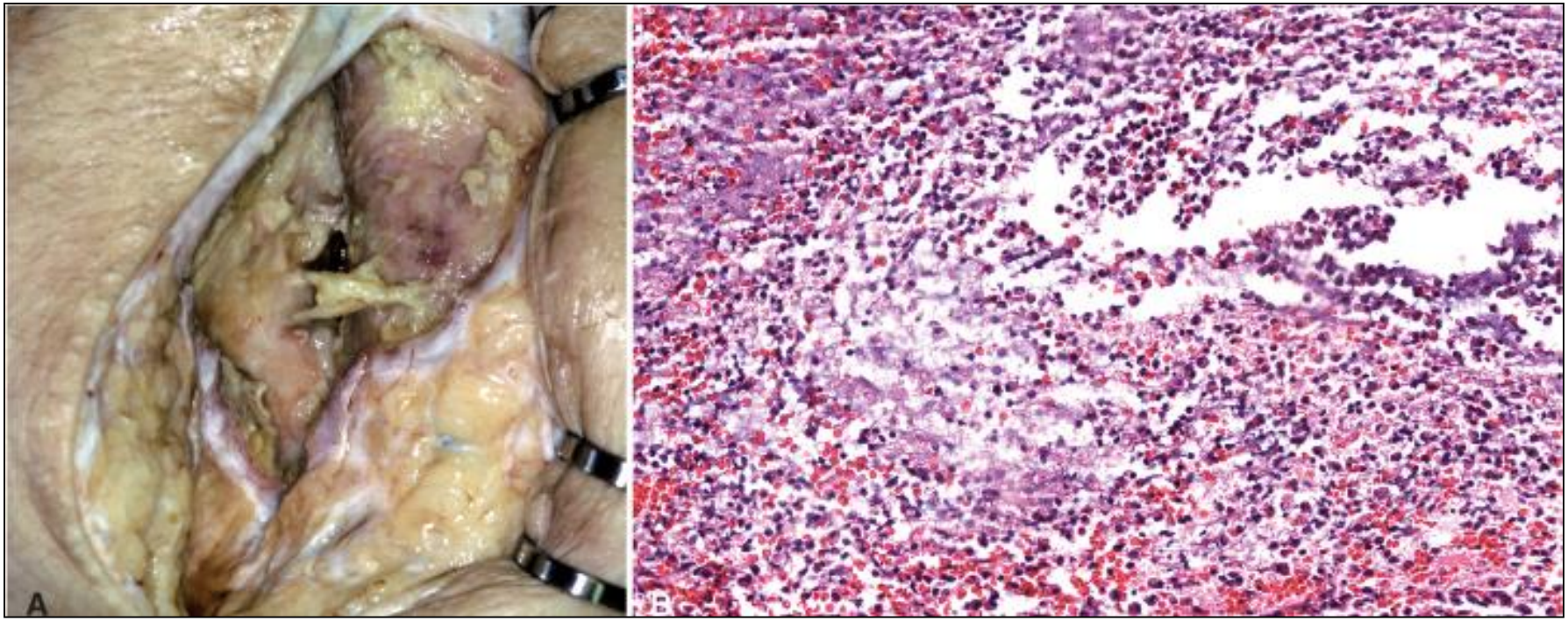
Morphologic Patterns of Acute Inflammation

- **FIBRINOUS INFLAMMATION**
  - Fibrinous exudates may be removed by fibrinolysis
  - But when the fibrin is not removed, it may stimulate the ingrowth of fibroblasts and blood vessels and thus lead to scarring (*organization*)

Morphologic Patterns of Acute Inflammation,

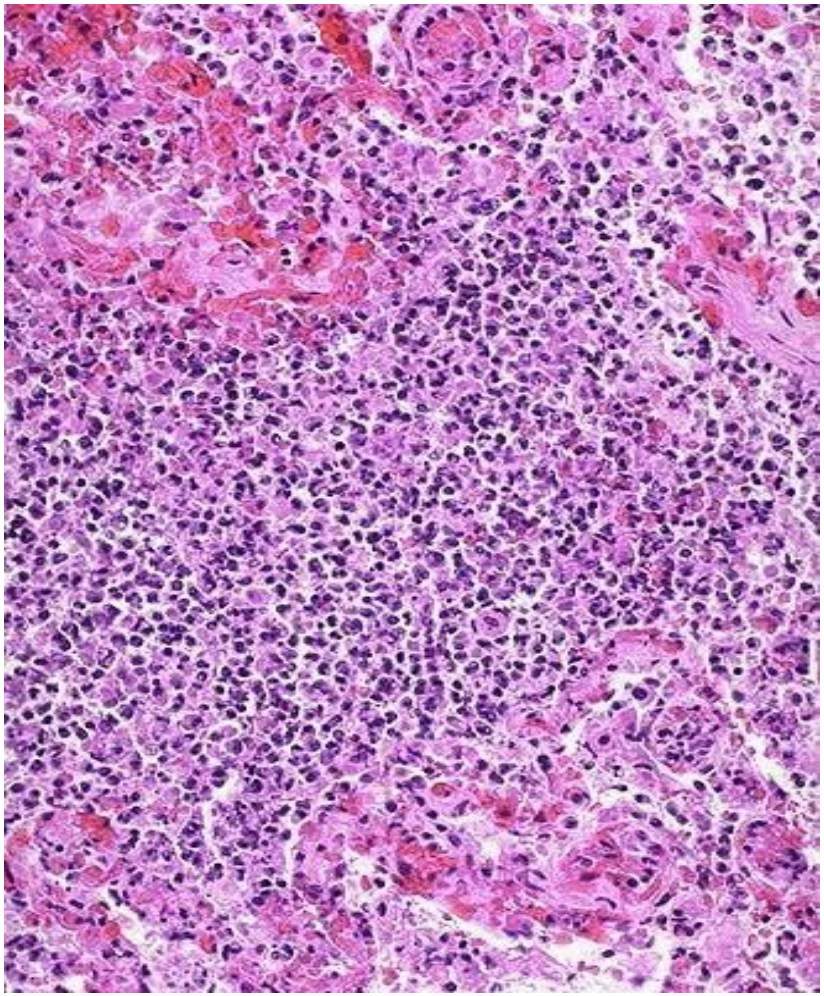
SUPPURATIVE OR PURULENT INFLAMMATION

- characterized by the production of large amounts of pus or purulent exudate consisting of neutrophils, necrotic cells, and edema fluid
- Certain bacteria (e.g., staphylococci) produce this localized suppuration and are therefore referred to as pyogenic (pus-producing) bacteria



Suppurative inflammation. A, A subcutaneous bacterial abscess with collections of pus. B, The abscess contains neutrophils, edema fluid, and cellular debris.

