ACUTE INFLAMMATION

Dr.Jagan.C
Associate Professor
Dept of Pathology
VMCH & RI

What is Inflammation?

- Response to injury (including infection)
- Reaction of blood vessels leads to:
  - Accumulation of fluid and leukocytes in extravascular tissues
- Destroys, dilutes, or walls off the injurious agent
- Initiates the repair process
- Fundamentally a protective response
- May be potentially harmful
  - Hypersensitivity reactions to insect bites, drugs, contrast media in radiology
  - Chronic diseases: arthritis, atherosclerosis
  - Disfiguring scars, visceral adhesions
- Consists of two general components
  - Vascular reaction
  - Cellular reaction
- Controlled by a variety of chemical mediators
  - Derived from plasma proteins
  - Derived from cells inside and outside of blood vessels

Historical Highlights

- Celsus, a first century A.D. Roman, listed four cardinal signs of acute inflammation:
  - *Rubor* (erythema [redness]): vasodilatation, increased blood flow
  - *Tumor* (swelling): extravascular accumulation of fluid
  - *Calor* (heat): vasodilatation, increased blood flow
  - *Dolor* (pain)
  - *Functio laesa* (loss of function)

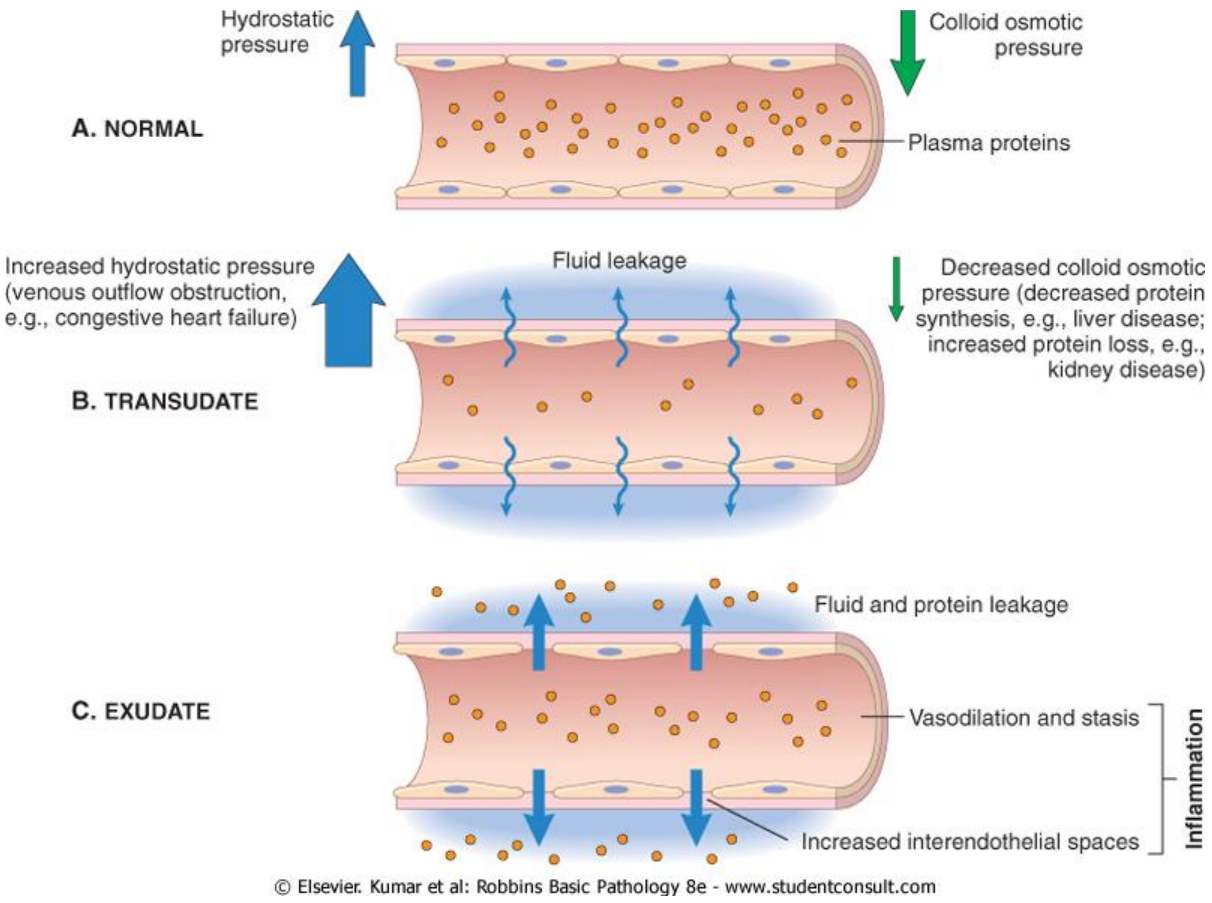
Types of Inflammation

- Acute inflammation
  - Short duration
  - Edema
  - Mainly neutrophils
- Granulomatous inflammation
  - Distinctive pattern of chronic inflammation
  - Activated macrophages (epithelioid cells) predominate
  - +/- Multinucleated giant cells
- Chronic inflammation
  - Longer duration
  - Lymphocytes & macrophages predominate
  - Fibrosis
  - New blood vessels (angiogenesis)

Acute Inflammation

- Three major components:
  - Increase in blood flow (redness & warmth)
  - Edema results from increased hydrostatic pressure (vasodilation) and lowered intravascular osmotic pressure (protein leakage)
  - Leukocytes emigrate from microcirculation and accumulate in the focus of injury
- Stimuli: infections, trauma, physical or chemical agents, foreign bodies, immune reactions

Edema in inflammation



Edema is a general term for swelling (usu. due to fluid)

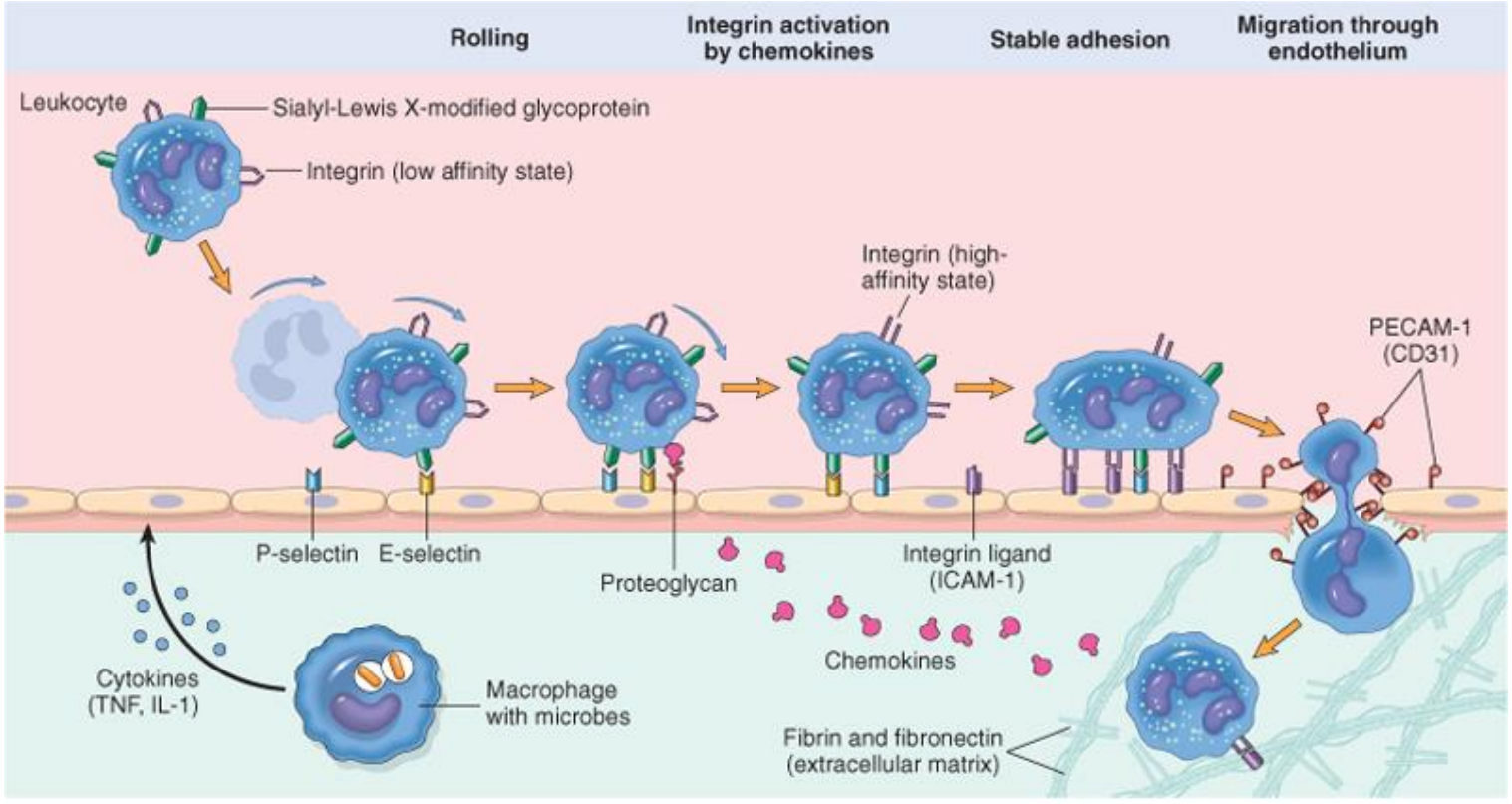
Plasma proteins in blood maintain a "colloid osmotic pressure" to help draw fluid that leaks out into tissue bed via hydrostatic pressure

Dysregulation of hydrostatic pressure (e.g. heart failure) and/or colloid pressure (decreased protein synthesis/retention) pushes out more fluid (transudate) into tissue bed

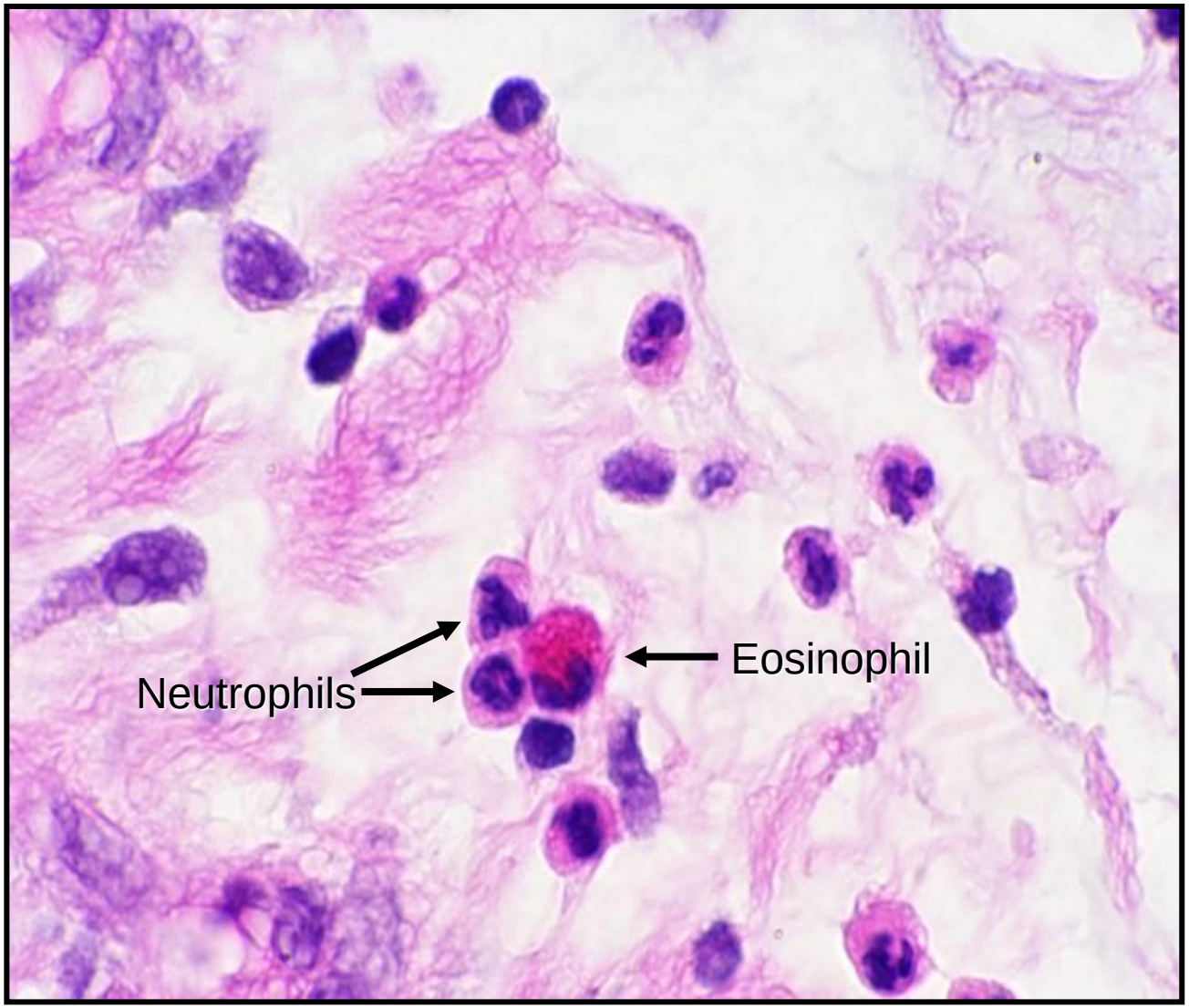
Inflammation causes endothelial cells to separate, thus allowing fluid + protein (exudate) to enter tissue bed.

