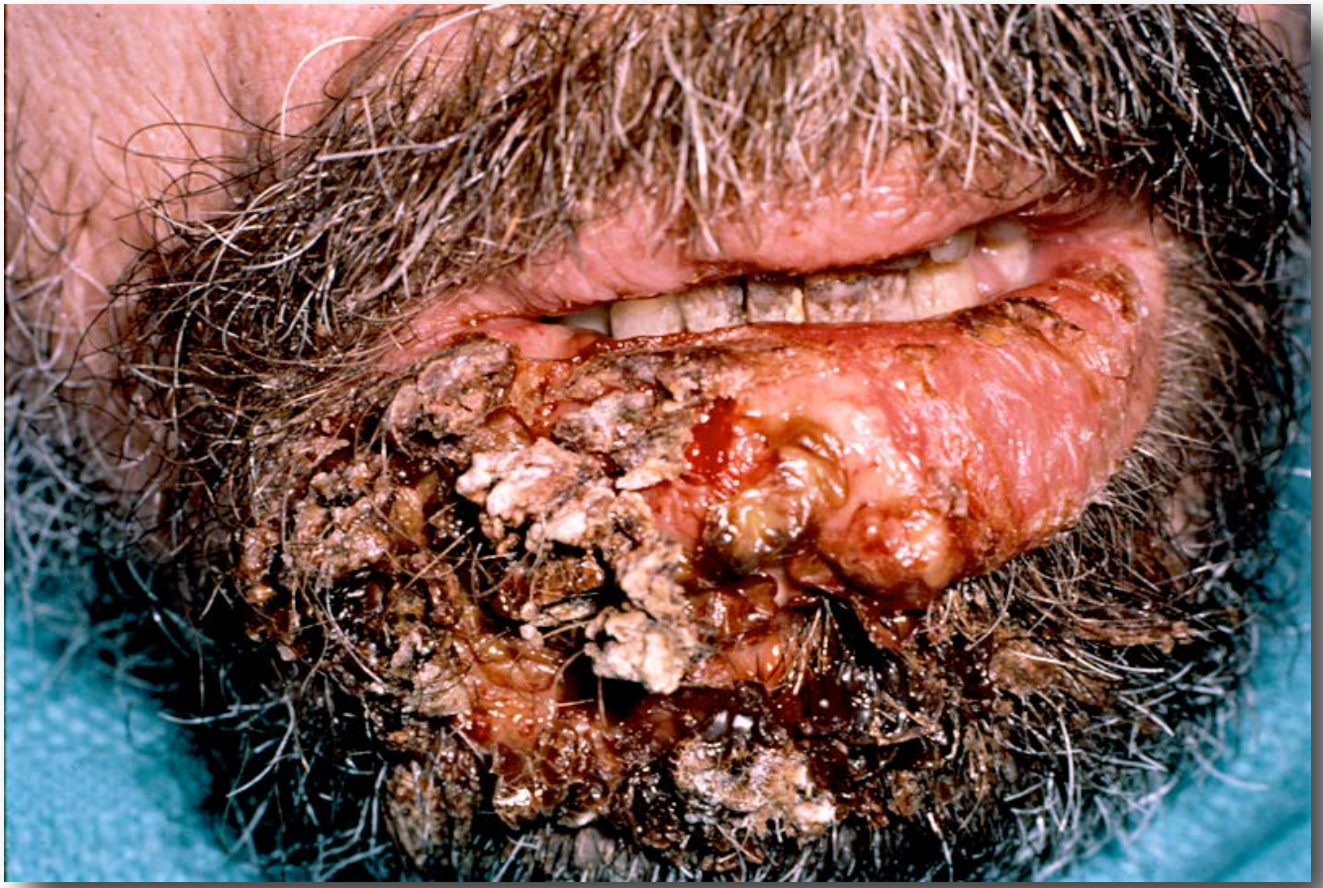
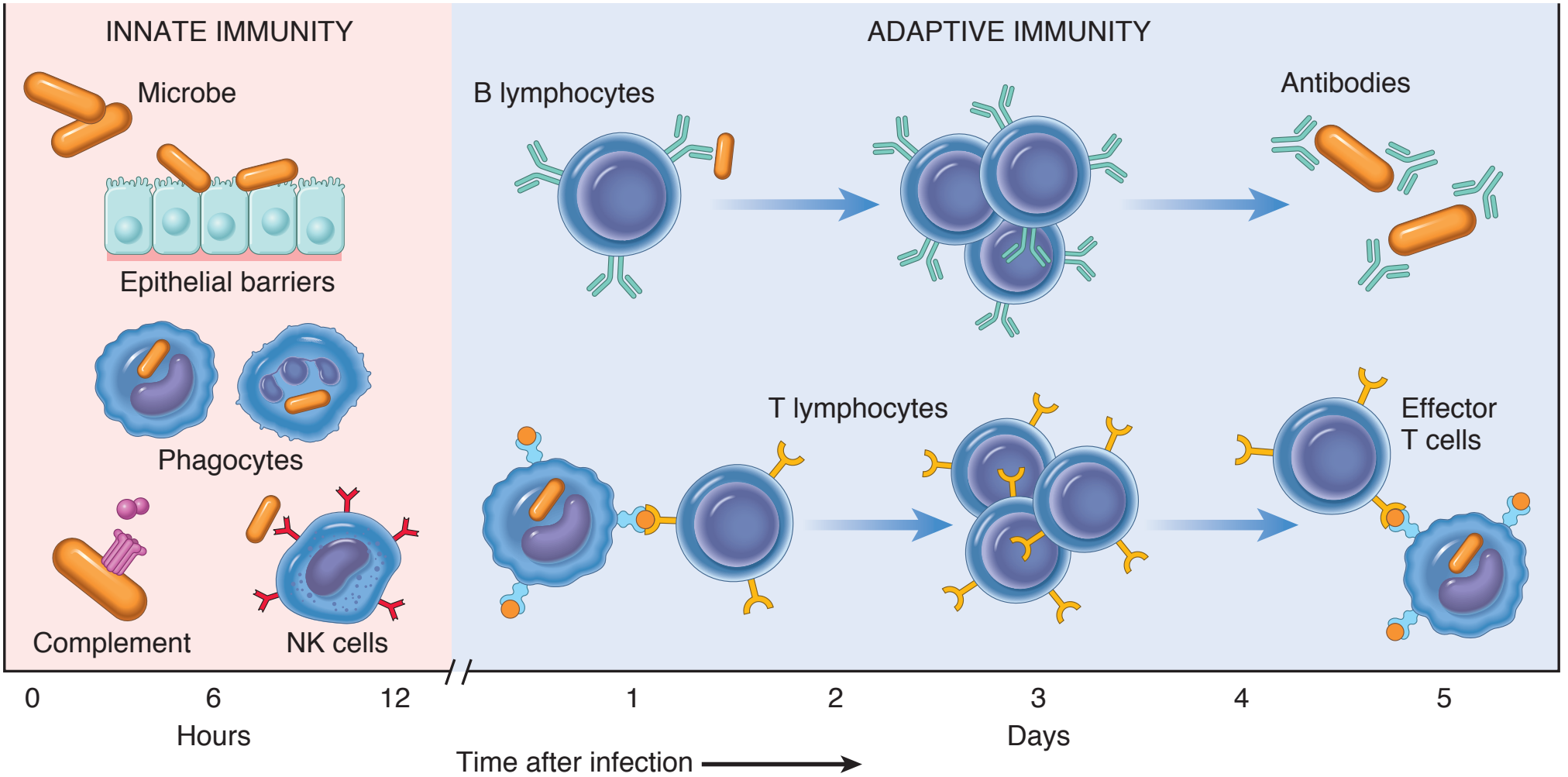
Acute Inflammation