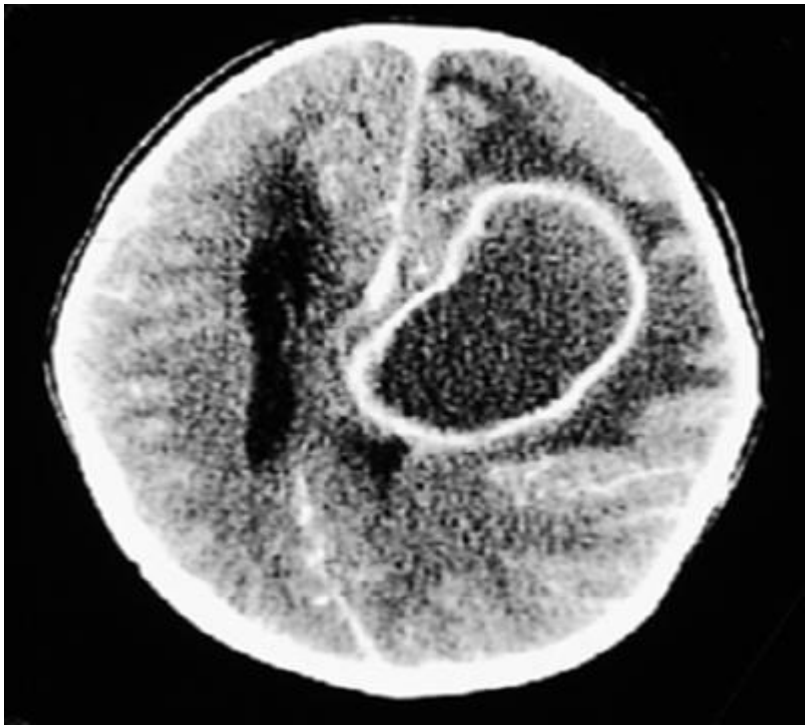
Purulent inflammation

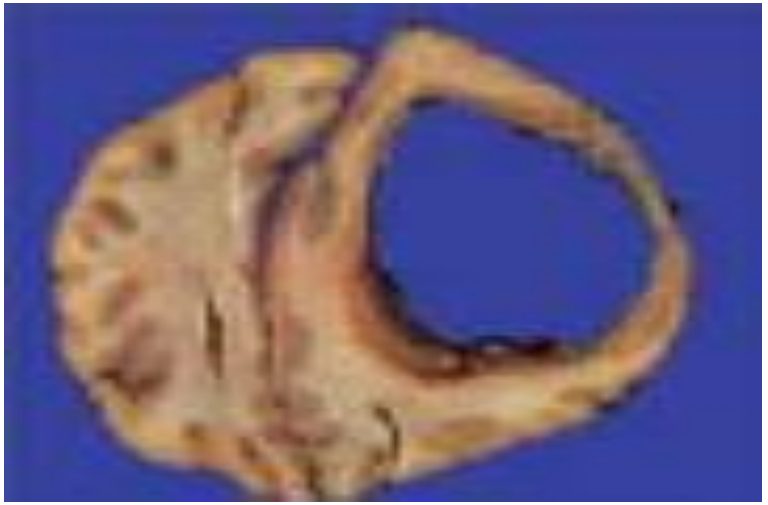


SUPPURATIVE OR PURULENT INFLAMMATION

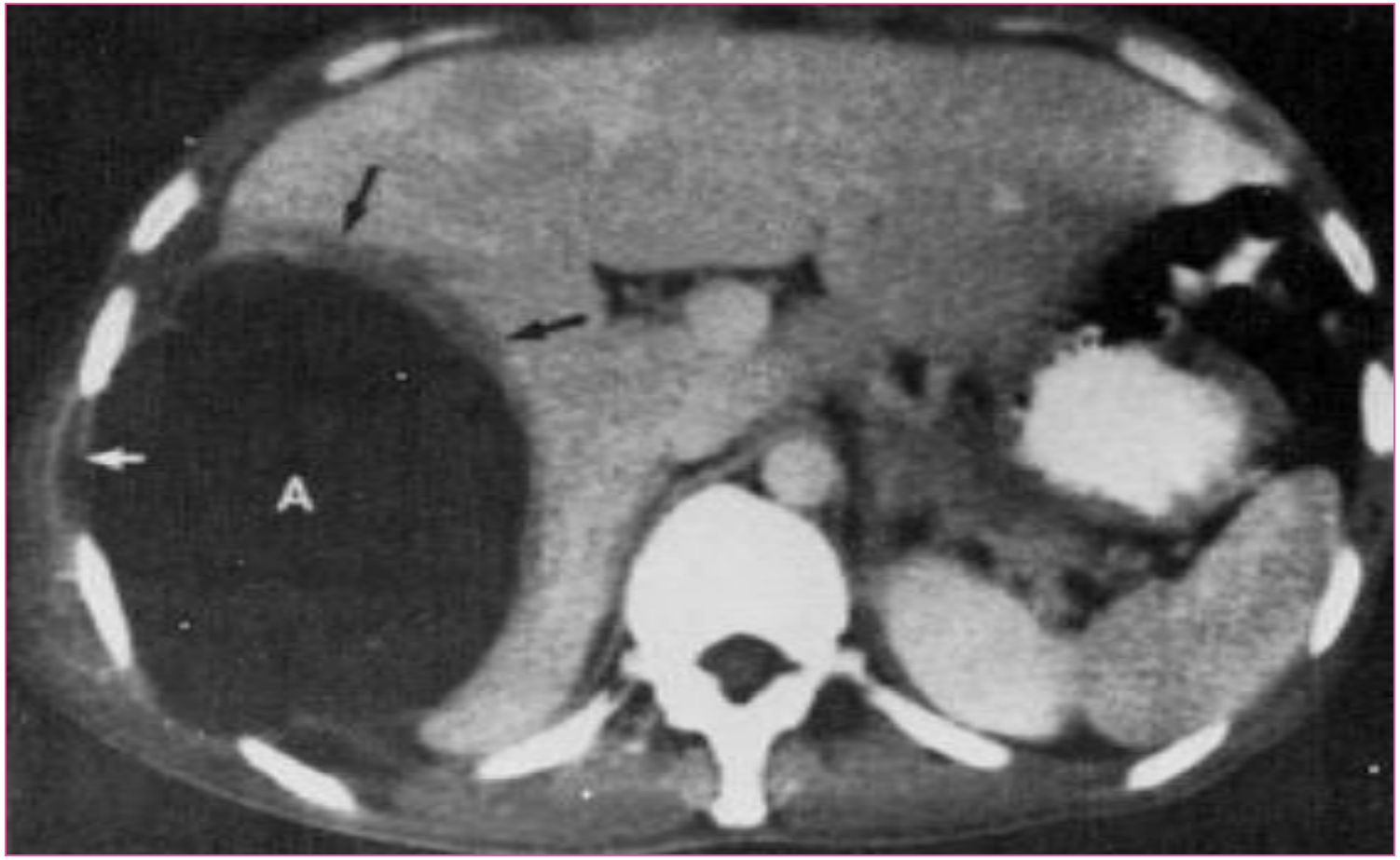
- **Abscesses : localized collections of purulent inflammatory tissue caused by suppuration buried in a tissue, an organ, or a confined space**