Leukocyte Extravasation

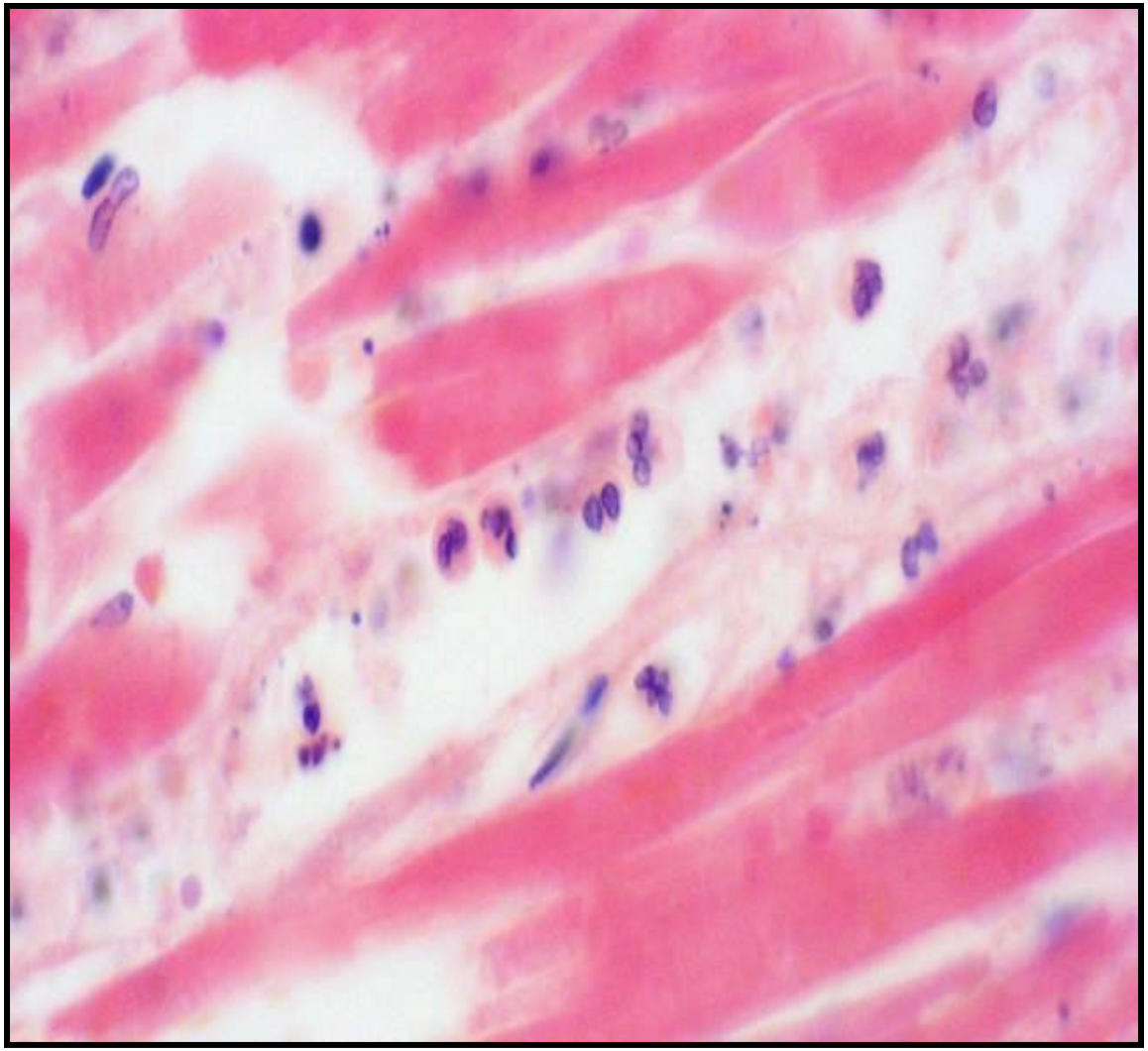
- Extravasation: delivery of leukocytes from the vessel lumen to the interstitium
  - In the lumen: margination, rolling, and adhesion
  - Migration across the endothelium (*diapedesis*)
  - Migration in the interstitial tissue (*chemotaxis*)
- Leukocytes ingest offending agents (phagocytosis), kill microbes, and degrade necrotic tissue and foreign antigens
- There is a balance between the helpful and harmful effects of extravasated leukocytes



Neutrophil Morphology

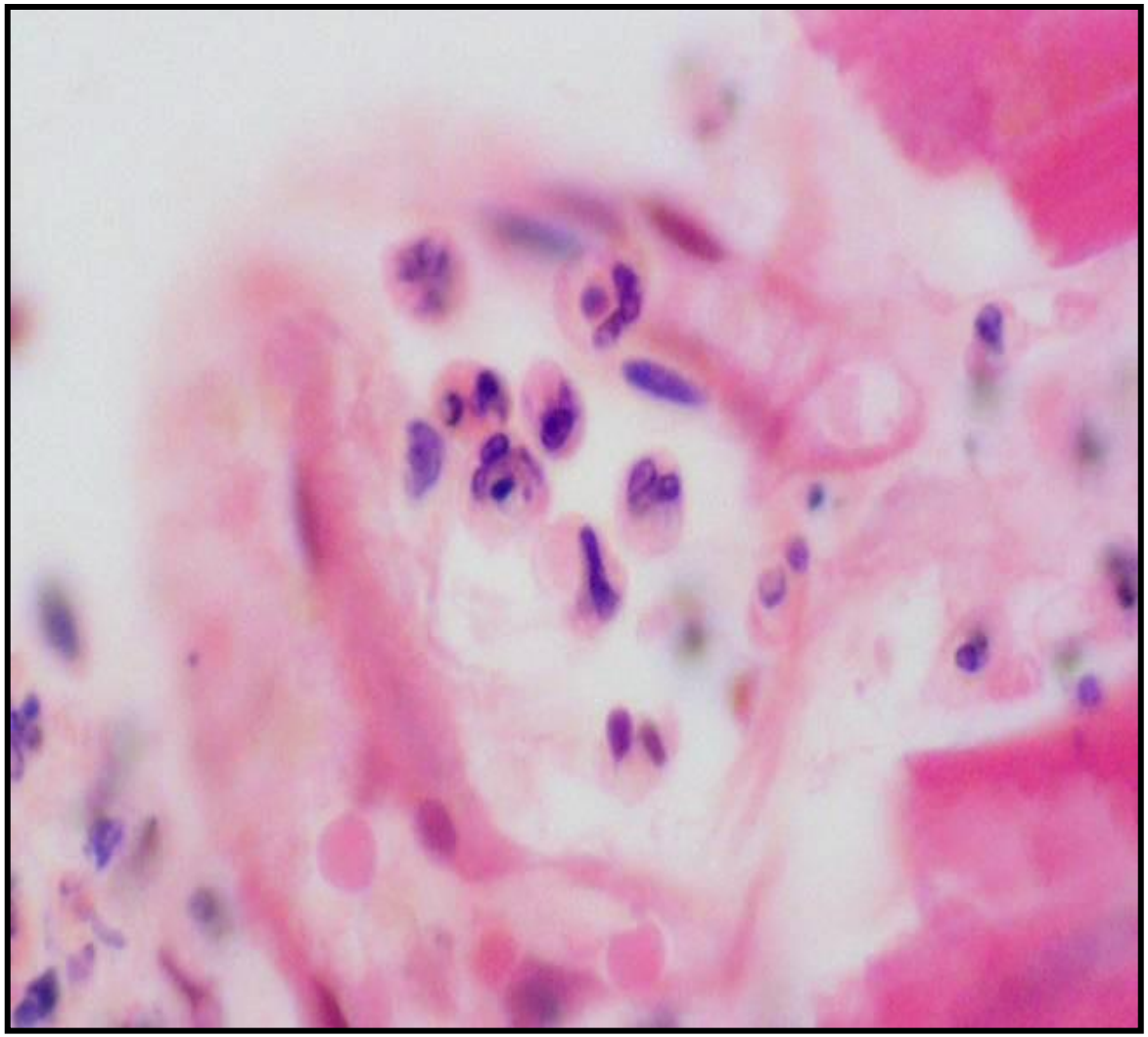


Leukocyte Margination



Photomicrograph courtesy of Dr. James G. Lewis

Leukocyte Diapedesis

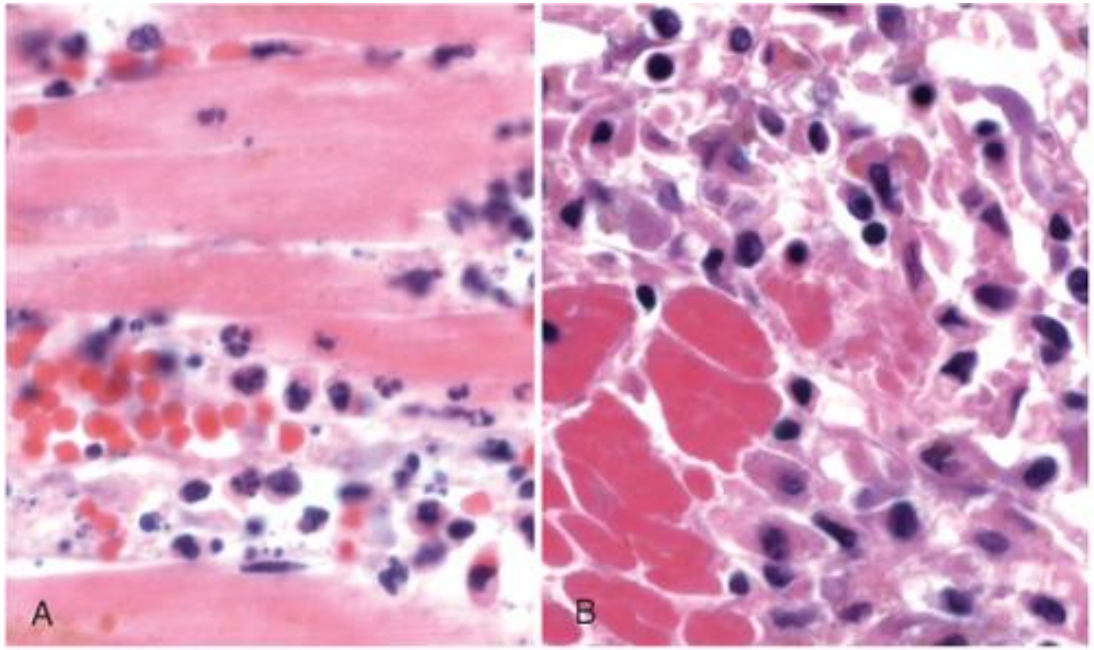


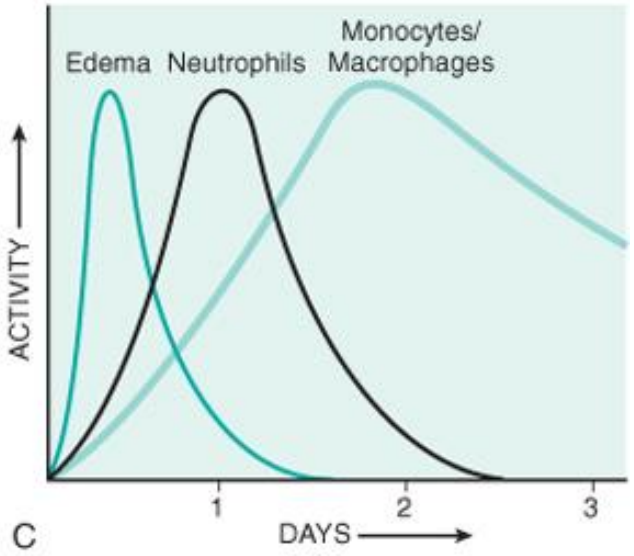
Photomicrograph courtesy of Dr. James G. Lewis