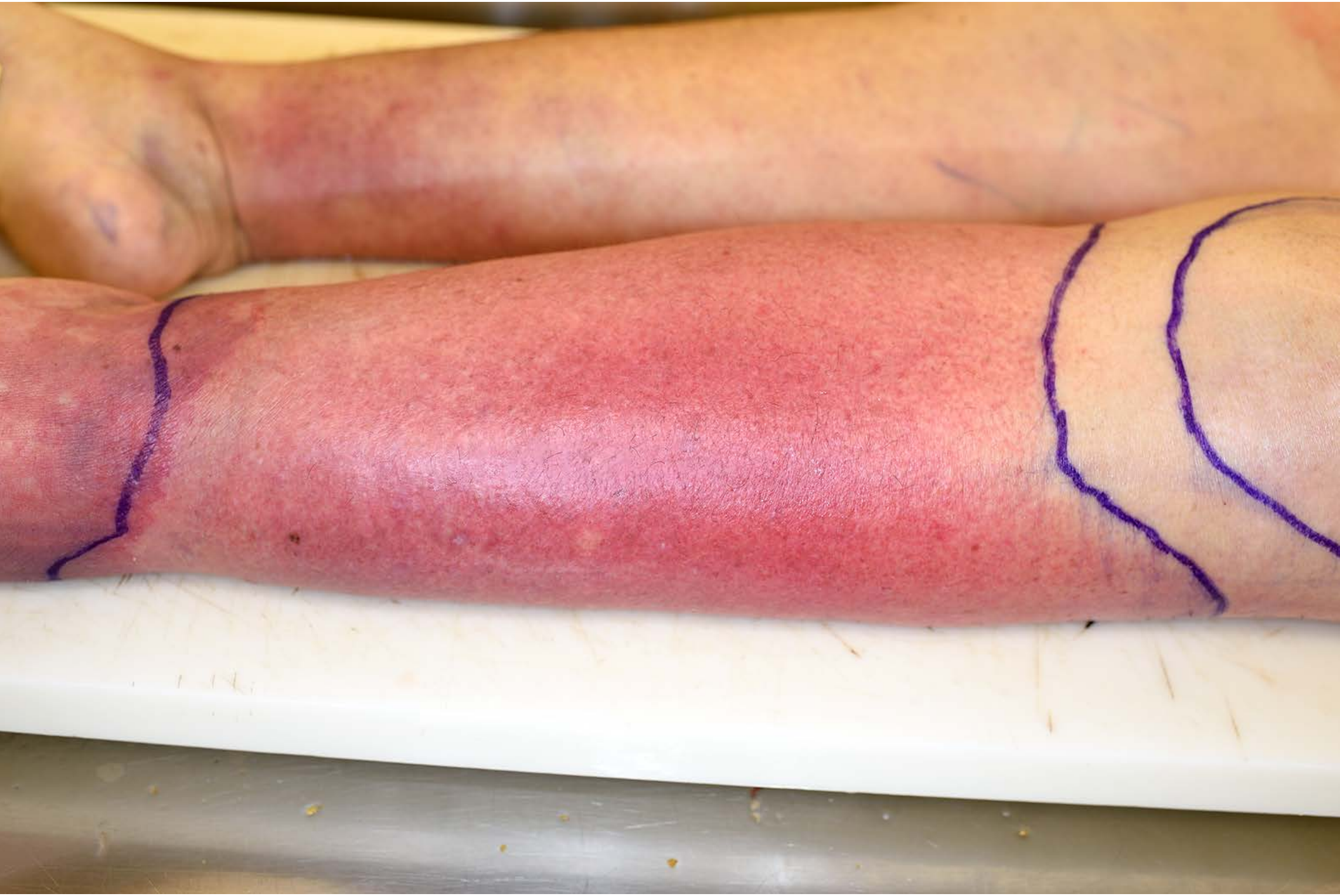


Dr. Henry Sanchez, M.D.