Brain Abscess

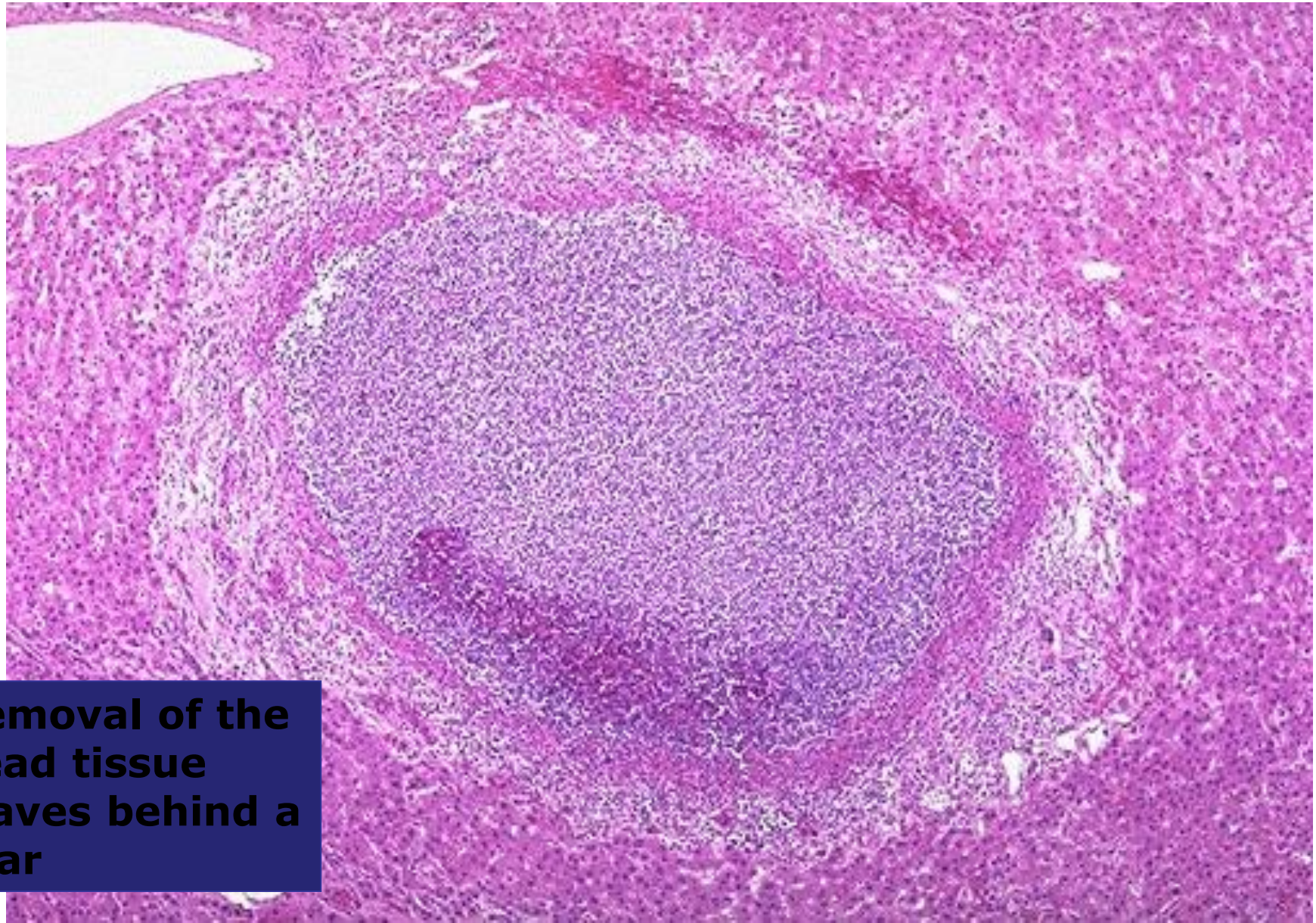




Liver abscess



Localized liquefactive necrosis liver abscess



Removal of the dead tissue leaves behind a scar

Morphologic Patterns of Acute Inflammation – ULCERS

- An ulcer is a local defect of the surface of an organ or tissue that is produced by the sloughing (shedding) of inflammatory necrotic tissue

Morphologic Patterns of Acute Inflammation

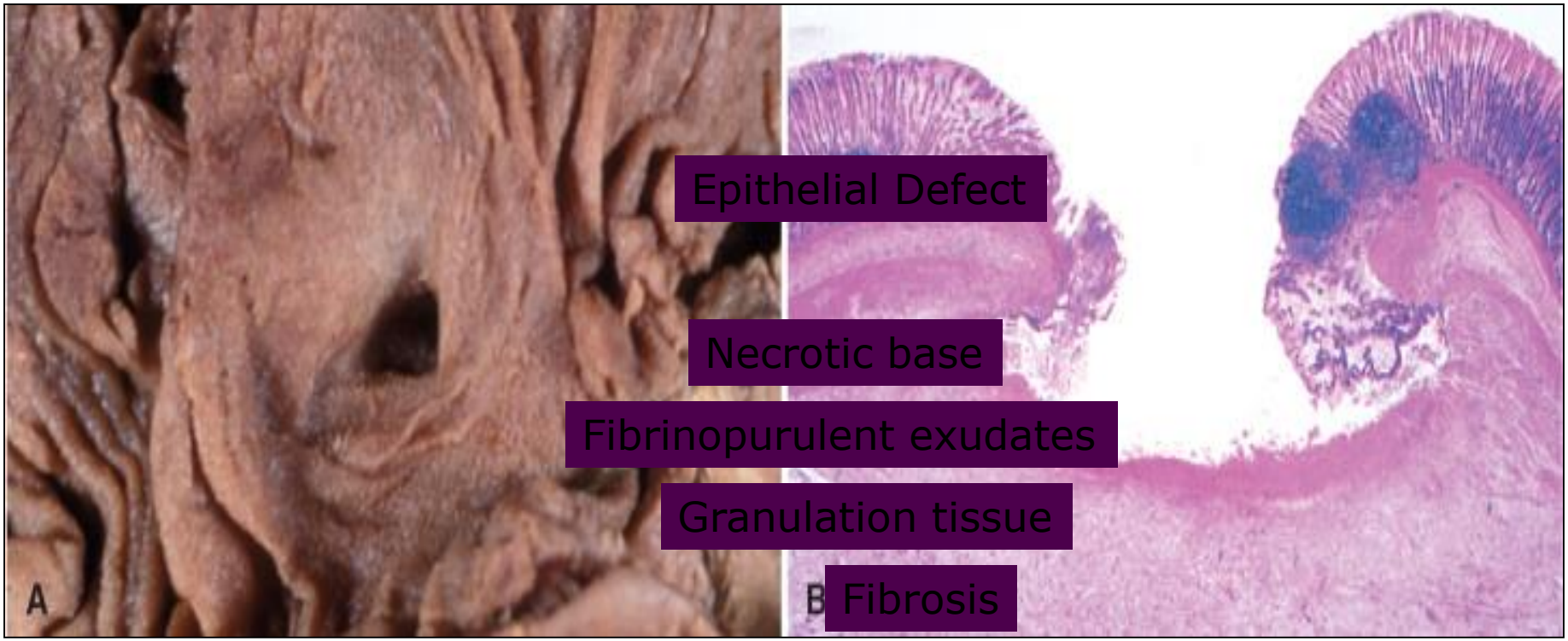
ULCERS

encountered in:

1) inflammatory necrosis of the mucosa of the mouth, stomach, intestines, or genitourinary tract

2) subcutaneous inflammation of the lower extremities in older persons who have circulatory disturbances

Ulceration can occur only when tissue necrosis and resultant inflammation exist on or near a surface



Termination of acute response

- Inflammation declines spontaneously
  - Mediators of inflammation are produced in rapid bursts only while the stimulus persists
  - Mediators have short half-lives and are degraded after their release.
  - Neutrophils also have short half-lives in tissues and die by apoptosis within a few hours after leaving the blood
- Active termination mechanisms include
  - Switch from pro-inflammatory leukotrienes to anti-inflammatory lipoxins
  - Release of anti-inflammatory cytokines, including transforming growth factor-β (TGF-β) and IL-10, from macrophages
  - production of anti-inflammatory lipid mediators, called resolvins and protectins, derived from polyunsaturated fatty acids
  - neural impulses (cholinergic discharge) that inhibit the production of TNF in macrophages

Outcomes of Acute Inflammation

- Acute inflammation may have one of the four outcomes:

  - *Complete resolution*
  - *Healing by connective tissue replacement (fibrosis)*
  - *Progression of the tissue response to chronic inflammation*
  - *Abcess formation*

Outcomes of Acute Inflammation

Complete resolution

When?

1) the injury is limited or short-lived
2) there has been little tissue destruction
3) the damaged parenchymal cells can regenerate