Sequence of Leukocyte Emigration

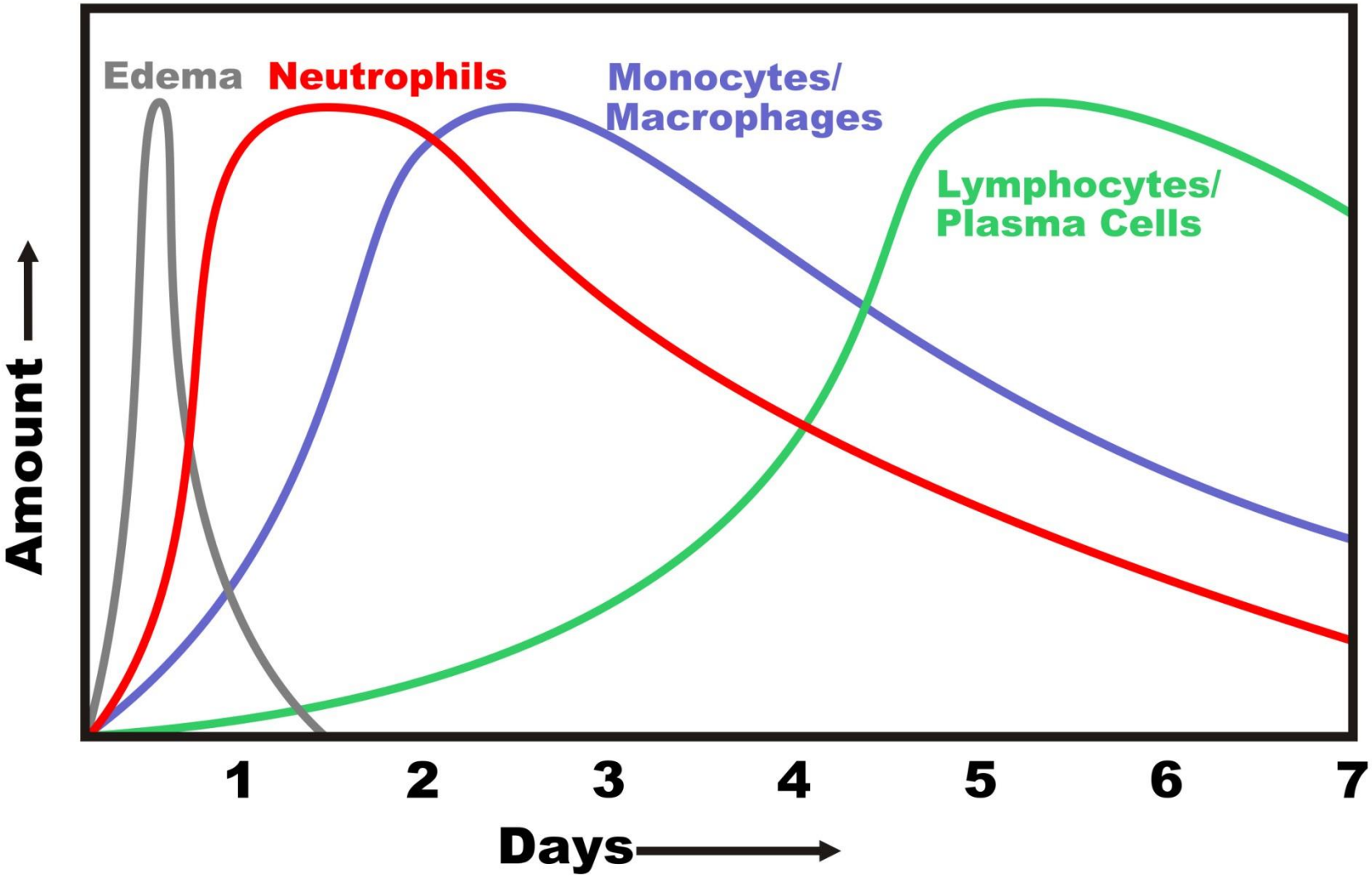
- Neutrophils predominate during the first 6 to 24 hours
- Monocytes in 24 to 48 hours
- Induction/activation of different adhesion molecule pairs and specific chemotactic factors in different phases of inflammation

Sequence of Events - Injury





Sequence of Events - Infection

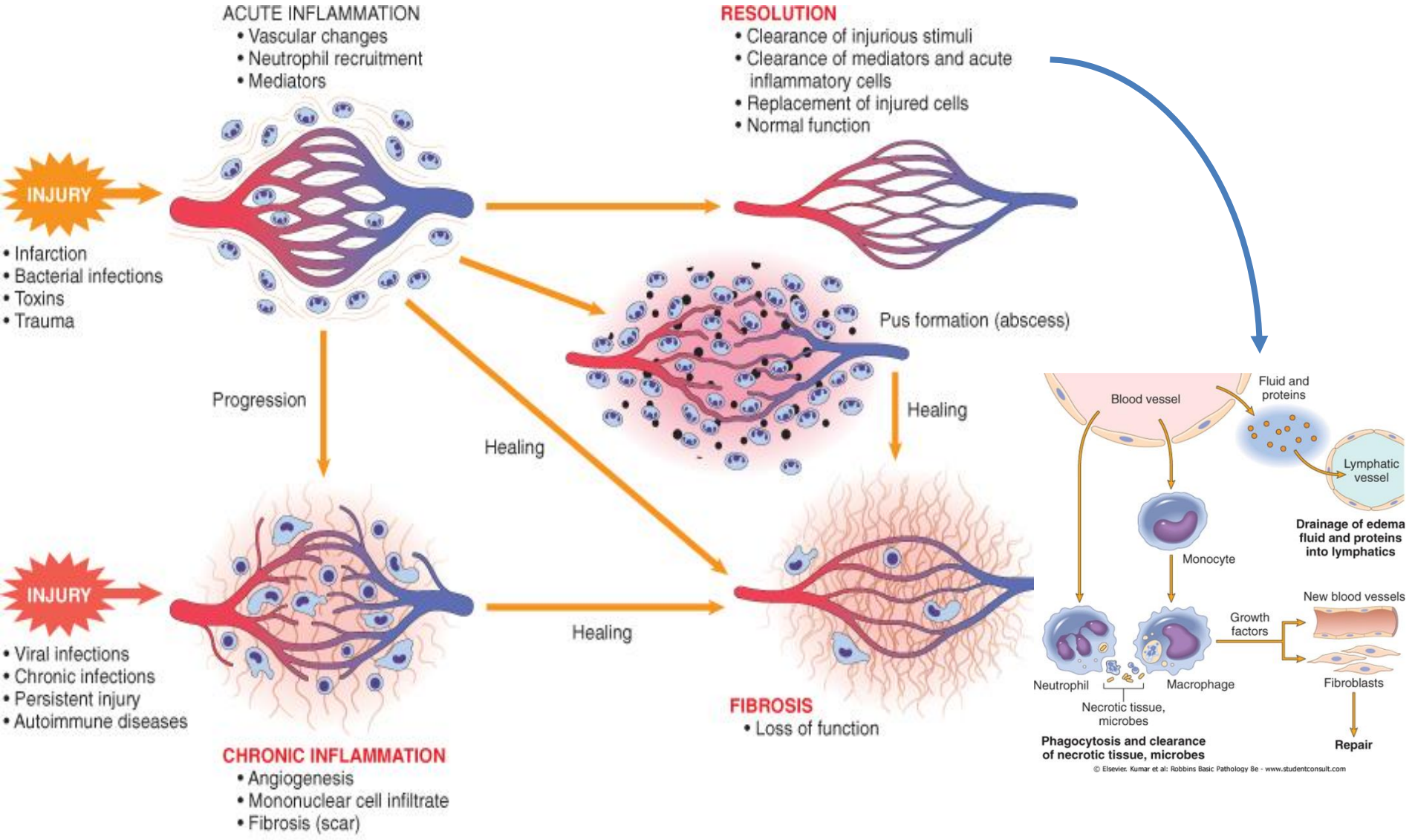


Outcomes of Acute Inflammation

- Complete resolution
- Abscess formation
- Fibrosis
  - After substantial tissue destruction
  - In tissues that do not regenerate
  - After abundant fibrin exudation, especially in serous cavities (pleura, peritoneum)
- Progression to chronic inflammation

Types of Inflammation: acute vs. chronic

Types of repair: resolution vs. organization (fibrosis)



Acute Inflammation — Morphological types

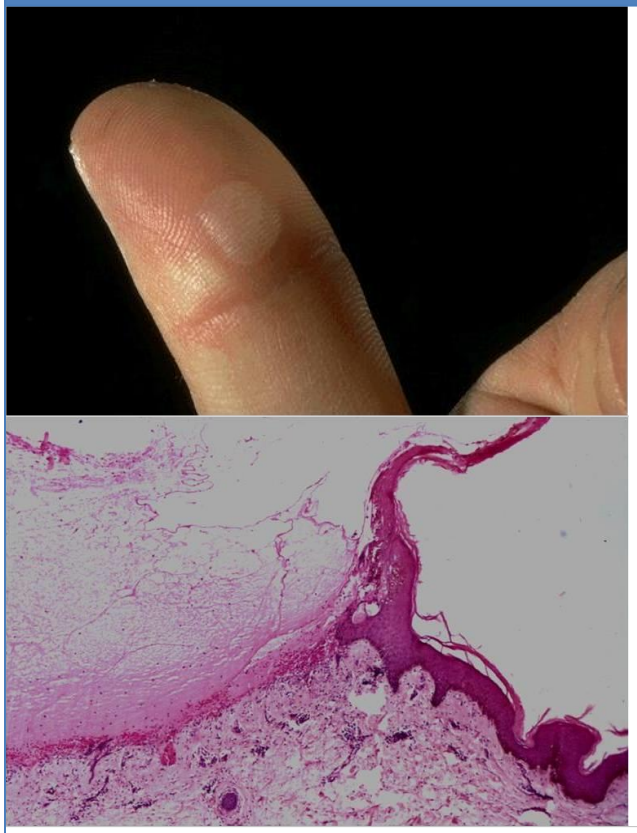
1. Serous inflammation
2. Fibrinous inflammation
3. Suppurative inflammation
4. Pseudomembranous inflammation
5. Catarrhal inflammation
6. Serosanguinous inflammation

Morphologic Patterns of Acute Inflammation

- Serous inflammation: Outpouring of thin fluid (serous effusion, blisters)
- Fibrinous inflammation: Body cavities; leakage of fibrin; may lead to scar tissue (adhesions)
- Suppurative (purulent) inflammation: Pus or purulent exudate (neutrophils, debris, edema fluid); abscess: localized collections of pus
- Ulcers: Local defect of the surface of an organ or tissue produced by the sloughing (shedding) of inflammatory necrotic tissue