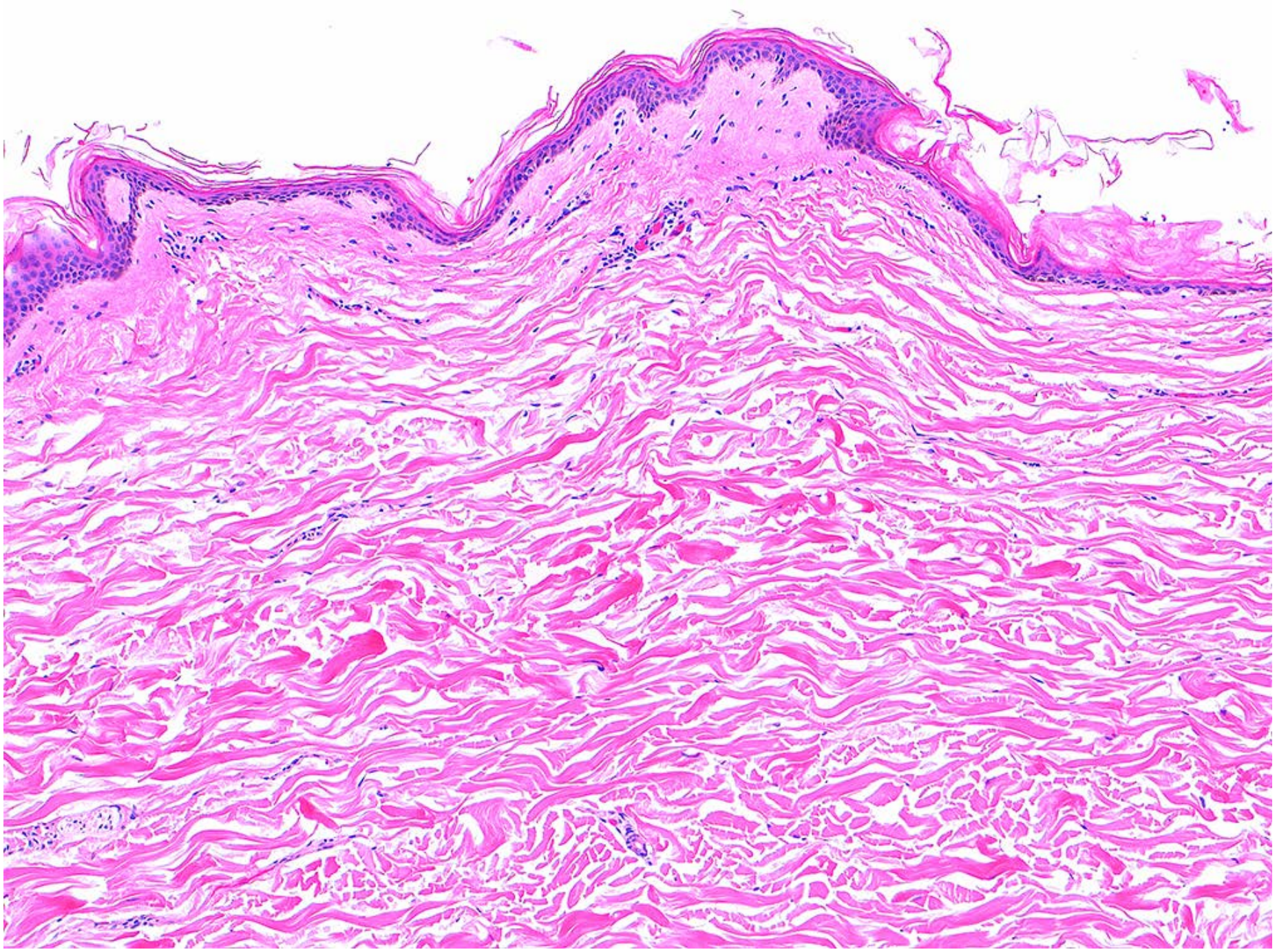
Components of Immunity



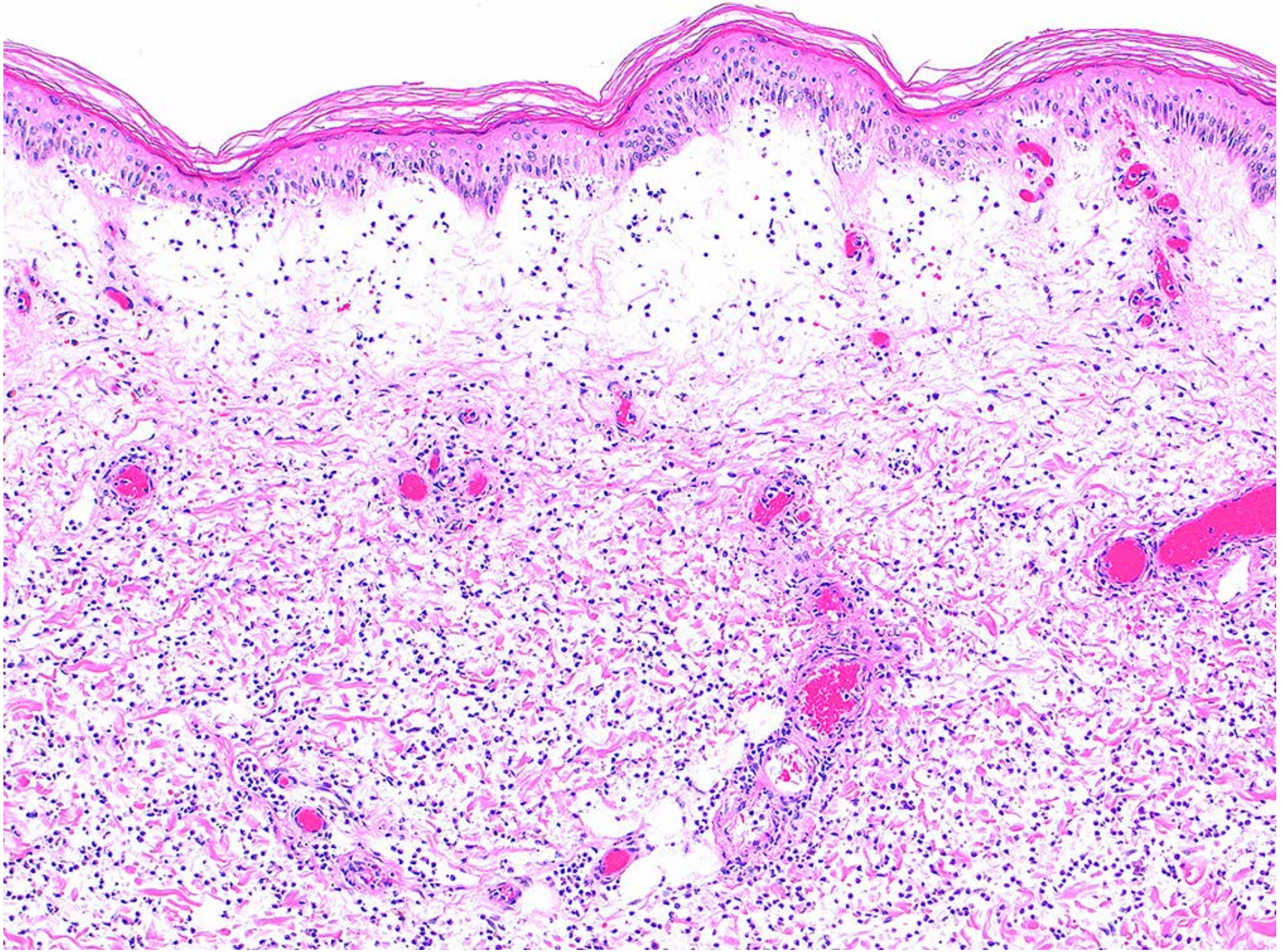
Acute Cellulitis



Uninvolved Normal Skin



Acute Cellulitis



Causes of Inflammation:

- Physical trauma
- Infection
- Tissue necrosis
- Immune reactions
- Thermal injury
- Foreign bodies
- Inoculated host-derived materials

Manifestations of an inflammatory response:

Variable:

- Fever
- Sleepiness (somnolence)
- Itching
- Local blood clotting

Components of the Acute Inflammatory Response

Universal (almost):

- Microvascular dilatation and leakiness
- Endothelial cell activation
- Leukocyte migration from blood into the tissue (“inflammatory infiltrate”)

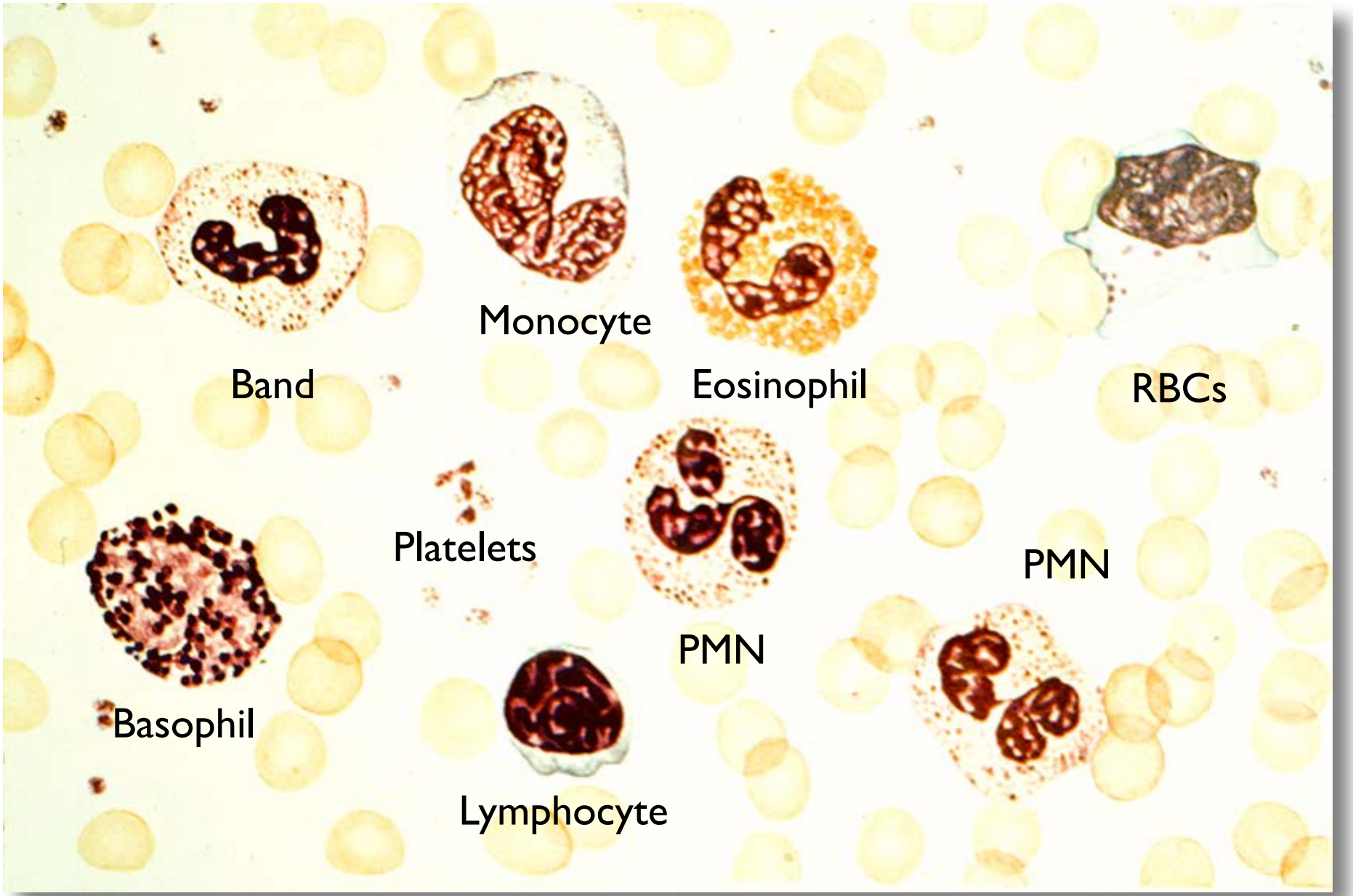
Cardinal Signs of Inflammation:

- Redness — ***rubor***
- Swelling (edema) — ***tumor***
- Warmth — ***calor***
- Pain — ***dolor***
- Loss of function