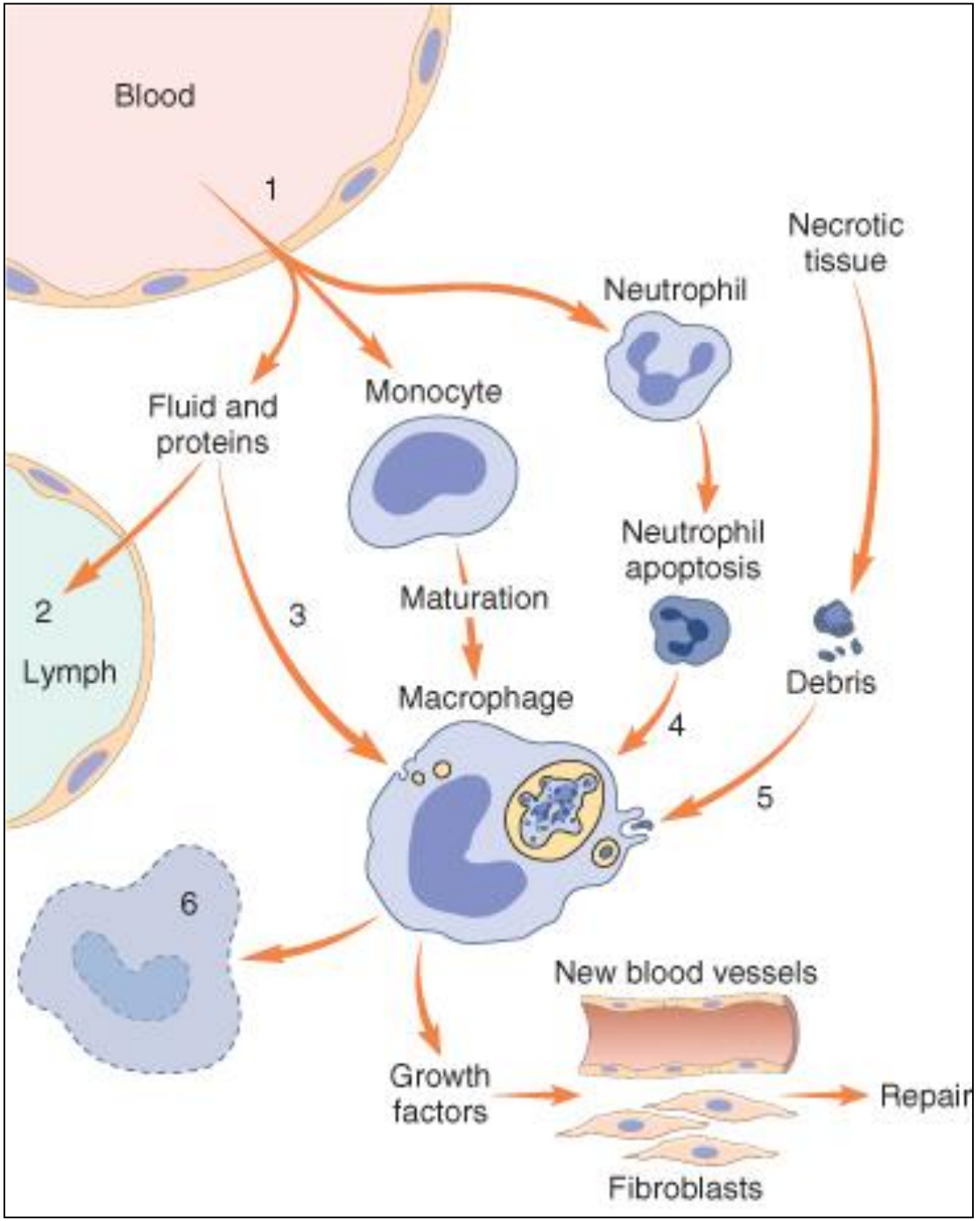
Outcomes of Acute Inflammation

Complete resolution

Mechanism:

- Neutralization and removal of chemical mediators
- Normalization of vascular permeability
- halting of leukocyte emigration
- Clearance of edema (lymphatic drainage) , inflammatory cells and necrotic debris (macrophages).

Events in the resolution of inflammation



Outcomes of Acute Inflammation

- Healing by connective tissue replacement (fibrosis):

- This occurs after substantial tissue destruction
  - the inflammatory injury involves tissues that are incapable of regeneration
  - there is abundant fibrin exudation.

  ❖ The destroyed tissue is reabsorbed and eventually replaced by fibrosis.

Outcomes of Acute Inflammation

- Progression of the tissue response to chronic inflammation:

  - occurs when the acute inflammatory response cannot be resolved
  - WHY?

Due to: 1. the persistence of the injurious agent

2. some interference with the normal process of healing

End of acute inflammation

Chronic Inflammation

Chronic inflammation

- Chronic inflammation is prolonged (weeks or months)
- Inflammation, tissue injury, and attempts at repair coexist, in varying combinations
- May follow acute inflammation
- May begin insidiously without any manifestations of an acute reaction

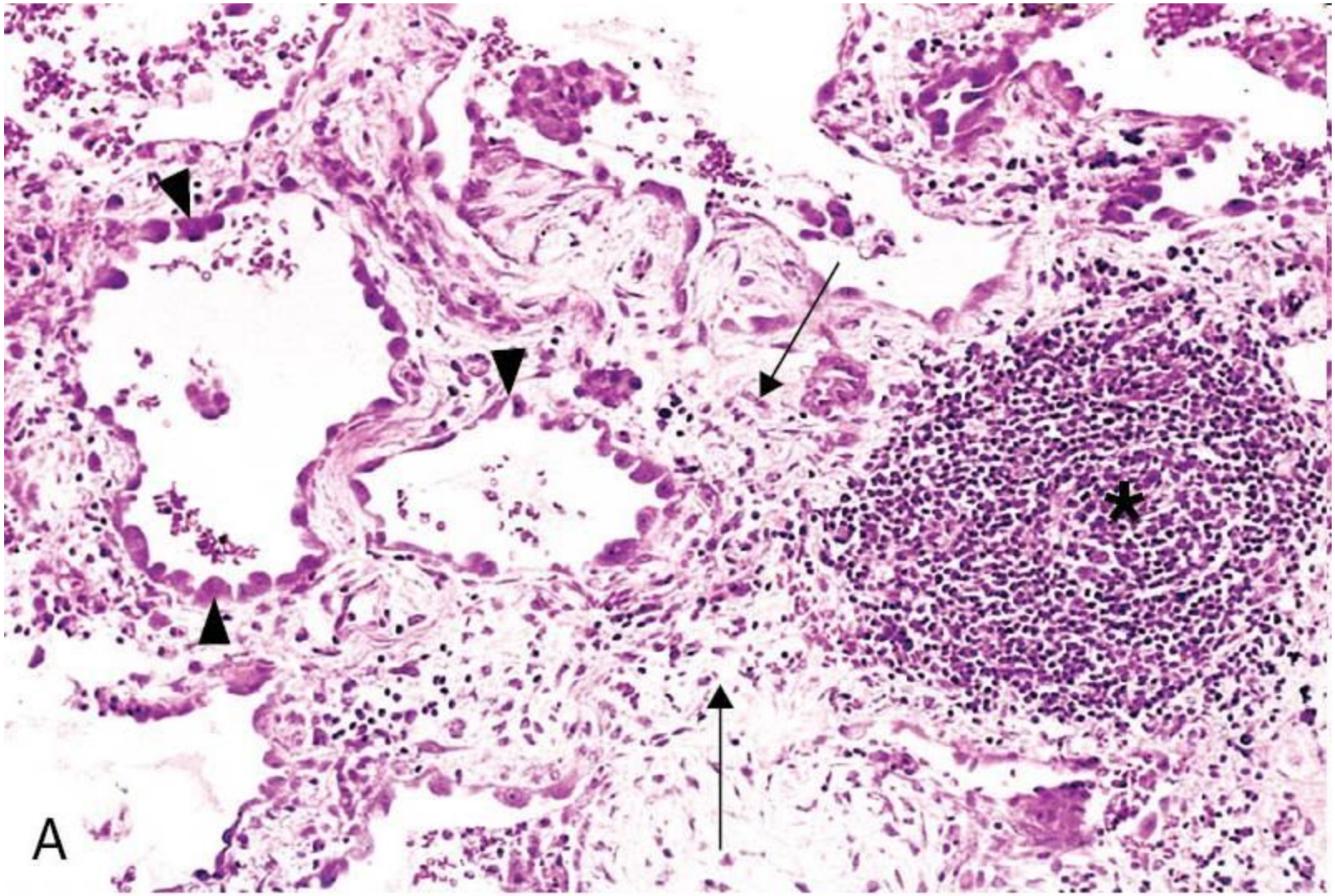
Causes of chronic inflammation

- Persistent infections
  - Organisms usually of low toxicity that invoke delayed hypersensitivity reaction
  - *M. tuberculosis* and *T. pallidum* causes granulomatous reaction
- Prolonged exposure to potentially toxic agents
  - Exogenous agents include silica which causes silicosis
  - Endogenous causes include atherosclerosis caused by toxic plasma lipid components
- Autoimmunity
  - Auto-antigens provoke self-perpetuating immune responses that cause chronic inflammatory diseases like RA, MS
  - Responses against common environmental substances cause chronic allergic diseases, such as bronchial asthma