Inflammation

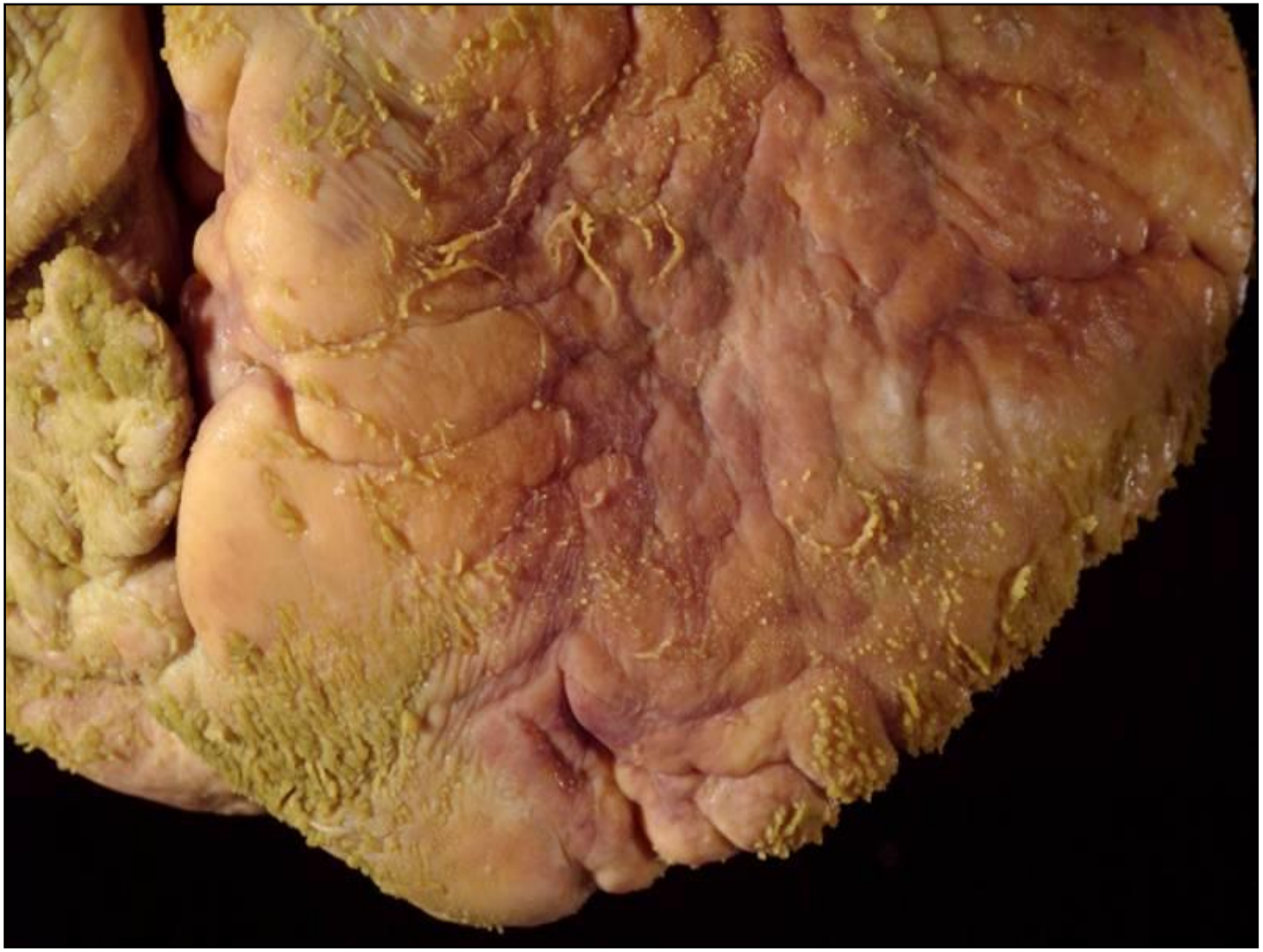
Serous Inflammation



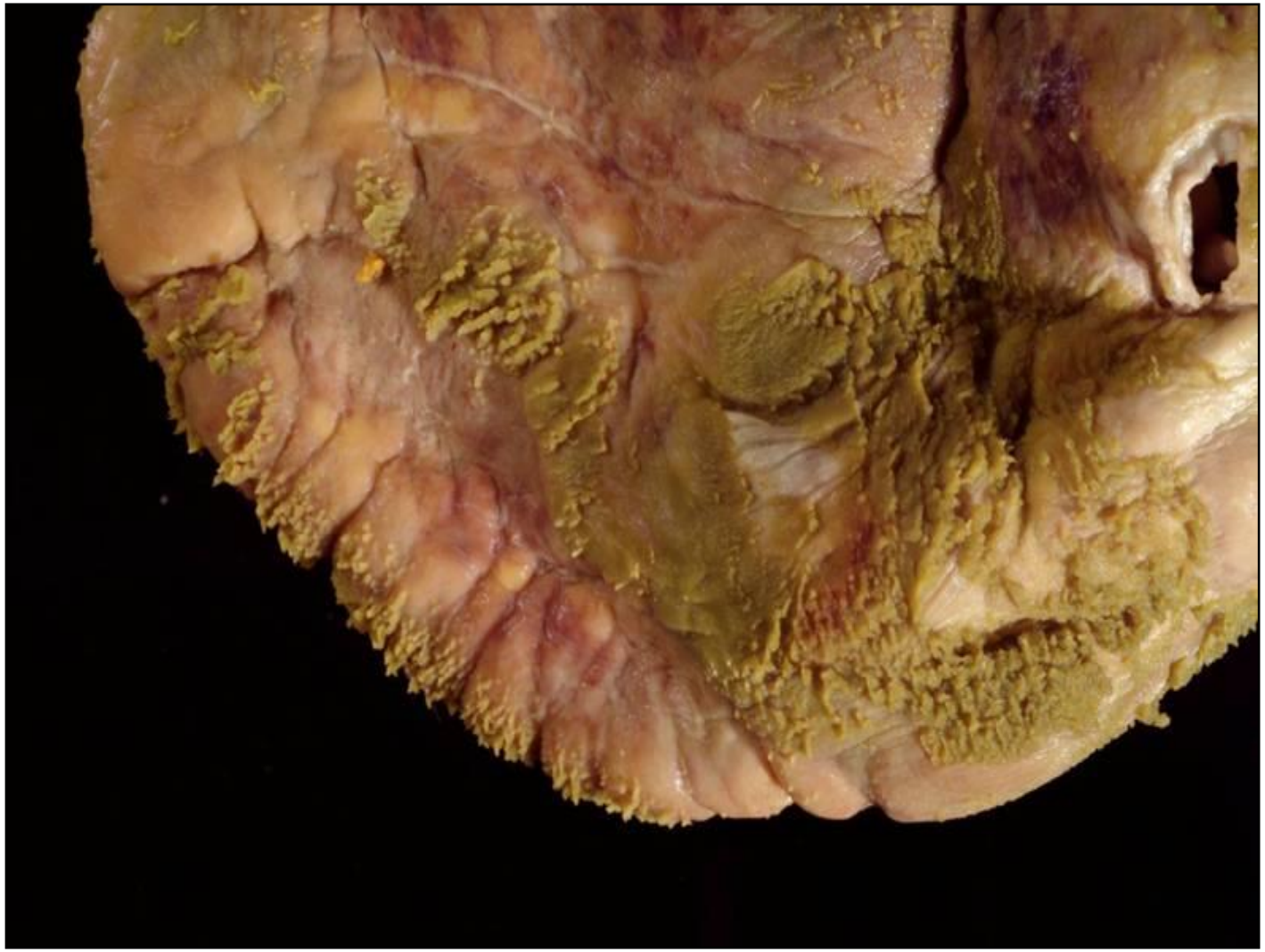
Blister

This example of serous exudate collection, a blister of the skin, occurs after minor burns or friction.