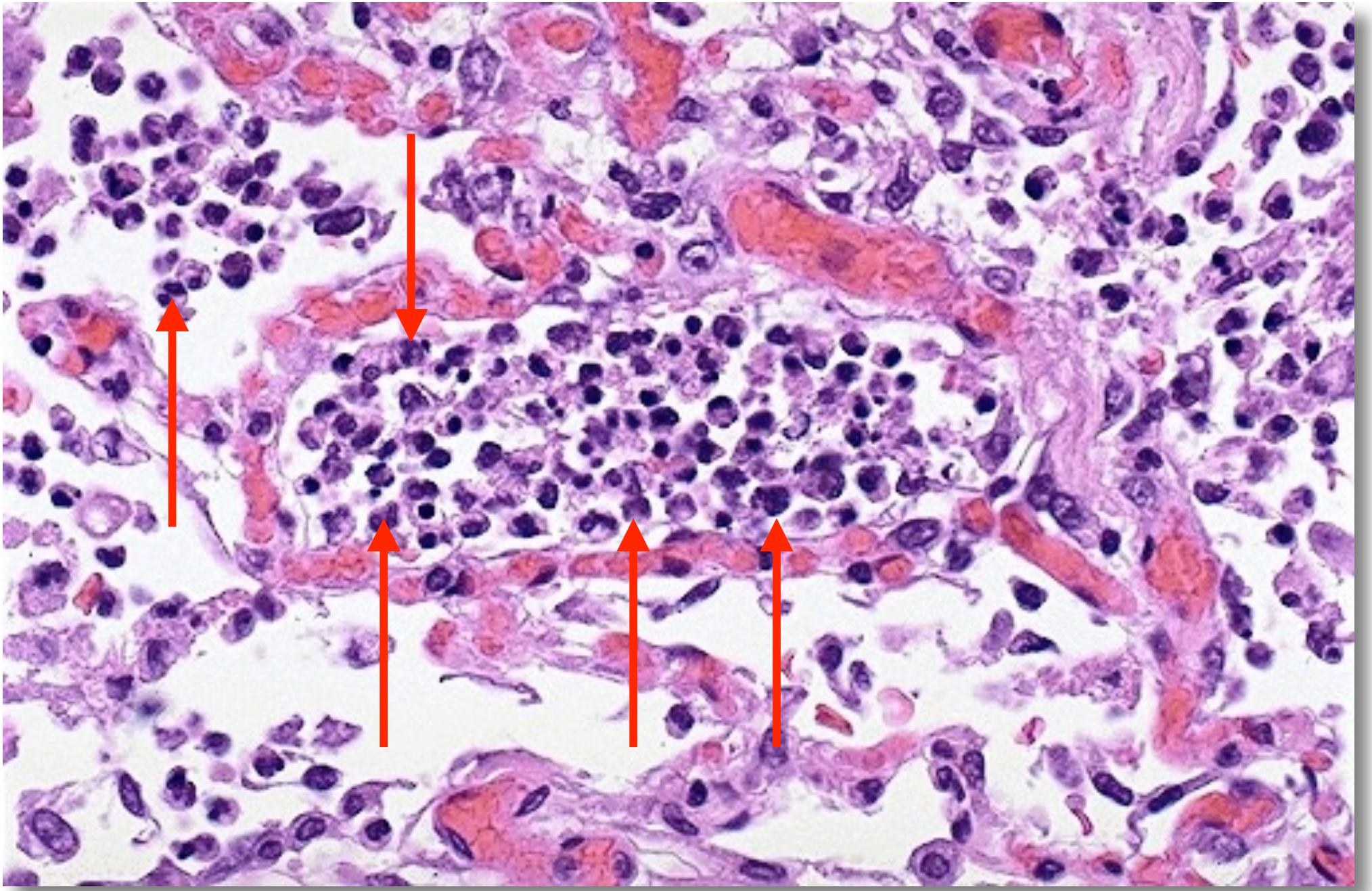
Acute vs Chronic Inflammation

	Onset	Cellular Infiltrate	Cardinal Signs
Acute	Fast (seconds to hours)	Neutrophils	Prominent
Chronic	Slow (days)	Macrophages and Lymphocytes	Less Prominent