Histologic features

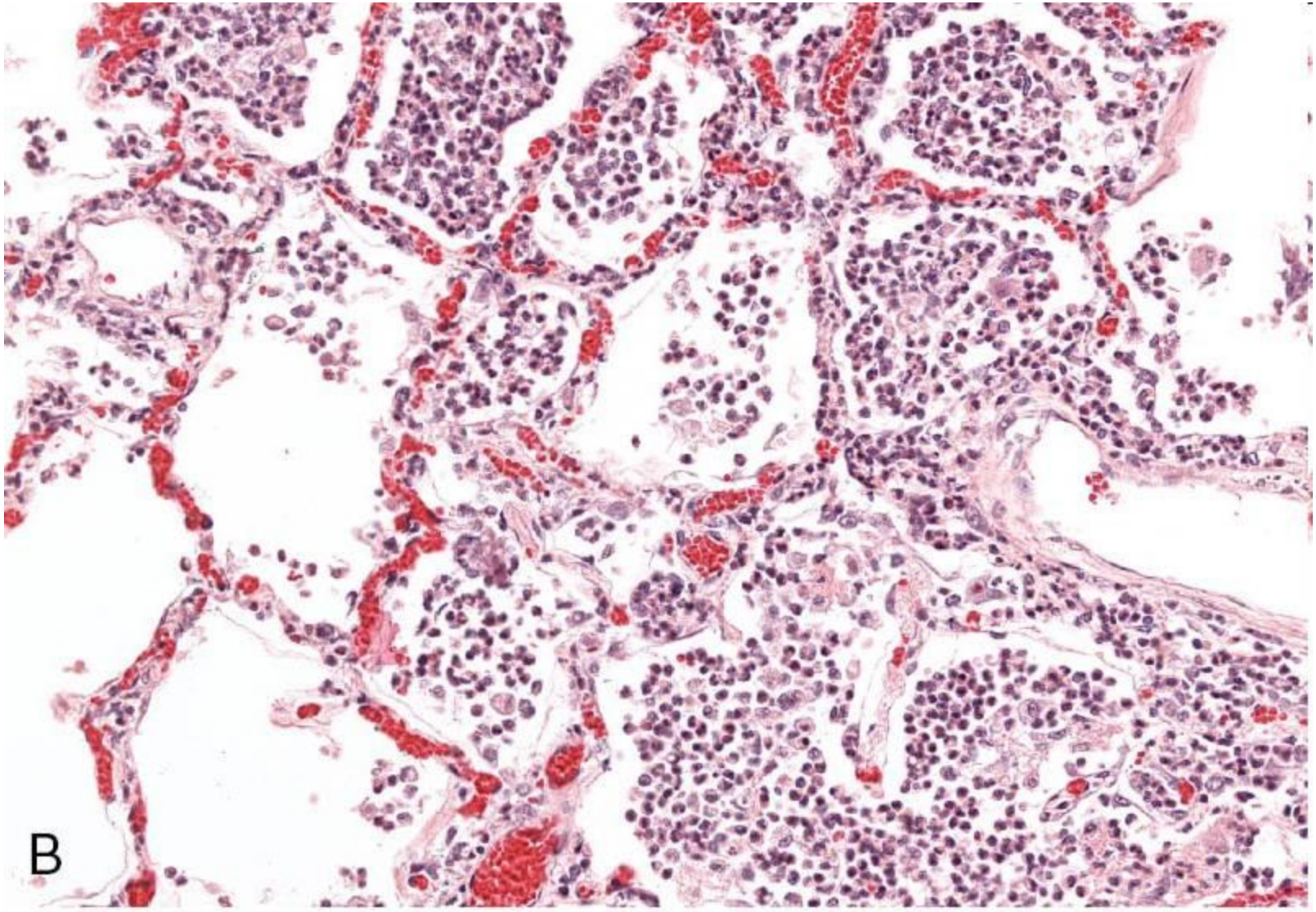
- Infiltration with mononuclear cells (eg. macrophages, lymphocytes and plasma cells) due to persistent reaction to injury
- Tissue destruction induced by persistent agent or inflammatory cells
- Attempts at healing by connective tissue replacement of damaged tissue with angiogenesis and fibrosis

Chronic inflammation



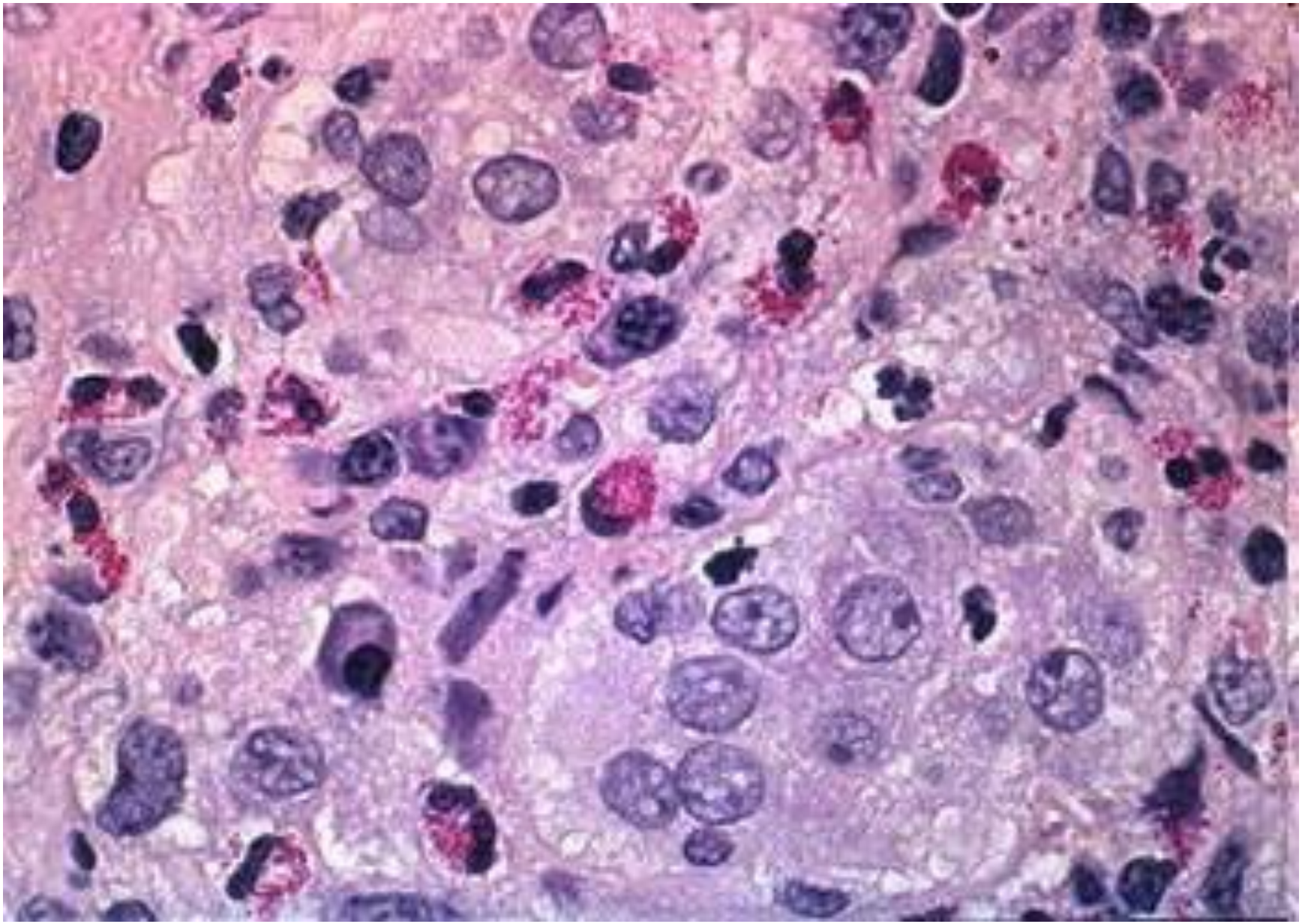
Copyright © 2010 by Saunders, an imprint of Elsevier Inc.

Acute inflammation



Copyright © 2010 by Saunders, an imprint of Elsevier Inc.