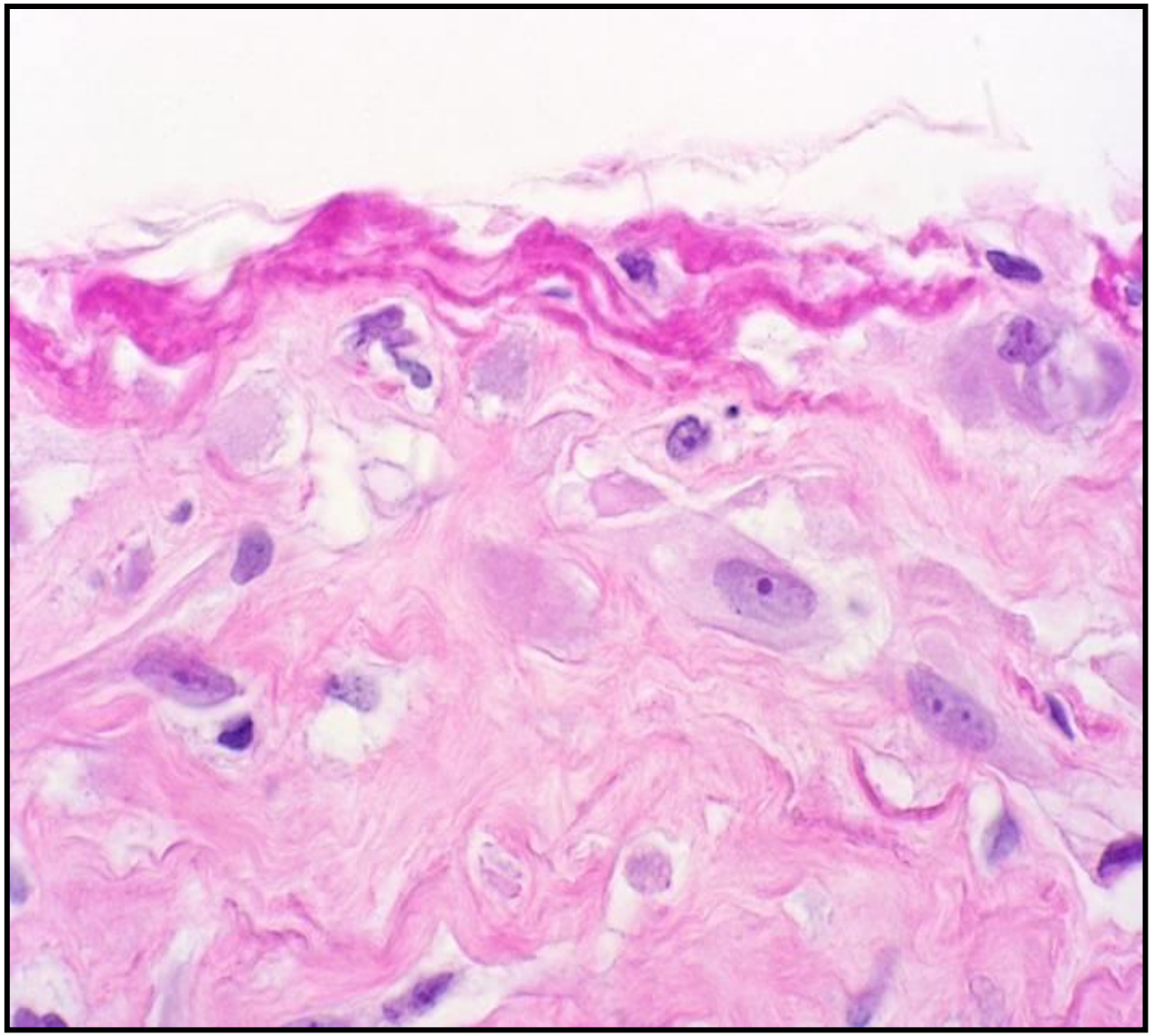
Fibrinous Pericarditis



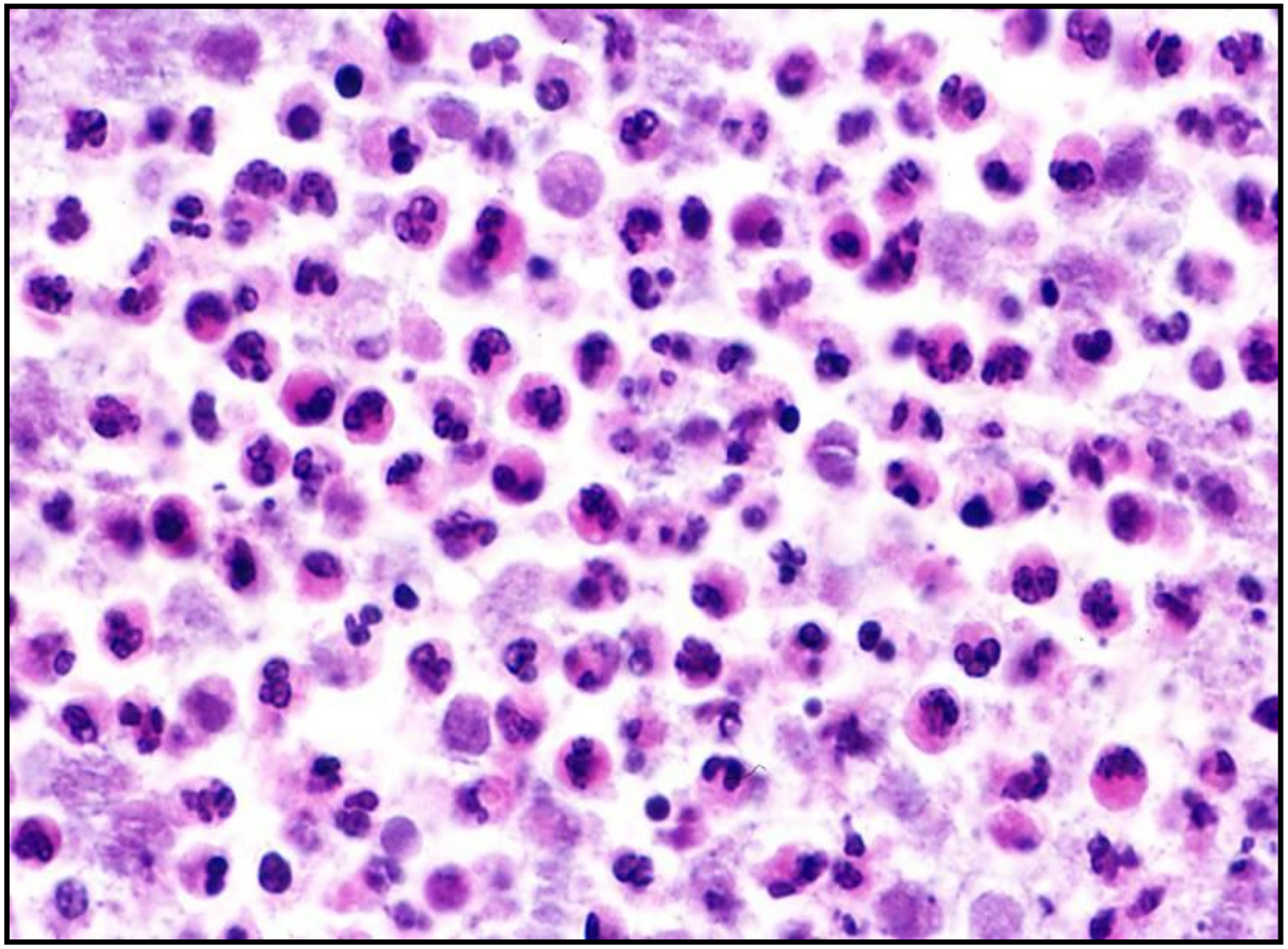
Fibrinous Pericarditis



Fibrinous Pleuritis

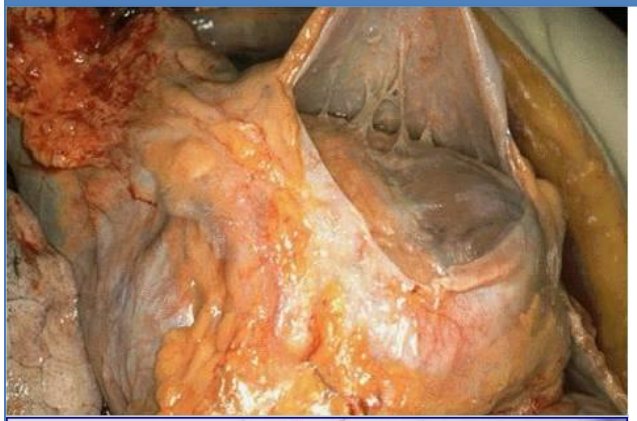


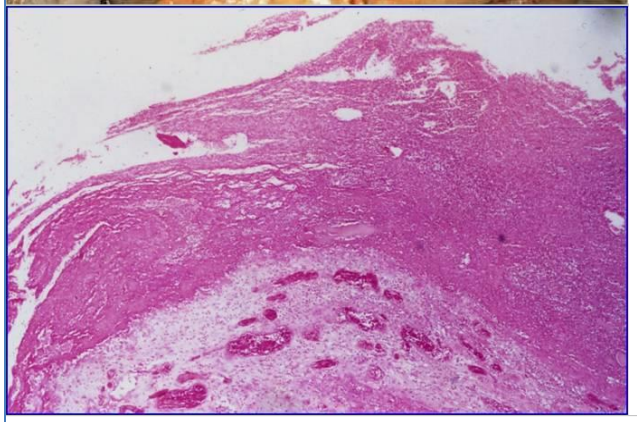
Suppurative (purulent) inflammation: Abscess



Inflammation

Fibrinous Inflammation

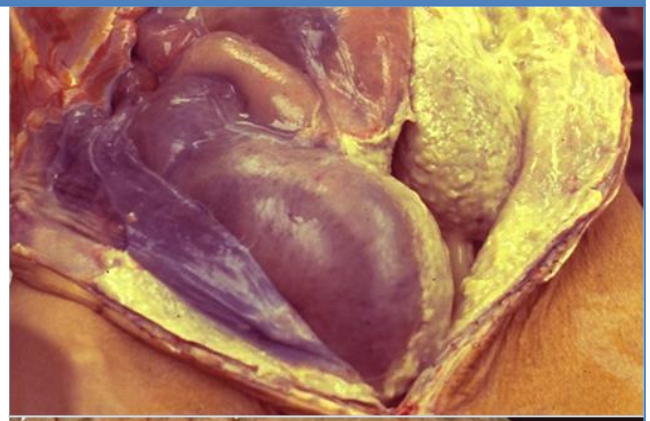




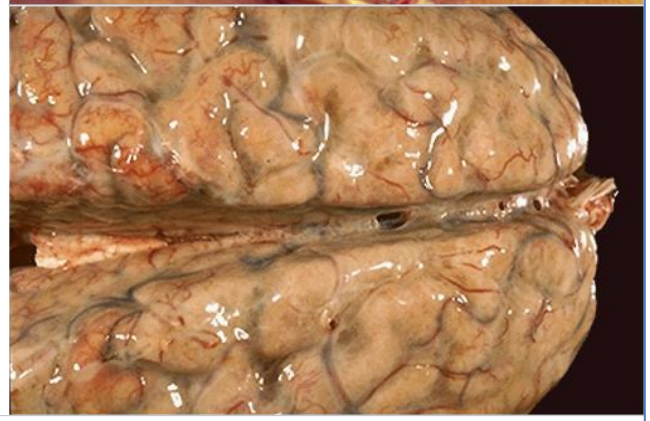
Here, the pericardial cavity has been opened to reveal a fibrinous pericarditis with strands of stringy pale fibrin between visceral and parietal pericardium (fibrinous exudate is rich in fibrin). Fibrin may organise into fibrous tissue giving raise to adhesive pericarditis

Suppurative Inflammation

The abdominal cavity is opened at autopsy here to reveal an extensive purulent peritonitis that resulted from rupture of the colon. The exudate is Pus (purulent). It is thick, yellow fluid rich in neutrophils

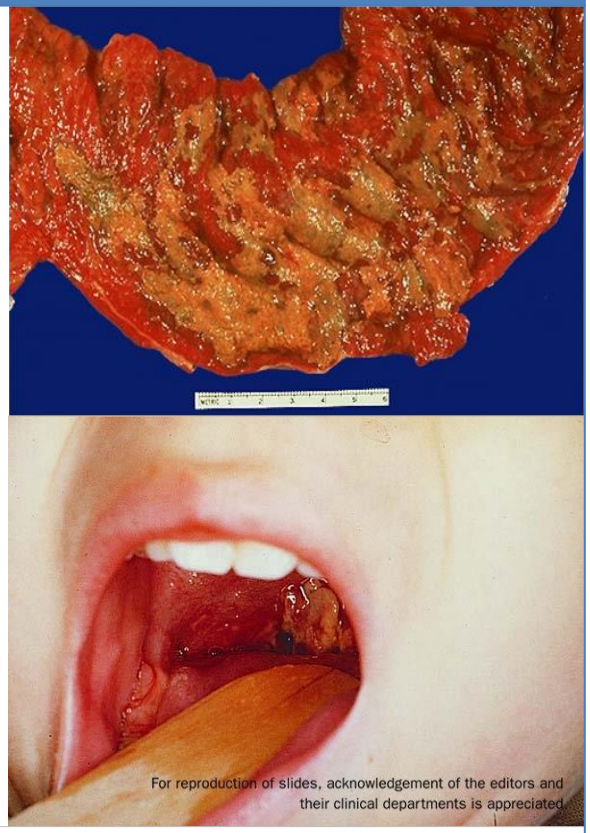


A purulent exudate is seen beneath the meninges in the brain of this patient with acute meningitis from Streptococcus pneumoniae infection. The exudate obscures the sulci.



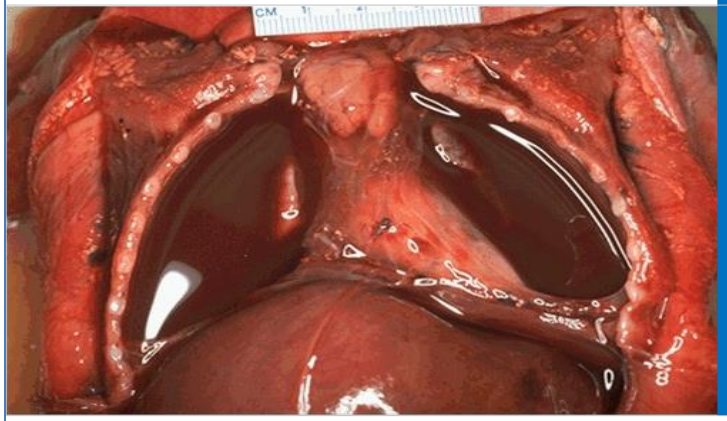
Pseudomembranous Inflammation

This yellow-green exudate on the surface of an inflamed, hyperemic (erythematous) mucosa (bowel & throat) consists of many neutrophils along with fibrin and amorphous debris from dying cells. This type of exudate forms a pseudomembrane in *Clostridium difficile* caused colitis & Diphtheria



Serosanguinous Inflammation

Here is an example of bilateral pleural effusions. Note that the fluid appears reddish, because there has been hemorrhage into the effusion. This is a serosanguinous effusion.