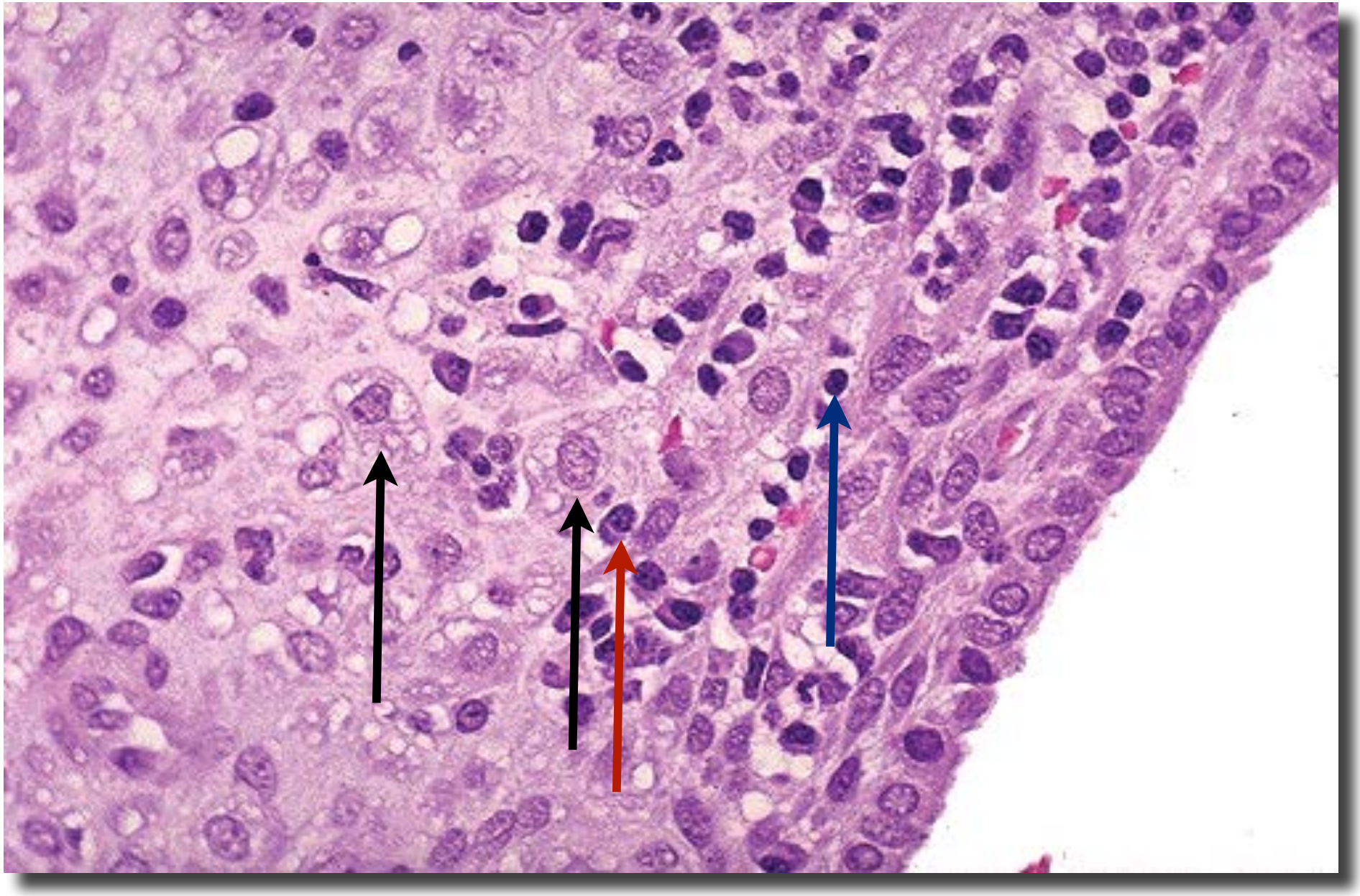
Peripheral Blood



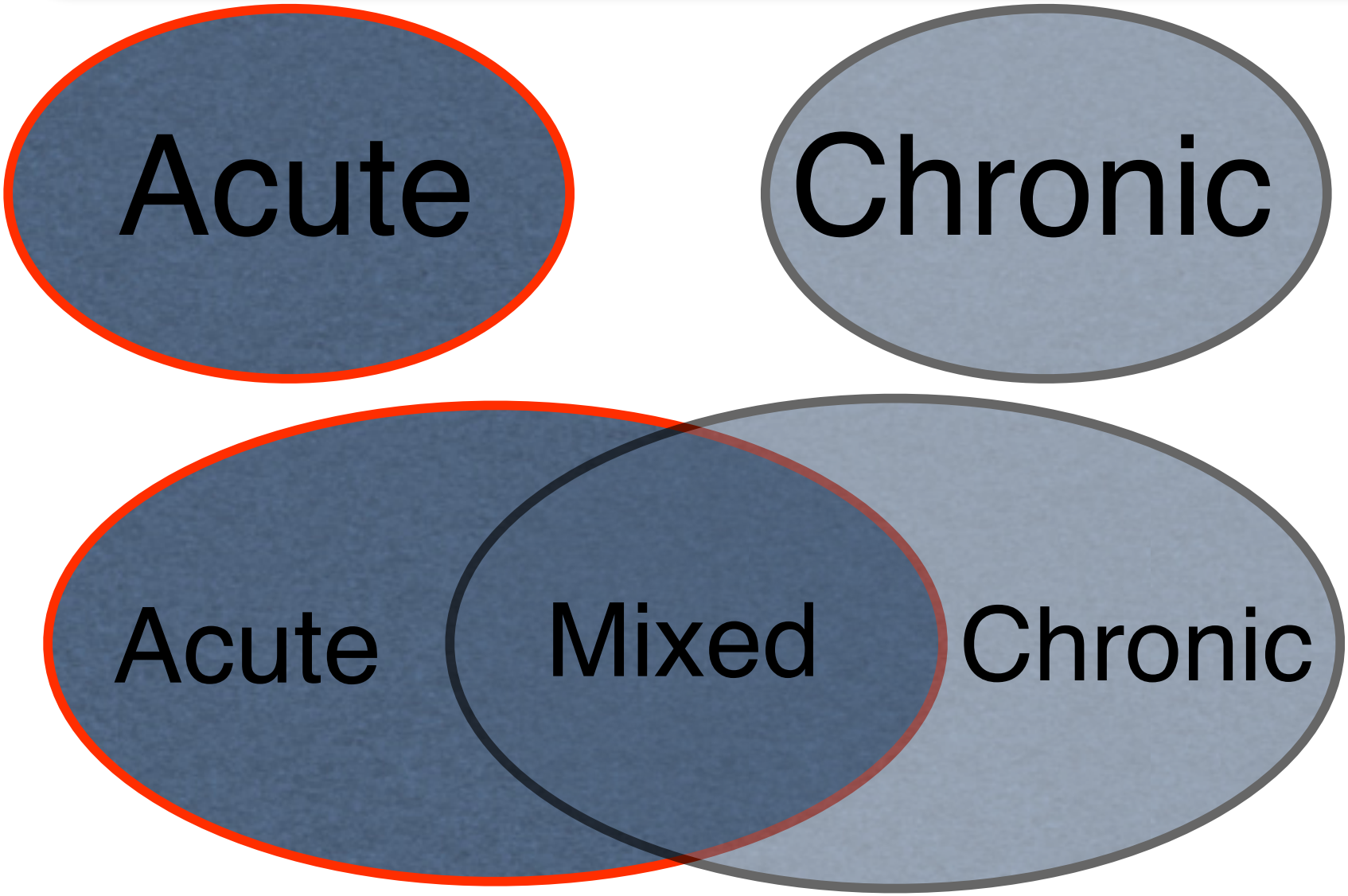
Acute Pneumonia



Chronic Inflammation

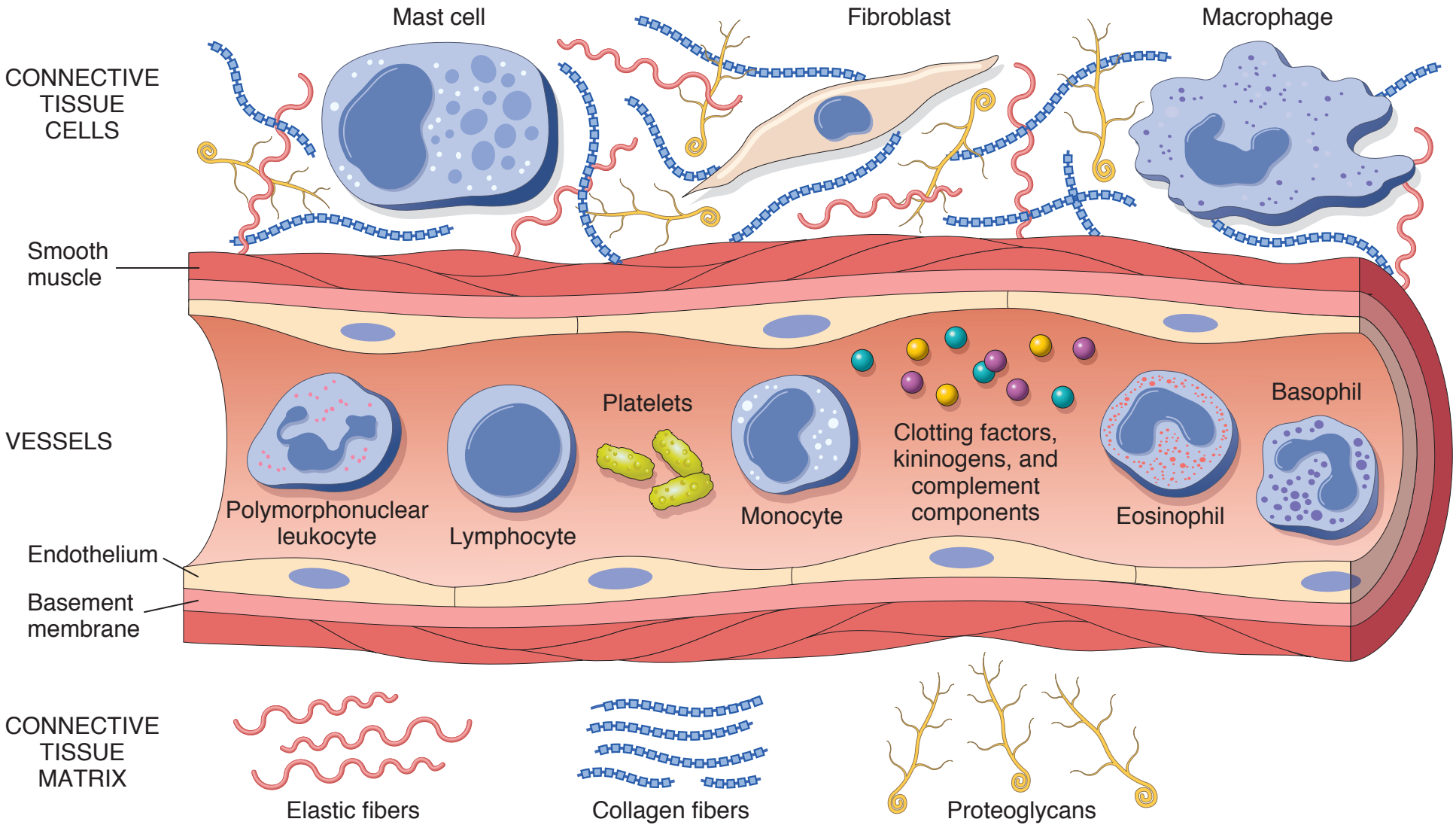


Types of Inflammation



Acute → Chronic

Intravascular and Extravascular Spaces



Components of the Acute Inflammatory Response:

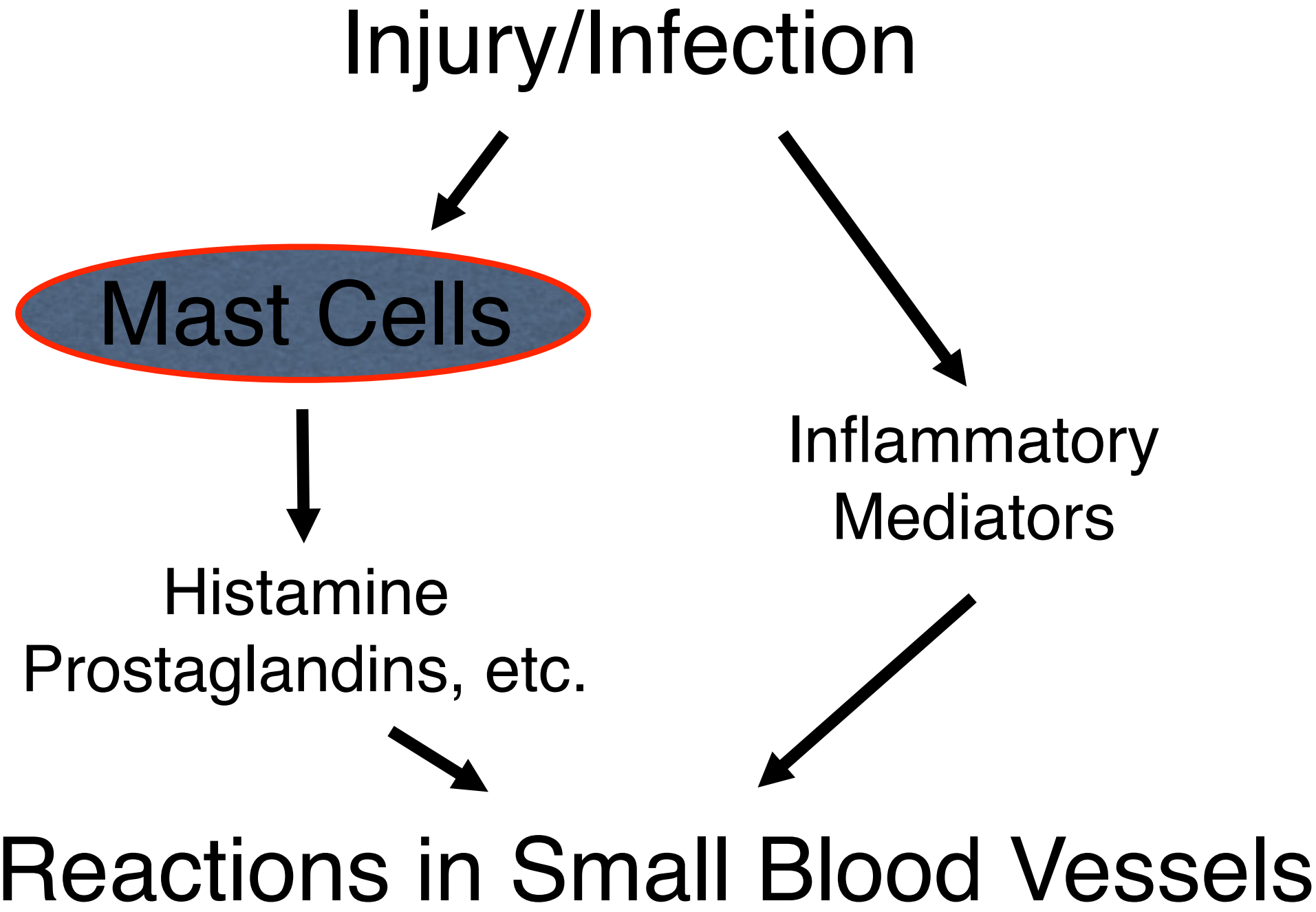
- Microvascular dilatation & leakiness
- Endothelial cell activation
- Leukocyte migration from blood (intravascular space) into the tissue (extravascular space)