eosinophils, plasma cells, and macrophages

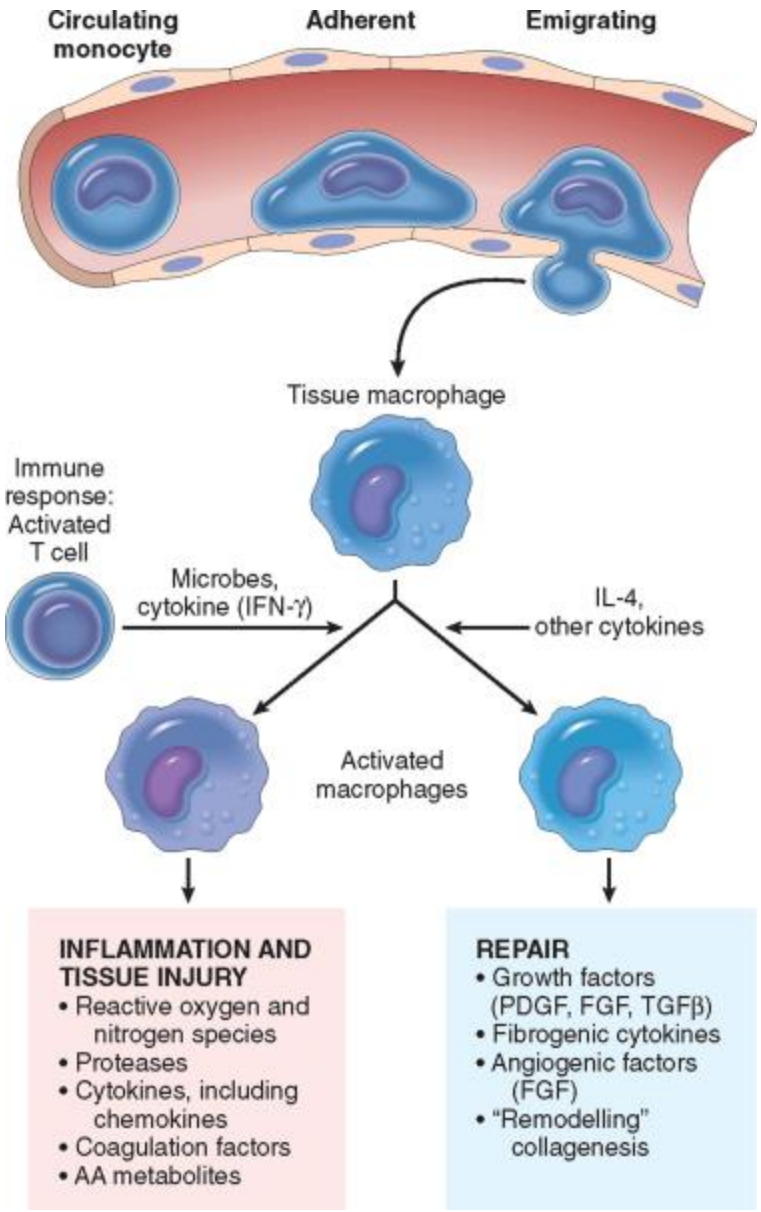


Macrophages in chronic inflammation

- Mononuclear phagocytes arise from a common precursor in the bone marrow
- From the blood, monocytes migrate into various tissues and differentiate into macrophages
  - The half-life of blood monocytes is about 1 day
  - The life span of tissue macrophages is several months or years
- Monocytes begin to emigrate into extravascular tissues quite early in acute inflammation
- In chronic inflammation, macrophage accumulation persists as a result of continuous recruitment from the circulation and local proliferation at the site of inflammation

Resident and activated macrophages

- Kupffer cells - liver
- Sinus Histiocytes - spleen and lymph nodes
- Alveolar Macrophages – Lungs
- Microglia – brain



Lymphocytes in chronic inflammation

- T and B cells
  - Cytokines from activated macrophages, mainly TNF, IL-1, and chemokines, promote leukocyte recruitment
  - Macrophages display antigens to T cells and produce membrane molecules (costimulators) and cytokines (notably IL-12) that stimulate T-cell responses
  - Activated T lymphocytes recruit monocytes from the circulation with IFN-γ, a powerful activator of macrophages
  - Plasma cells develop from activated B lymphocytes and produce antibodies
  - Accumulations of lymphocytes, antigen-presenting cells, and plasma cells may assume the morphologic features of lymph nodes, called tertiary lymphoid organs

Other cells in chronic inflammation

- Eosinophils
  - abundant in immune reactions mediated by IgE and in parasitic infections, recruited by eotaxin
  - granules contain major basic protein, a highly cationic protein that is toxic to parasites but also causes lysis of host epithelial cells
- Mast cells
  - express on their surface the receptor (FcεRI) that binds the Fc portion of IgE antibody
  - granules release histamine and prostaglandins during allergic reactions to foods, insect venom, or drugs, sometimes with catastrophic results (e.g. anaphylactic shock)
- Neutrophils
  - induced either by persistent microbes or by mediators produced by activated macrophages and T lymphocytes
  - neutrophilic exudate can persist for many months in osteomyelitis
  - cause chronic damage induced in lungs by smoking and other irritant stimuli