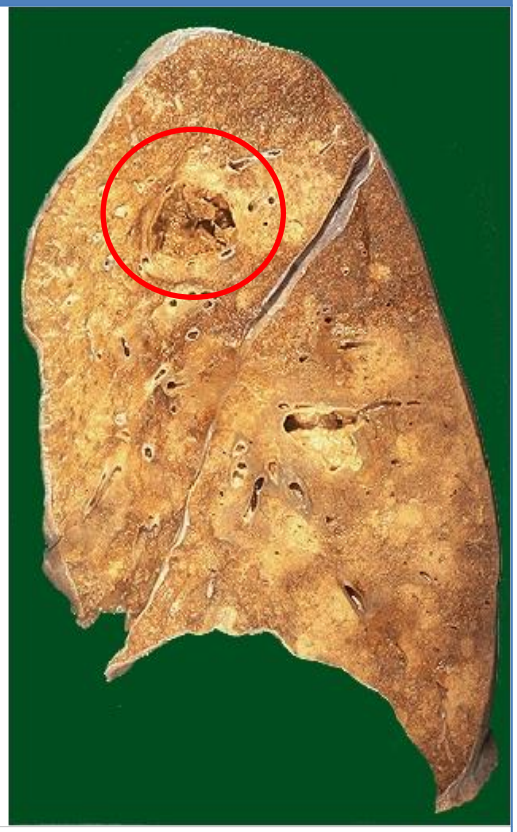


Catarrhal Inflammation

Catarrh is the inflammation of the mucous membrane, especially in the nose and throat, accompanied by increased production of mucus. It is most commonly associated with the common cold.

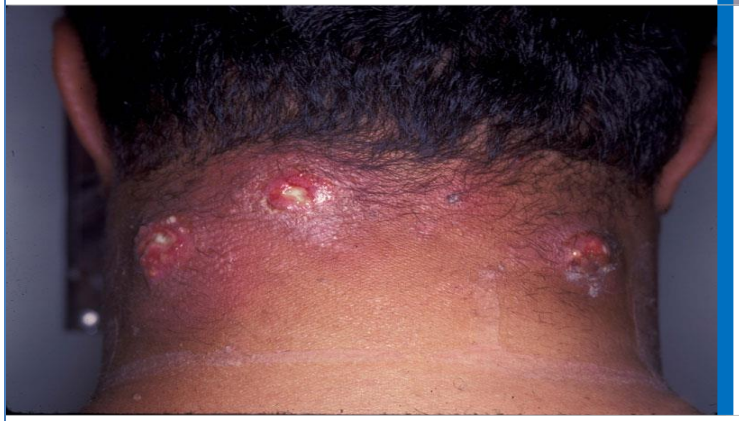
Abscess

(Localised collection of pus)
is the result of a Liquefactive necrosis of the parechyma caused by pyogenic organism resulting in the formation of one or more cavities filled with pus (purulent exudate).
It has a central necrosis, rimmed by neutrophils and surrounded by fibroblasts.
If pus collects within pleural cavity, gall bladder, it is callled empyema

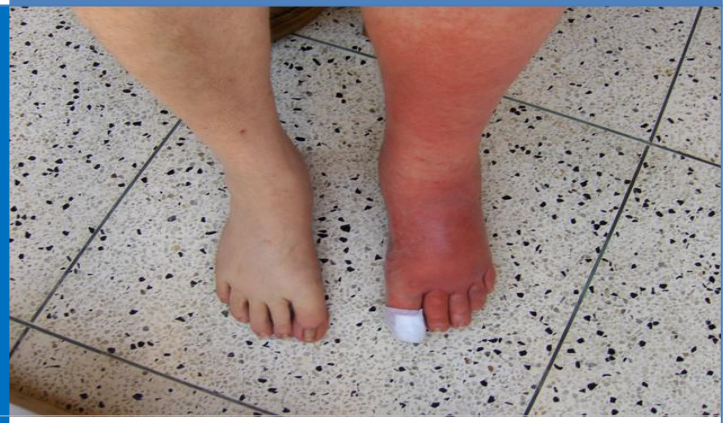


Carbuncles

Sometimes boils occur in clusters called carbuncles. Although anyone can develop, people who have diabetes, a suppressed immune system are at increased risk.

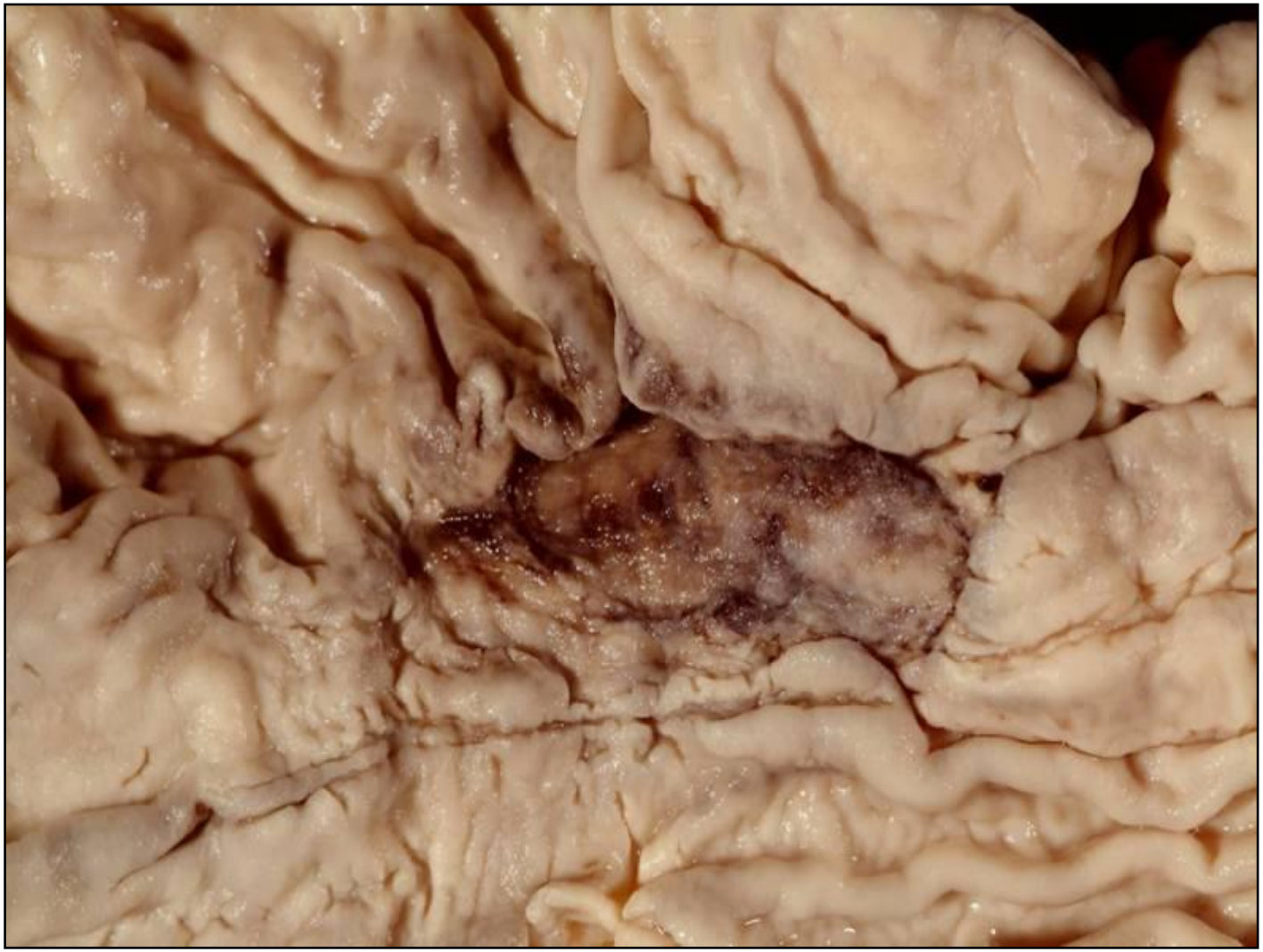


Cellulitis



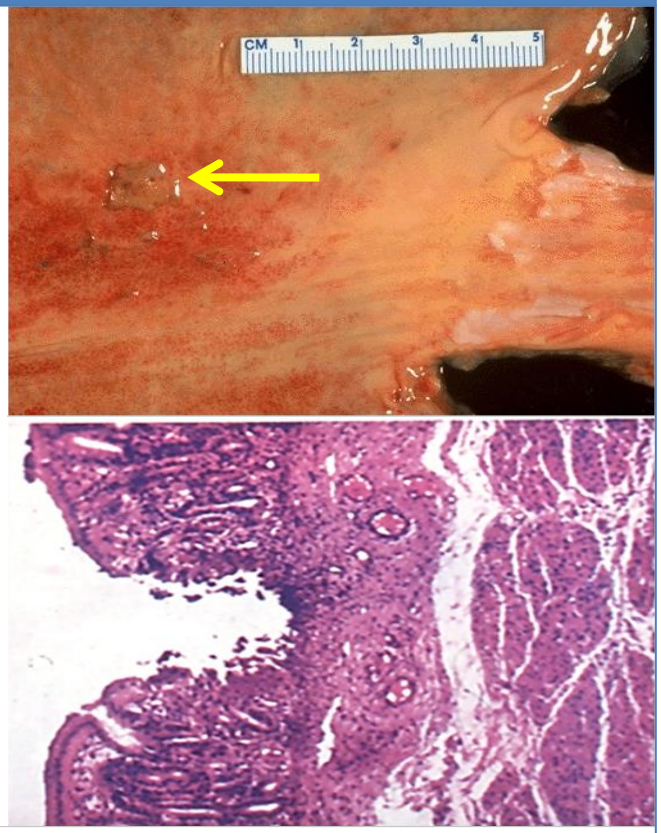
an infection of the skin and underlying tissues caused most commonly by group *A Streptococcus* and *Staphylococcus aureus.*

Gastric Ulcer

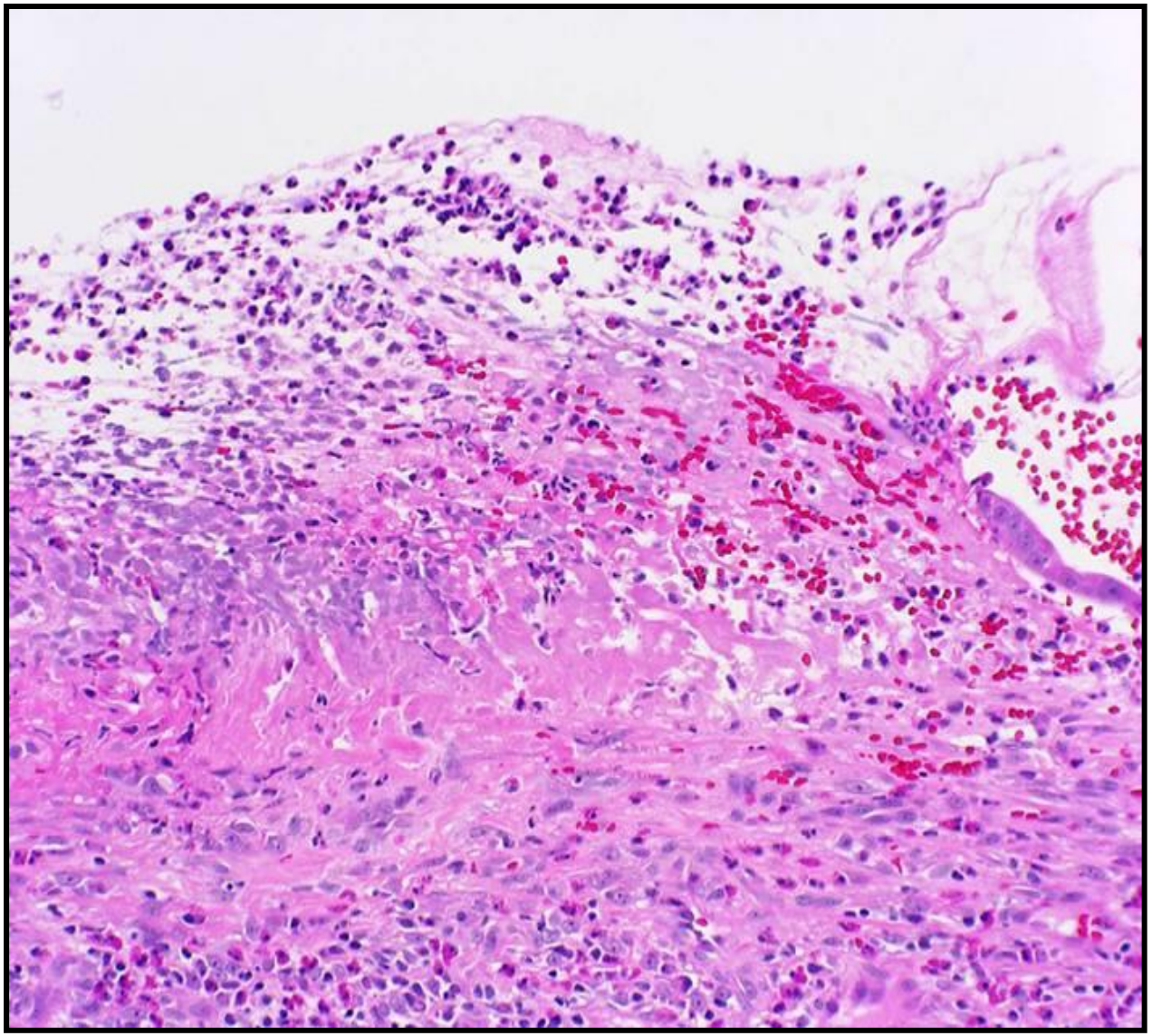


Ulcer

An ulcer is a local defect/discontinuity of mucosal lining produced by shedding of necrotic tissue. Superficial ulcers are called erosions