Inflammatory Mediators:

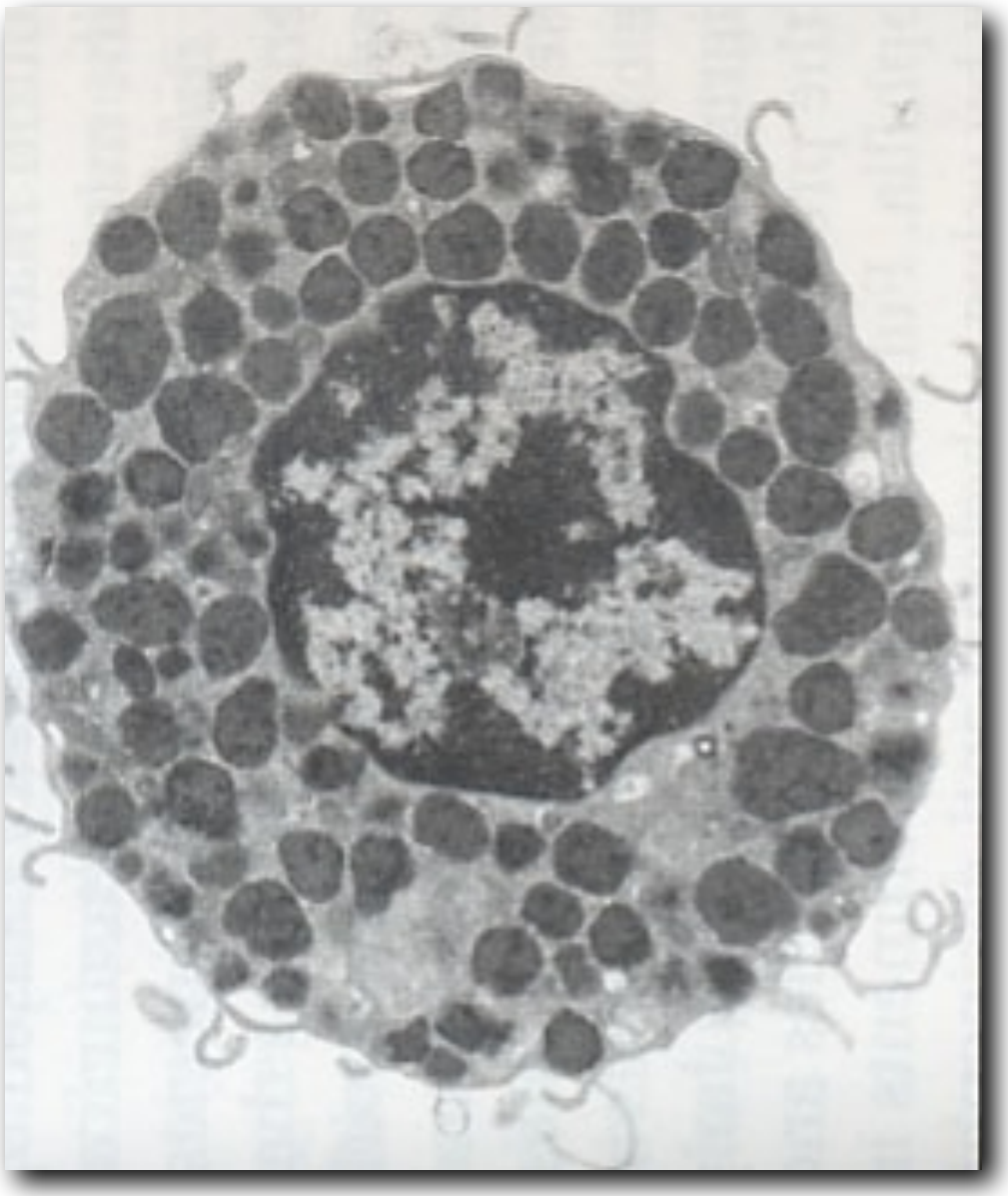
Soluble molecules that activate or regulate facets of the acute inflammatory response

Three major sources:

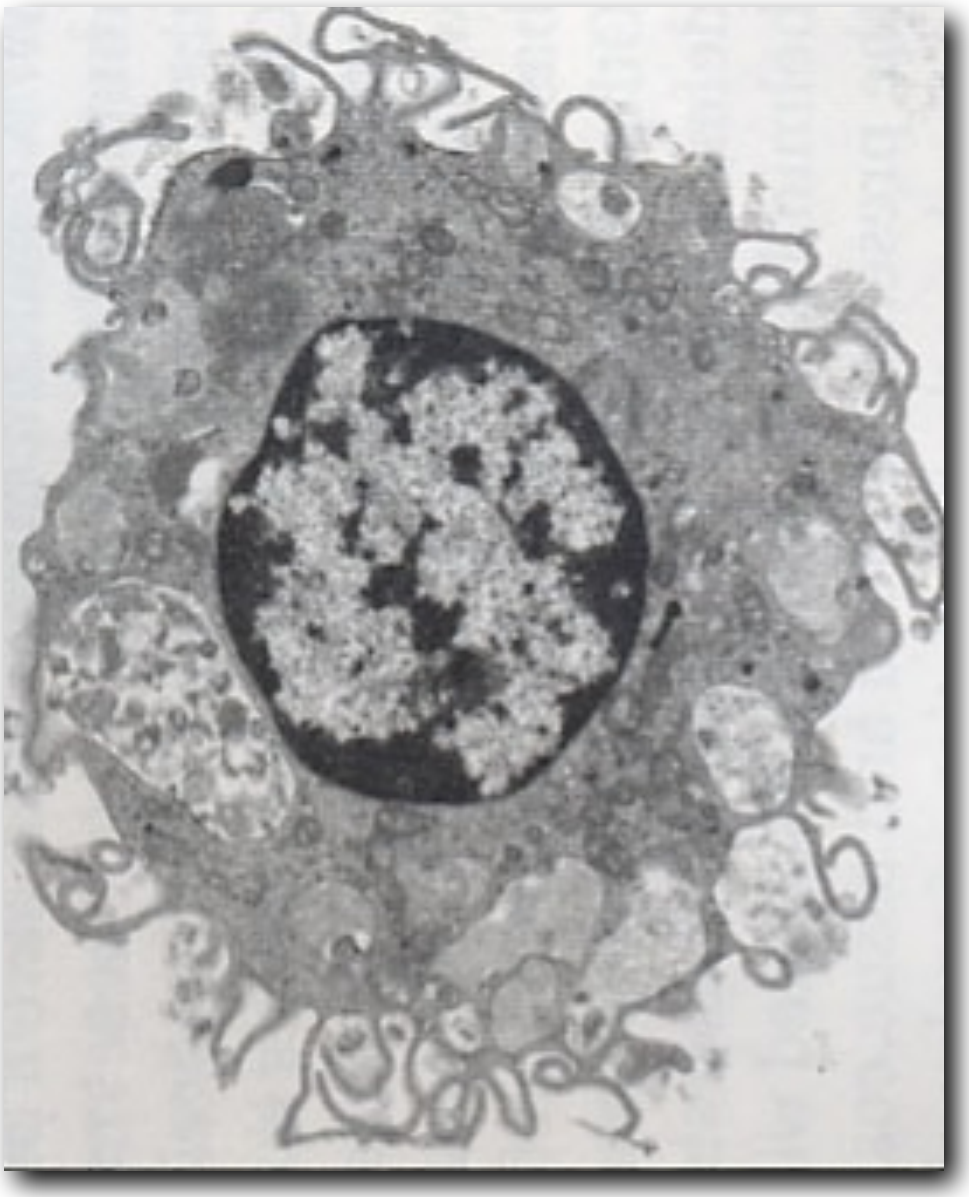
- Secreted by injured/distressed cells
- Byproducts of tissue injury and/or host response from plasma proteins - blood clotting, complement
- Unique microbial products


Injury/Infection
Mast Cells
Inflammatory Mediators
Histamine
Prostaglandins, etc.
Reactions in Small Blood Vessels