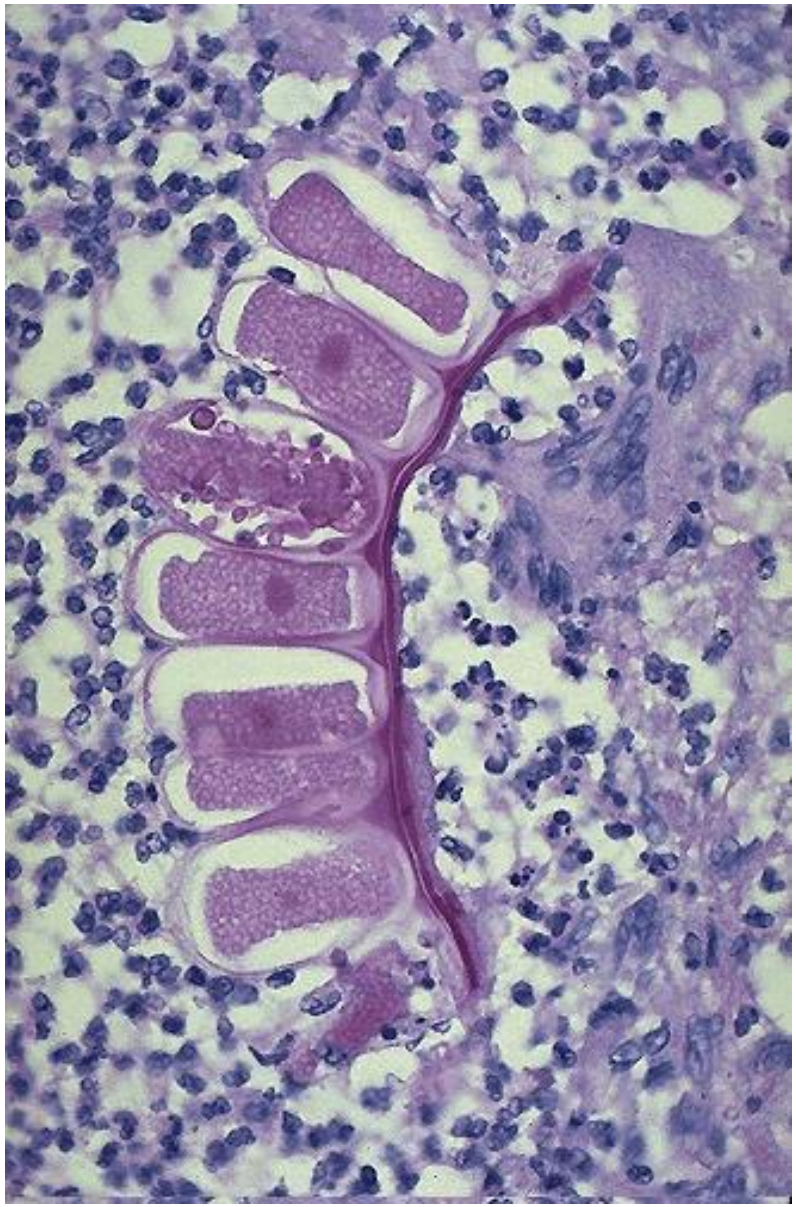
Granulomatous inflammation

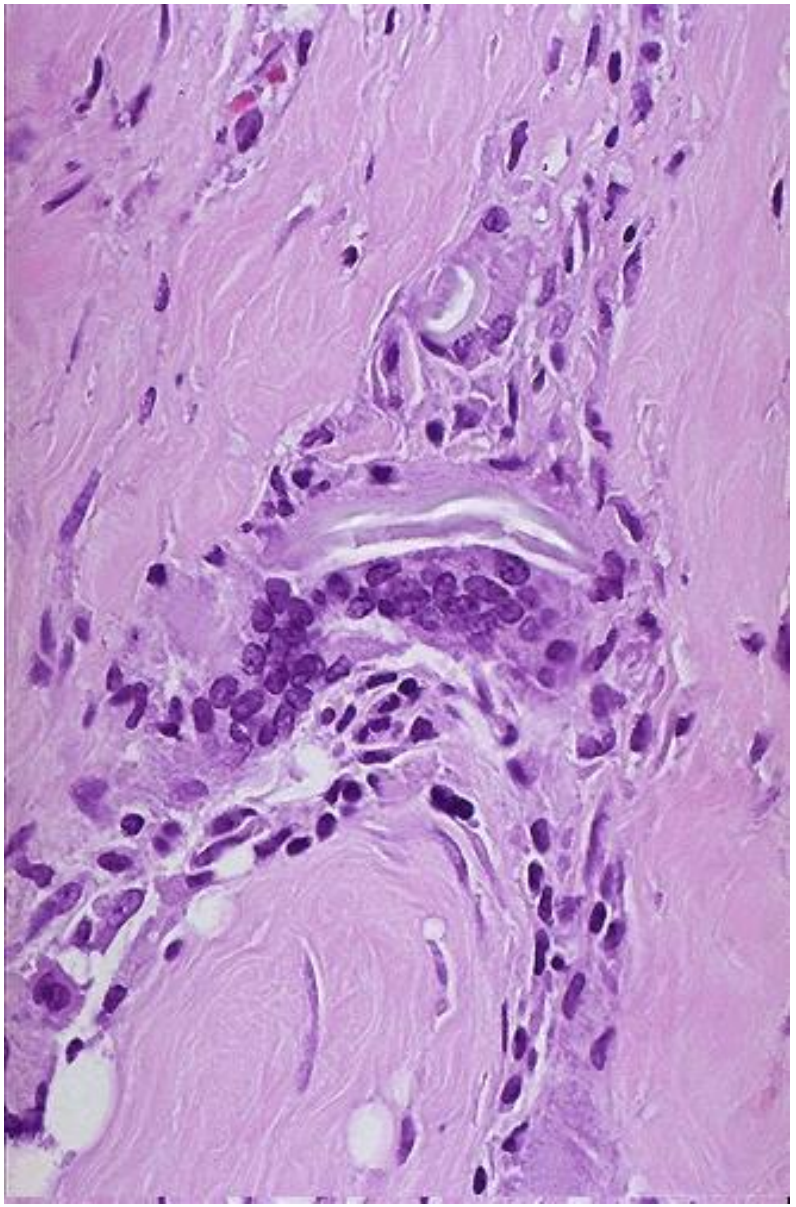
- Focus of chronic inflammation encountered in a limited number of conditions
- Cellular attempt to contain an offending agent that is difficult to eradicate (i.e. Tb)
- Consists of a microscopic aggregation of macrophages that are transformed into epithelioid cells, surrounded by a collar of mononuclear leukocytes, principally lymphocytes and occasionally plasma cells
- Epithelioid cells have a pale pink granular cytoplasm with indistinct cell boundaries, often appearing to merge into one another as giant cells
- Foreign body granulomas are incited by relatively inert foreign bodies (i.e. talc, sutures)
- Immune granulomas are caused by several infectious agents that provoke a cell-mediated immune response

Causes of granulomas

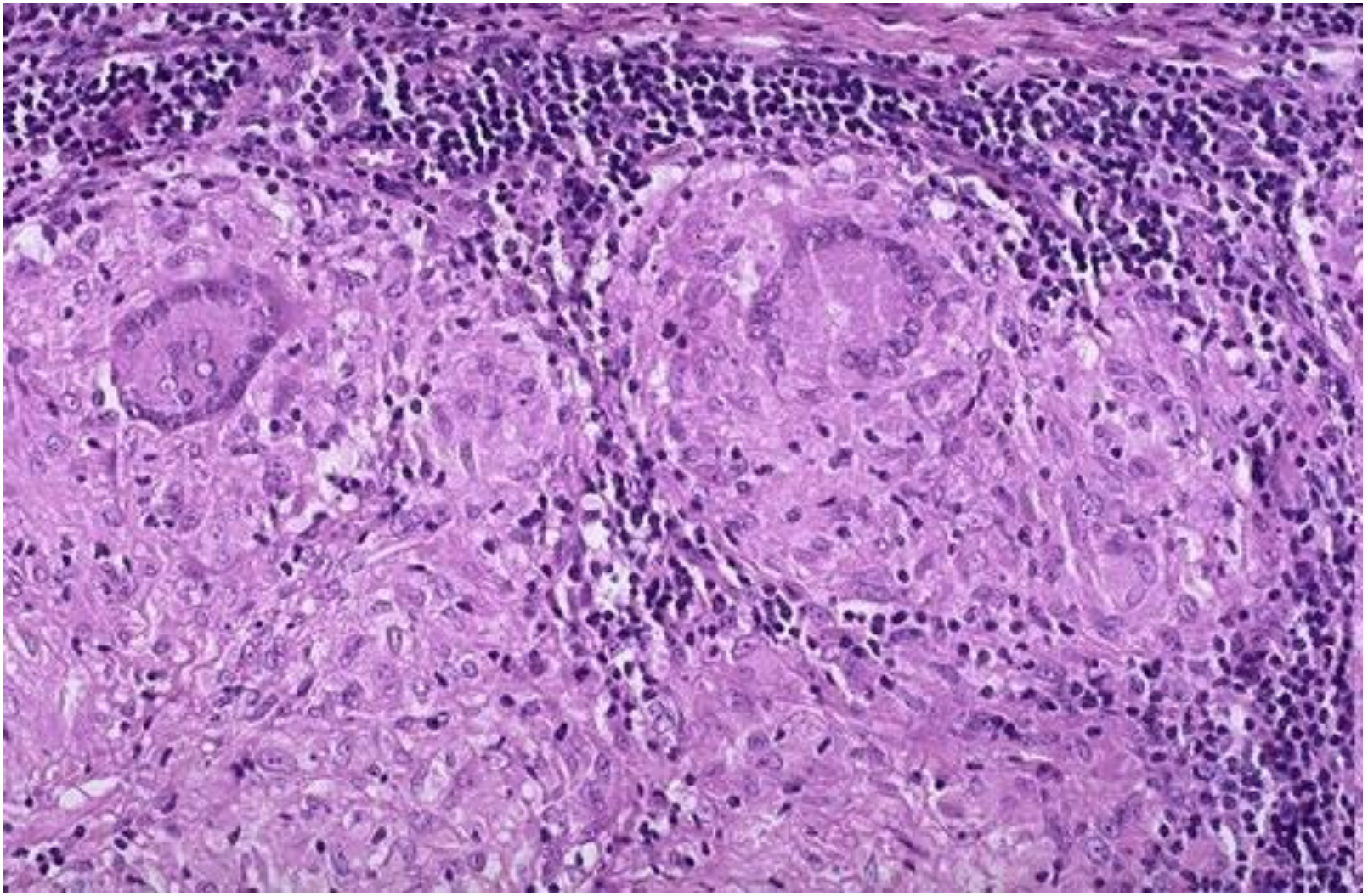
Disease	Cause	Tissue Reaction
Tuberculosis	*Mycobacterium tuberculosis*	Caseating granuloma (tubercle): focus of activated macrophages (epithelioid cells), rimmed by fibroblasts, lymphocytes, histiocytes, occasional Langhans giant cells; central necrosis with amorphous granular debris; acid-fast bacilli
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

Foreign body granuloma





Granuloma



Comparison of acute and chronic inflammation

Initiators	Microbial surfaces & fragments Injured tissue & tissue fragments	Non-digestible organisms Non-degradable foreign matter Auto-immune reactions
Mediators	Mast cell products (histamine) Bradykinin Lysosomal components Lipid mediators	T-lymphocyte & macrophage products: cytokines & GF Proteases and reactive oxygen Complement, Lipid mediators
Cell Populations	Neutrophils Macrophages	T-lymphocytes, plasma cells Macrophages Fibroblasts
Time Course	Acute onset, days	Insidious onset: weeks-years
Outcome	Resolution, Abscess formation Chronic inflammation	Tissue destruction; fibrosis

Mediators of inflammation

- Vasoactive amines
- Plasma proteases
  - Clotting system
  - Fibrinolytic system
  - Kinin system
  - Complement system
- Arachidonic acid metabolites
  - Eicosanoids
  - Prostaglandins
  - Leukotrienes
- Platelet Activating Factor
- Cytokines
- ROS and NO
- Lysosomal constituents