Gastric Ulcer



Systemic Manifestations

- Endocrine and metabolic
  - Secretion of acute phase proteins by the liver
  - Increased production of glucocorticoids (stress response)
  - Decreased secretion of vasopressin leads to reduced volume of body fluid to be warmed
- Fever
  - Improves efficiency of leukocyte killing
  - Impairs replication of many offending organisms

Systemic Manifestations

- Autonomic
  - Redirection of blood flow from skin to deep vascular beds minimizes heat loss
  - Increased pulse and blood pressure
- Behavioral
  - Shivering (rigors), chills (search for warmth), anorexia (loss of appetite), somnolence, and malaise

Systemic Manifestations

- Leukocytosis: increased leukocyte count in the blood
  - Neutrophilia: bacterial infections
  - Lymphocytosis: infectious mononucleosis, mumps, measles
  - Eosinophilia: Parasites, asthma, hay fever
- Leukopenia: reduced leukocyte count
  - Typhoid fever, some viruses, rickettsiae, protozoa

CHEMICAL MEDIATORS OF INFLAMMATION

Dr.Jagan.C
Associate Professor
Dept of Pathology
VMCH & RI

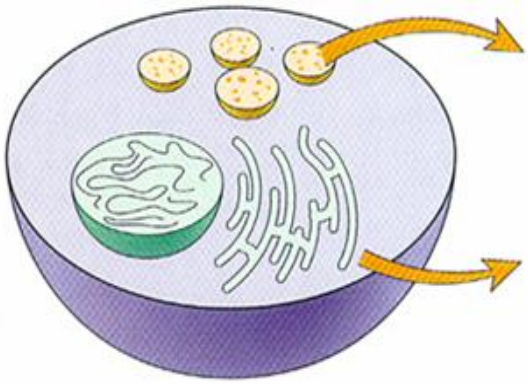
BRIEF OVERVIEW OF TOPIC

- General principles
- Classification
- Discussion of individual types
- Summary

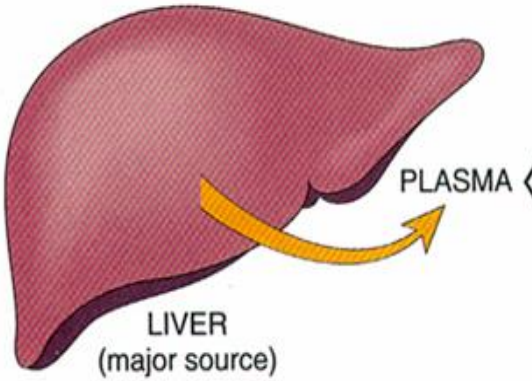
General Principles

- May be derived from plasma or cells
- Most bind to specific receptors on target cells
- Can stimulate release of mediators by target cells, which may amplify or ameliorate the inflammatory response
- May act on one or a few target cells, have widespread targets, and may have differing effects depending on cell and tissue types
- Usually short-lived
- Most have potential to cause harmful effects

CLASSIFICATION



	MEDIATORS	SOURCE
Preformed mediators in secretory granules	Histamine	Mast cells, basophils, platelets
	Serotonin	Platelets
	Lysosomal enzymes	Neutrophils, macrophages
Newly synthesized	Prostaglandins	All leukocytes, platelets, EC
	Leukotrienes	All leukocytes
	Platelet-activating factors	All leukocytes, EC
	Activated oxygen species	All leukocytes
	Nitric oxide	Macrophages
	Cytokines	Lymphocytes, macrophages, EC



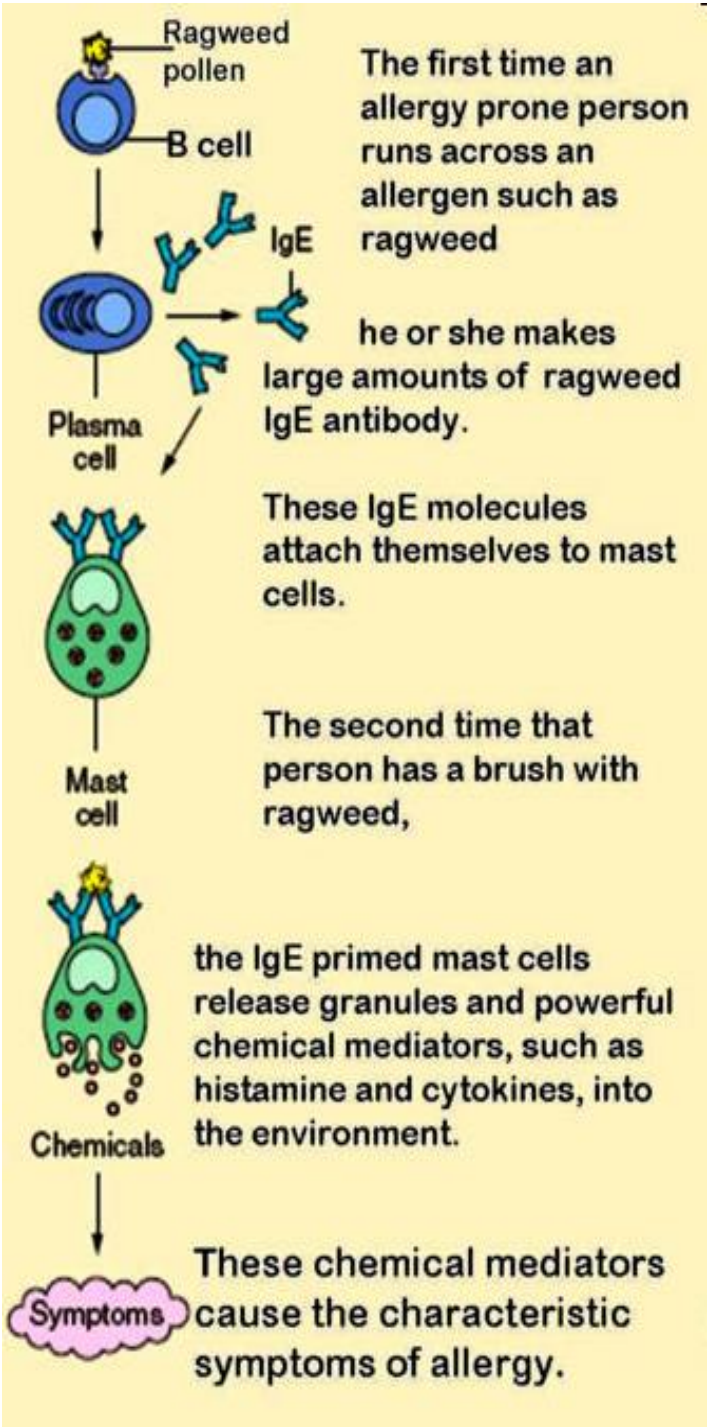
Factor XII (Hageman factor) activation	Kinin system (bradykinin)	
	Coagulation / fibrinolysis system	
Complement activation	C_{3a}	anaphylatoxins
	C_{5a}	anaphylatoxins
	C_{3b}	
	C_{5b-9}	(membrane attack complex)

CLASSIFICATION…

- Vasoactive mediators
  - Histamine
  - Bradykinin
  - Complement (C3a, C5a)
  - Prostaglandins/leukotrienes
  - Platelet activating factor
  - Nitric oxide
- Chemotactic factors
  - Complement (C5a)
  - Leukotriene (B4)
  - Platelet activating factor
  - Cytokines (IL-1, TNF)
  - Chemokines
  - Nitric oxide

Histamine

- Mast cells (also basophils and platelets)
- Release mechanisms
  - Binding of antigen (allergen) to IgE on mast cells releases histamine-containing granules
  - Release by nonimmune mechanisms such as cold, trauma, or other chemical mediators
  - Release by other mediators
- Dilates arterioles and increases permeability of venules (wheal and flare reaction)



Complement

- Proteins found in greatest concentration in the plasma
- Require activation
- Increase vascular permeability and cause vasodilation
  - Mainly by releasing histamine from mast cells
- Increase leukocyte adhesion, chemotaxis, and activation
- C3b attaches to bacterial wall and enhances phagocytosis by neutrophils & macrophages

Bradykinin

- Small peptide released from plasma precursors
- Increases vascular permeability
- Dilates blood vessels
- Causes pain
- Rapid inactivation

Arachidonic Acid Metabolites

- Prostaglandins
  - Vasodilators: prostacyclin (PGI_2), PGE_1, PGE_2, PGD_2
  - Vasoconstrictors: thromboxane A_2
  - Pain (PGE_2 makes tissue hypersensitive to bradykinin)
  - Fever (PGE_2)
  - Production blocked by steroids and nonsteroidal anti-inflammatory agents (NSAIDs)
- Leukotrienes
  - Increase vascular permeability: leukotrienes C_4, D_4, E_4
  - Vasoconstriction: leukotrienes C_4, D_4, E_4
  - Leukocyte adhesion & chemotaxis: leukotriene B_4, HETE, lipoxins
  - Production blocked by steroids but <u>not</u> conventional NSAIDs