Mast Cells

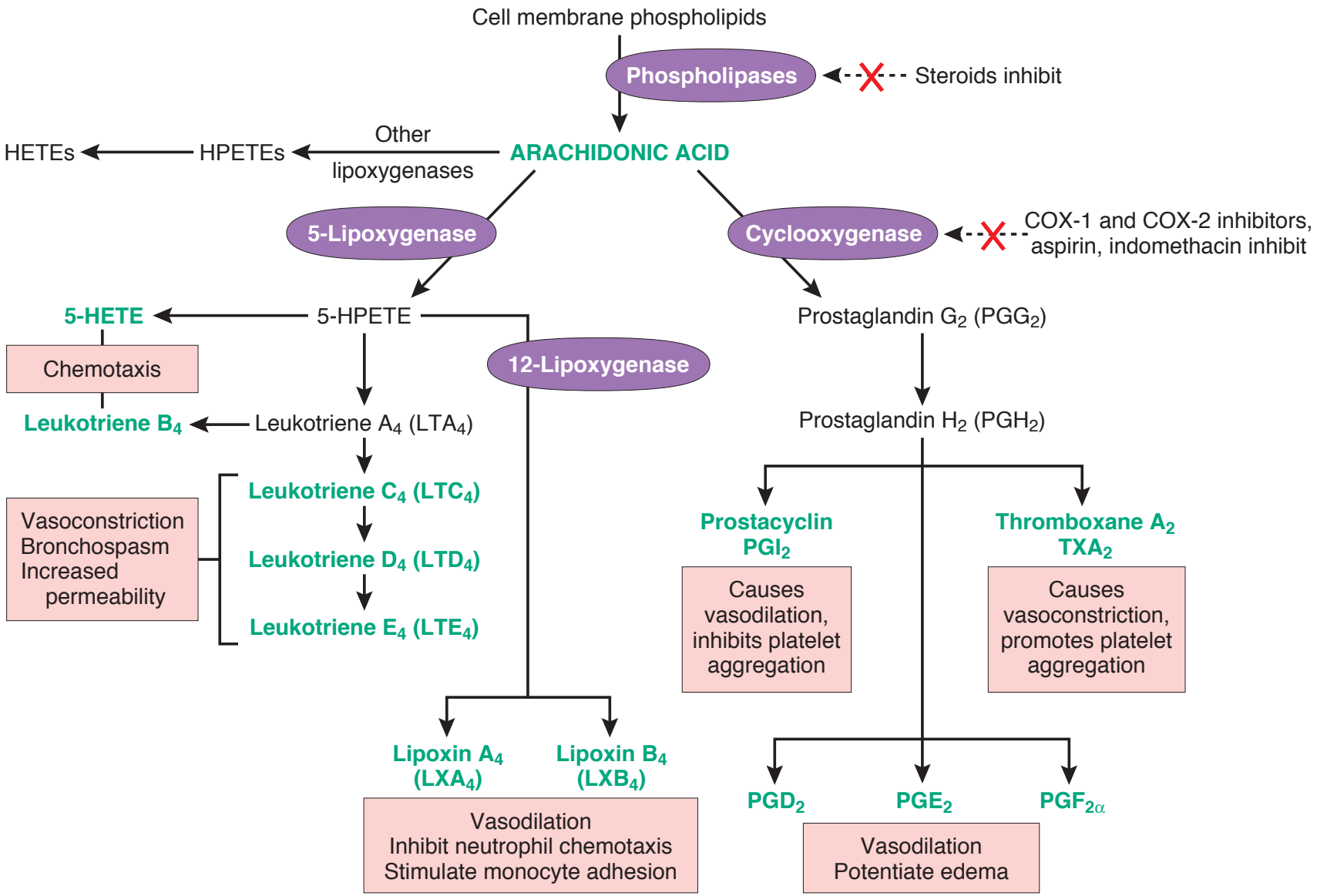


Resting

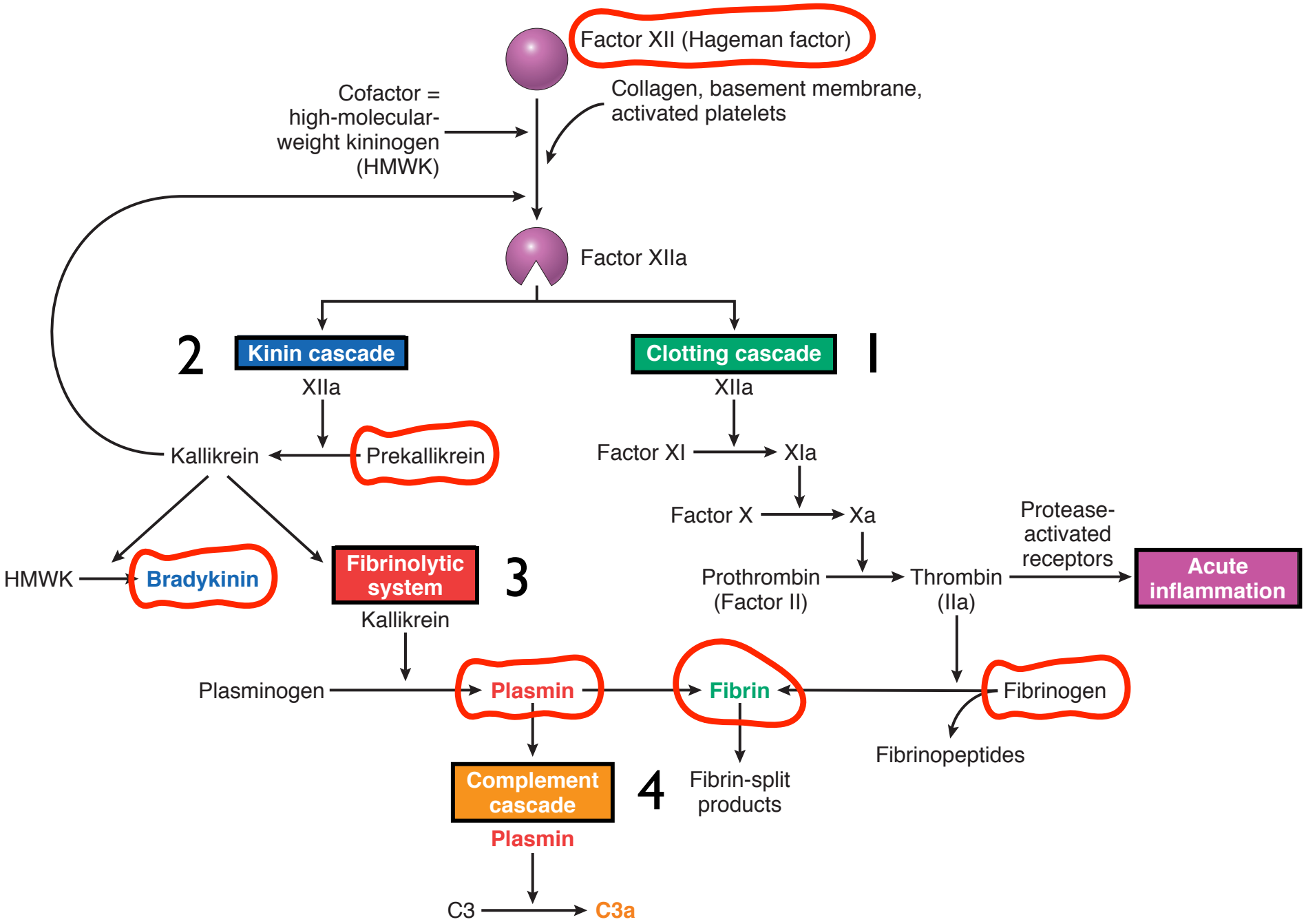


Degranulated

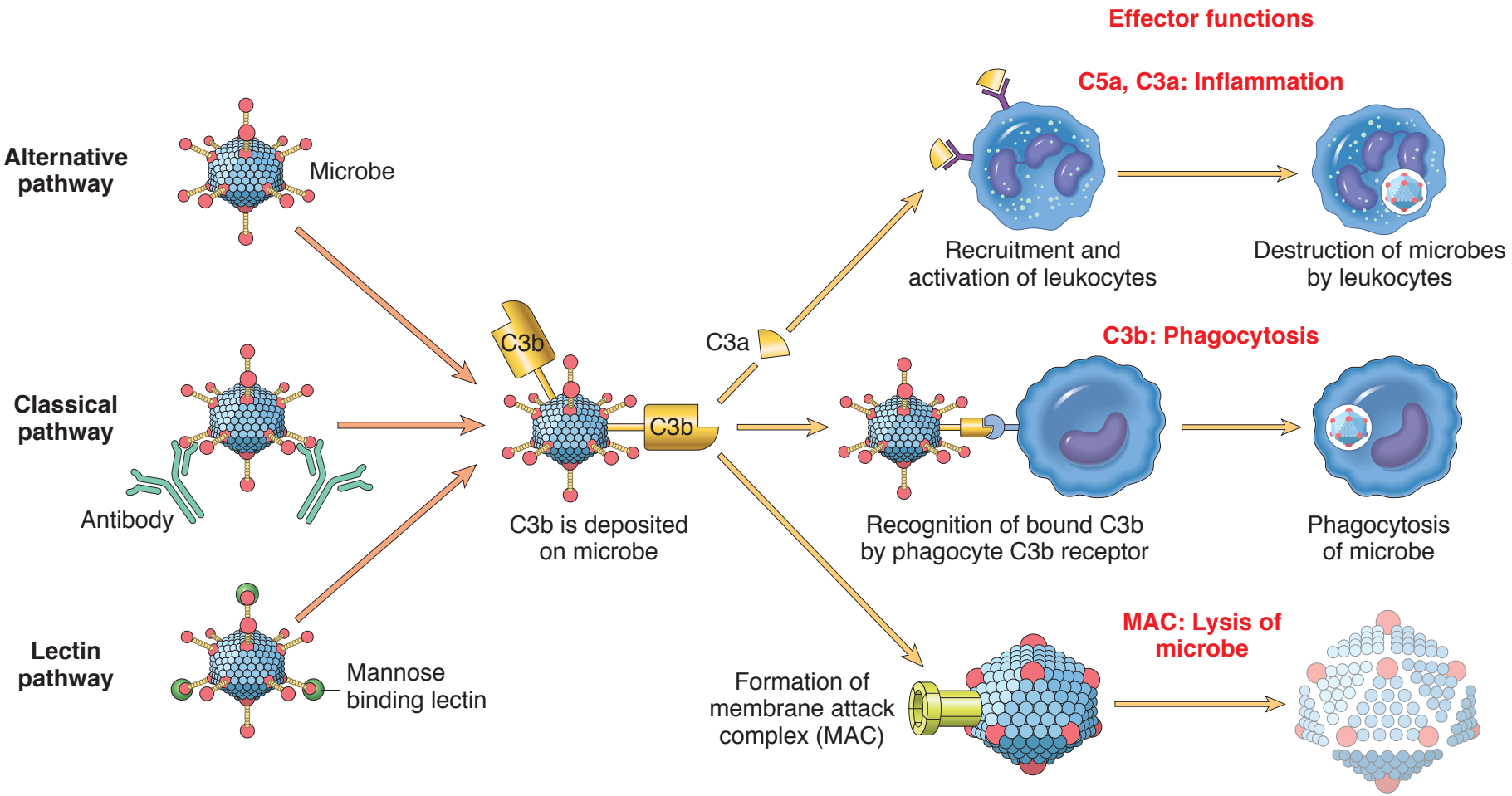
Arachidonic Acid Metabolites



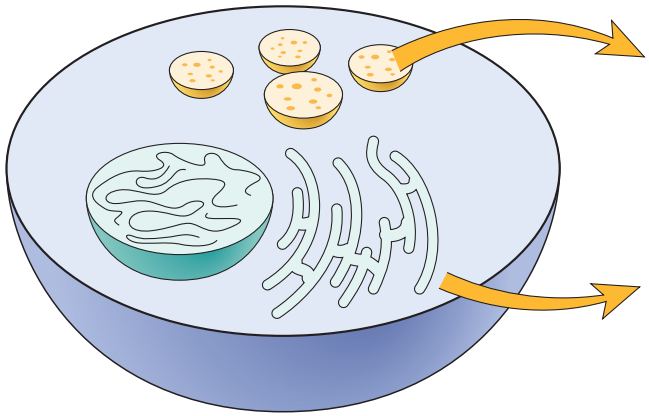
Plasma Proteins



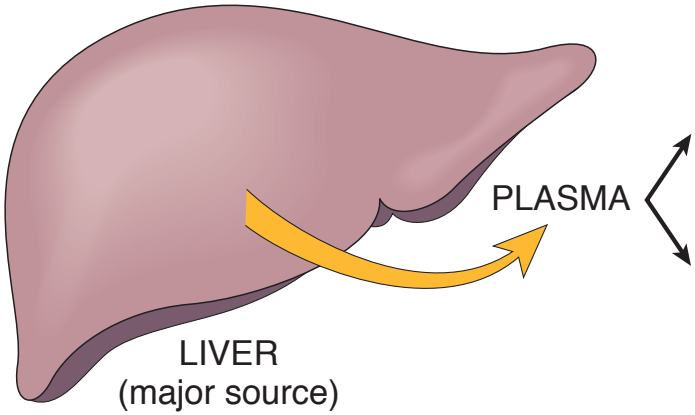
Activation and Functions of the Complement System