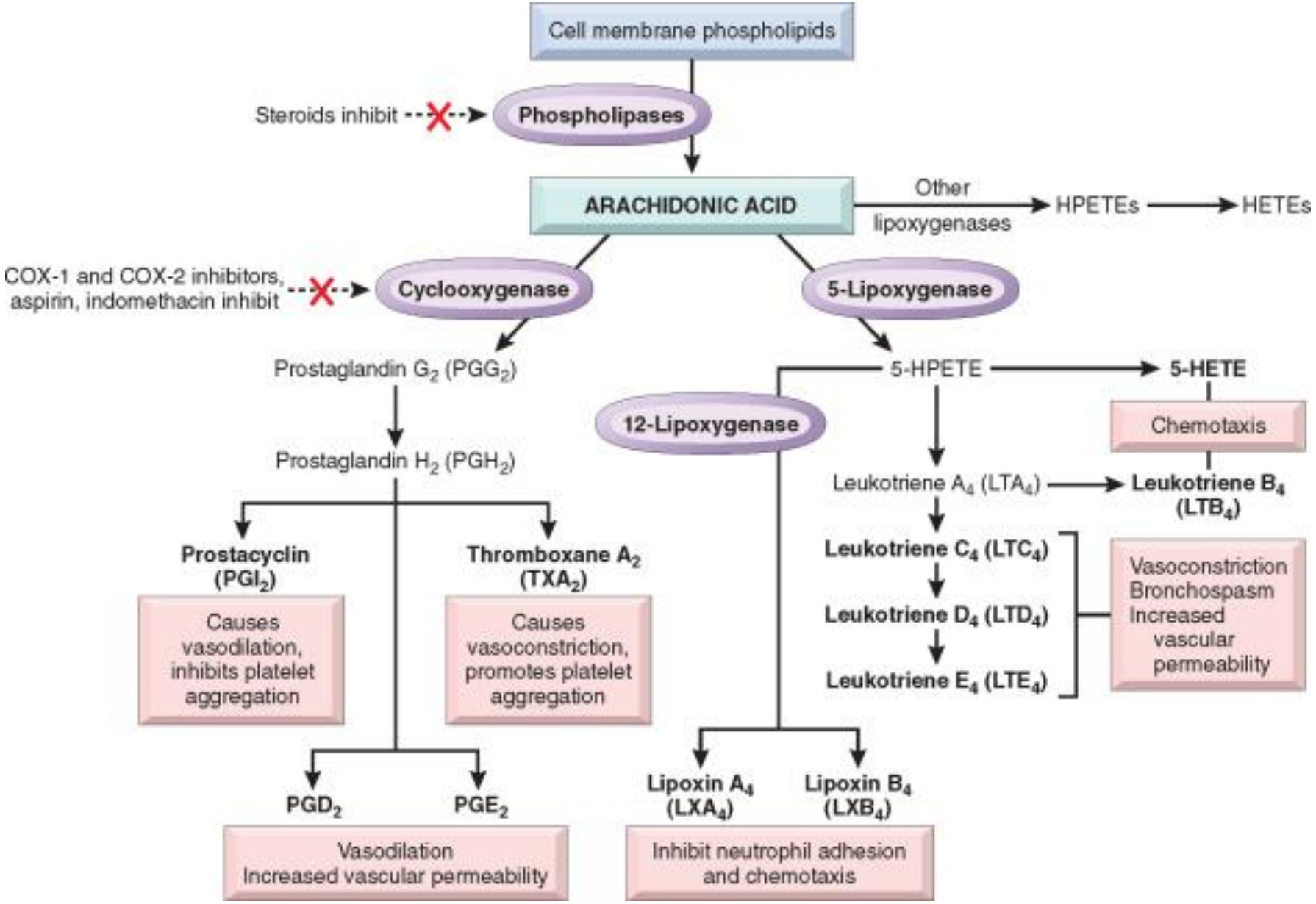
- Vasodilation
  - Prostaglandins
  - NO
- Vascular permeability
  - Vasoactive amines
  - C3a and C5a
  - Bradykinin
  - Leukotrienes C4, D4, E4
- Chemotaxis
  - C5a
  - Leukotriene B4
  - Bacterial products
  - Chemokines (IL-8)
- Fever
  - IL-1, IL-6, TNFa
  - Bradykinin
- Tissue damage
  - ROS and NO
  - Lysosomal constituents

Vasoactive amines

- Histamine
  - causes dilation of arterioles and increases the permeability of venules
  - mediated mainly via binding to H1 receptors on microvascular endothelial cells
  - liberated from blood basophils and connective tissue mast cells in response to
    - Injury, heat and cold
    - binding of specific antigen to membrane-bound IgE
    - binding of complement fragments C3a and C5a anaphylotoxins
    - Interleukin-1, IL-8
    - Factors from neutrophils, monocytes and platelets
- Serotonin
  - also known as 5-hydroxytryptamine
  - acts like histamine and derived from platelets

Prostaglandins, Leukotrienes, Lipoxins

- Receptor binding, kinase activation, Ca release activates PLA2
- Arachidonic Acid (AA) liberated from plasma membrane
- Cyclo-oxygenase activity (constitutive and inducible COX-1 and COX-2) makes prostaglandins
  - PGI2 and (PGF1α) is a vasodilator, a potent inhibitor of platelet aggregation, and also markedly potentiates the permeability-increasing and chemotactic effects of other mediators
  - TxA2, a potent platelet-aggregating agent and vasoconstrictor, is unstable and rapidly converted to inactive TxB2
  - PGD2 (mast cells) and PGE2 (more widely distributed) cause vasodilation and increase the permeability of post-capillary venules
  - PGD2 is a chemoattractant for neutrophils
  - PGE2 causes pain
- Lipoxygenase activity makes leukotrienes and lipoxins
  - LTB4 is a potent chemotactic agent and activator of neutrophils, causing aggregation and adhesion of the cells to venular endothelium, generation of ROS, and release of lysosomal enzymes
  - Cysteinyl-containing leukotrienes C4, D4, and E4 (LTC4, LTD4, LTE4) cause intense vasoconstriction, bronchospasm, and increased vascular permeability in venules
  - Lipoxins are anti-inflammatory


Cell membrane phospholipids
Steroids inhibit
Phospholipases
ARACHIDONIC ACID
Other lipoxygenases
HPETEs
HETEs
COX-1 and COX-2 inhibitors, aspirin, indomethacin inhibit
Cyclooxygenase
5-Lipoxygenase
Prostaglandin G2 (PGG2)
Prostaglandin H2 (PGH2)
5-HPETE
5-HETE
12-Lipoxygenase
Chemotaxis
Leukotriene A4 (LTA4)
Leukotriene B4 (LTB4)
Prostacyclin (PGI2)
Causes vasodilation, inhibits platelet aggregation
Thromboxane A2 (TXA2)
Causes vasoconstriction, promotes platelet aggregation
Leukotriene C4 (LTC4)
Leukotriene D4 (LTD4)
Leukotriene E4 (LTE4)
Vasoconstriction
Bronchospasm
Increased vascular permeability
PGD2
PGE2
Vasodilation
Increased vascular permeability
Lipoxin A4 (LXA4)
Lipoxin B4 (LXB4)
Inhibit neutrophil adhesion and chemotaxis

Cytokines and Chemokines

Cytokine	Principal Sources	Principal Actions in Inflammation
IN ACUTE INFLAMMATION		
TNF	Macrophages, mast cells, T lymphocytes	Stimulates expression of endothelial adhesion molecules and secretion of other cytokines; systemic effects
IL-1	Macrophages, endothelial cells, some epithelial cells	Similar to TNF; greater role in fever
IL-6	Macrophages, other cells	Systemic effects (acute-phase response)
Chemokine	Macrophages, endothelial cells, T lymphocytes, mast cells, other cell types	Recruitment of leukocytes to sites of inflammation; migration of cells to normal tissues
IN CHRONIC INFLAMMATION		
IL-12	Dendritic cells, macrophages	Increased production of IFN-γ
IFN-γ	T lymphocytes, NK cells	Activation of macrophages (increased ability to kill microbes and tumor cells)
IL-17	T lymphocytes	Recruitment of neutrophils and monocytes

Important mediators of inflammation

Mediator	Principal Sources	Actions
CELL-DERIVED		
Histamine	Mast cells, basophils, platelets	Vasodilation, increased vascular permeability, endothelial activation
Serotonin	Platelets	Vasodilation, increased vascular permeability
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)	Macrophages, endothelial cells, mast cells	Local endothelial activation (expression of adhesion molecules), fever/pain/anorexia/hypotension, decreased vascular resistance (shock)
Chemokines	Leukocytes, activated macrophages	Chemotaxis, leukocyte activation
PLASMA PROTEIN–DERIVED		
Complement products (C5a, C3a, C4a)	Plasma (produced in liver)	Leukocyte chemotaxis and activation, vasodilation (mast cell stimulation) Increased vascular permeability, smooth muscle contraction, vasodilation, pain Endothelial activation, leukocyte recruitment
Kinins	Plasma (produced in liver)	
Proteases activated during coagulation	Plasma (produced in liver)	

The end

- Reactions