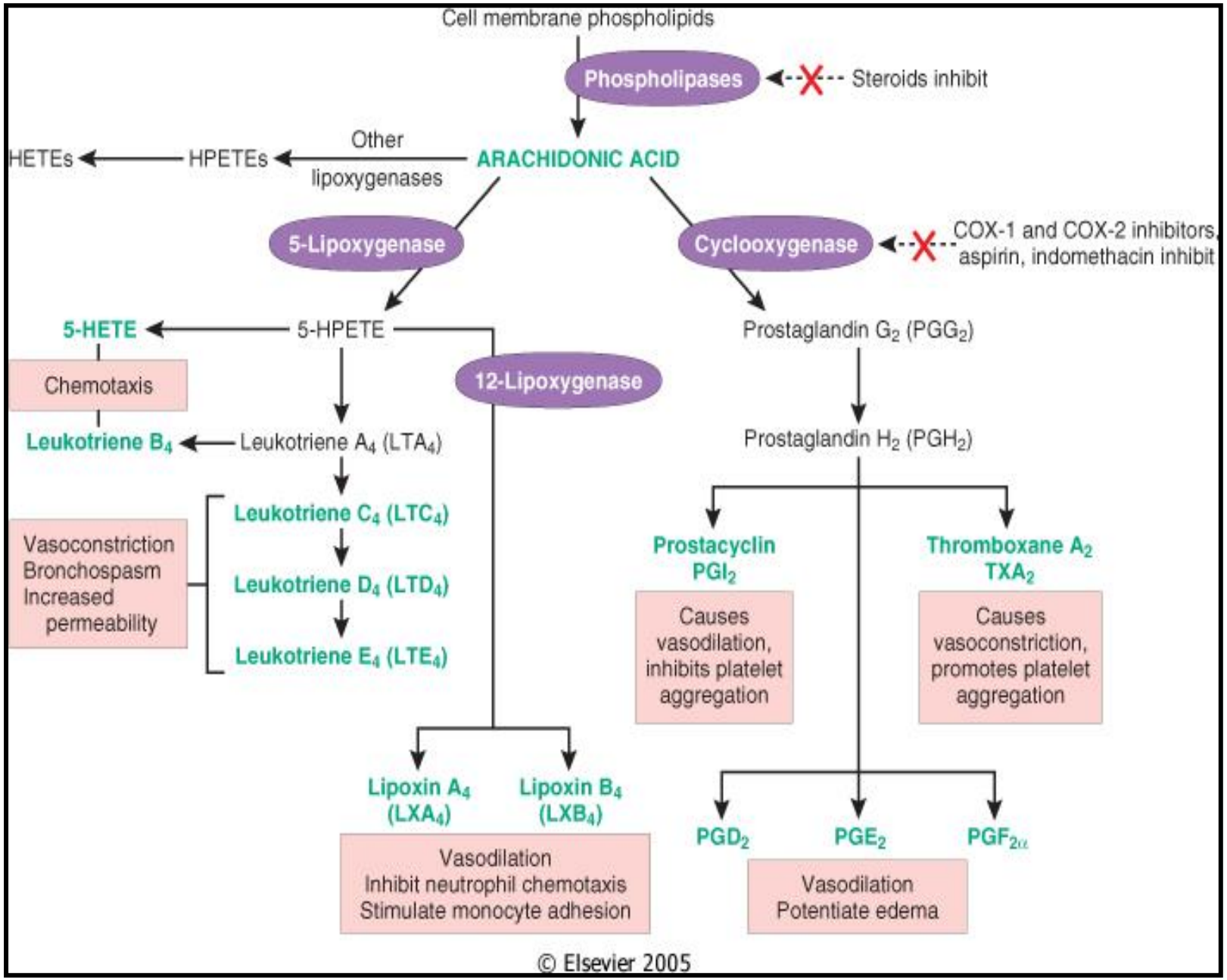


Figure 2-16 Robbins and Cotran Pathologic Basis of Disease, 7th Ed.

Platelet Activating Factor

- Subclass of phospholipids
- Synthesized by stimulated platelets, leukocytes, endothelium
- Inflammatory effects
  - Stimulates platelet aggregation
  - Vasoconstriction and bronchoconstriction
  - Vasodilation and increased venular permeability
  - Increased leukocyte adhesion to endothelium, chemotaxis, degranulation, and oxidative burst
  - Increases synthesis of arachidonic acid metabolites by leukocytes and other cells

Cytokines

- Proteins produced by many cell types (principally activated lymphocytes & macrophages)
- Modulate the function of other cell types
- Interleukin-1 (IL-1) and tumor necrosis factor (TNF) are the major cytokines that mediate inflammation

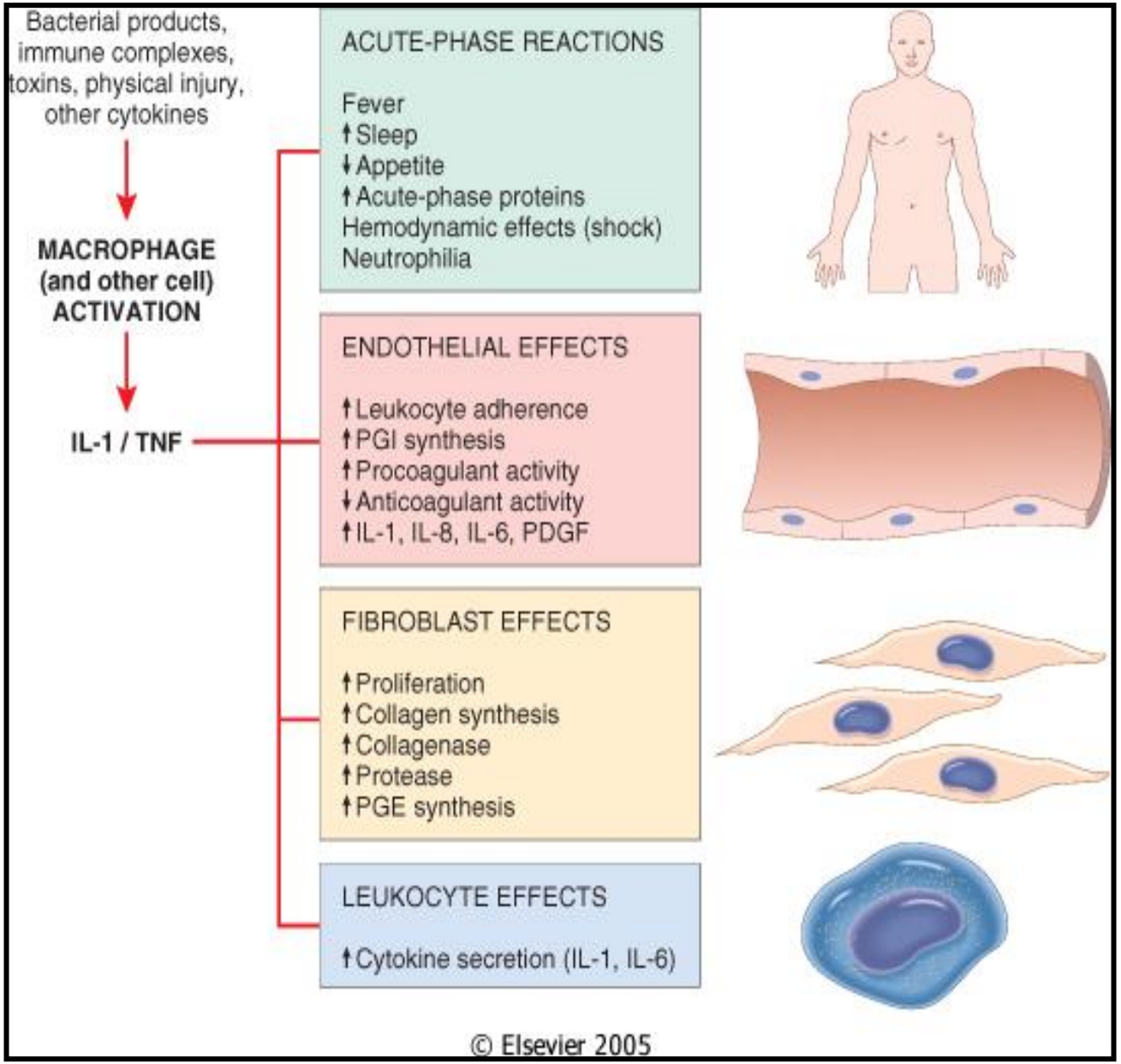


Figure 2-18 Robbins and Cotran Pathologic Basis of Disease, 7th Ed.

Chemokines

- Small proteins that act primarily as chemoattractants for specific types of leukocytes (approximately 40 known)
- Stimulate leukocyte recruitment in inflammation
- Control the normal migration of cells through tissues (organogenesis and maintenance of tissue organization)
- Examples: IL-8, eotaxin, lymphotactin

Nitric Oxide

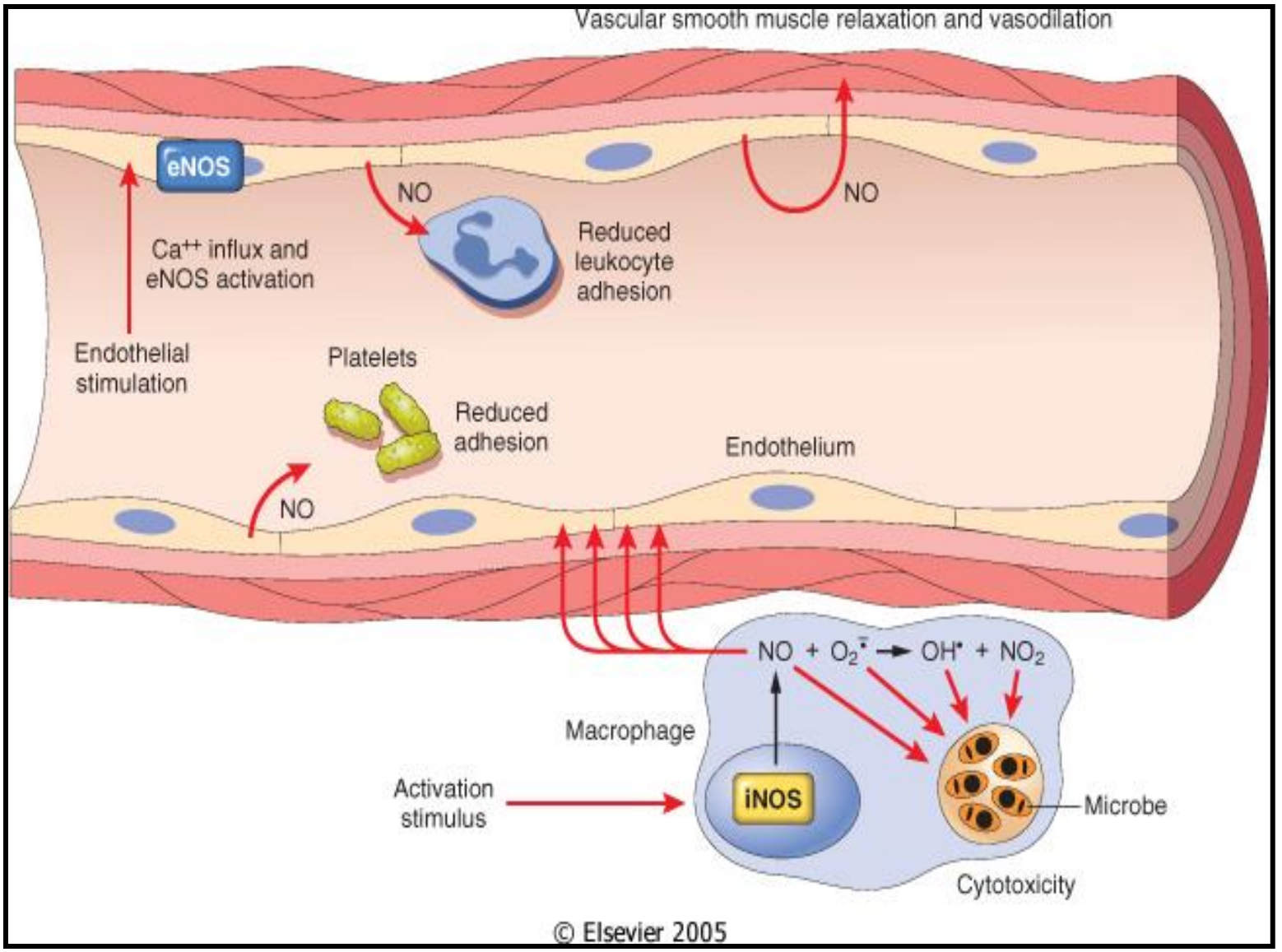


Figure 2-19 Robbins and Cotran Pathologic Basis of Disease, 7th Ed.

Other Mediators

- Neutrophil granules:
  - Cationic proteins increase vascular permeability, immobilize neutrophils, chemotactic for mononuclear phagocytes
  - Neutral proteases generate other mediators and degrade tissue
- Oxygen-Derived Free Radicals:
  - Produced during phagocytosis by neutrophils (“respiratory burst”)
  - Tissue damage including endothelium

Summary of Inflammatory Mediators

- Vasodilation
  - Prostaglandins
  - Nitric oxide
  - Histamine
- Increased vascular permeability
  - Histamine, serotonin
  - Complement (C3a, C5a)
  - Bradykinin
  - Leukotrienes (C_4, D_4, E_4)
  - Platelet Activating Factor
  - Substance P

Summary of Inflammatory Mediators

- Chemotaxis, leukocyte activation
  - Complement (C5a)
  - Leukotriene B_4
  - Chemokines
  - IL-1, TNF
  - Bacterial products
- Fever
  - Interleukin-1
  - Tumor necrosis factor
  - Prostaglandins

Summary of Inflammatory Mediators

- Pain
  - Prostaglandins
  - Bradykinin
- Tissue Damage
  - Neutrophil and macrophage lysosomal enzymes
  - Oxygen metabolites
  - Nitric oxide

THANK YOU