Summary of Chemical Mediators



CELLULAR



PLASMA

LIVER
(major source)

	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)

Summary of the Major Mediators of Inflammation

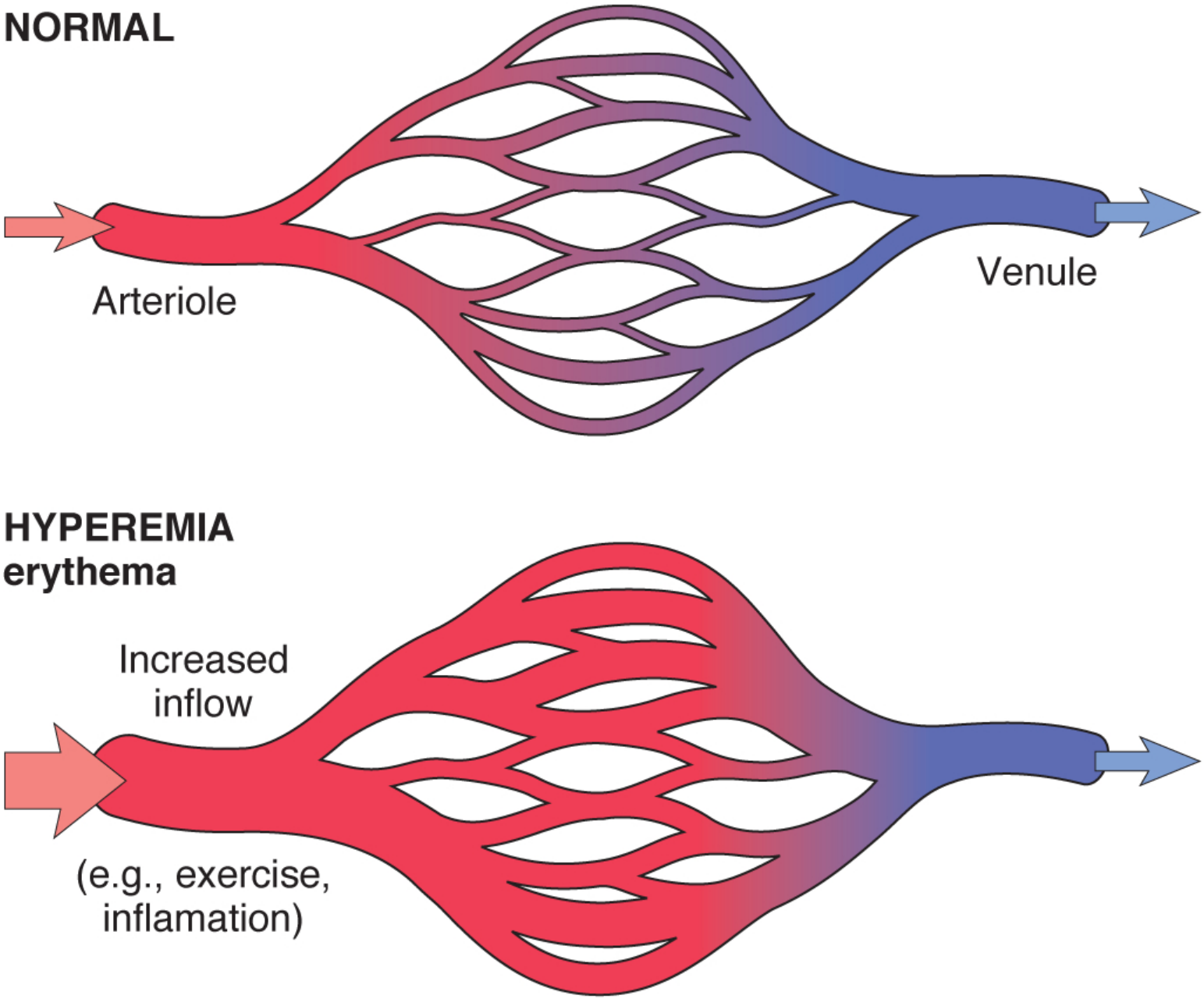
	Vascular Dilatation	Vascular Permeability	Endothelial Activation	Leukocyte Attraction	Pain	Fever
Secreted by Host Cells						
Histamine	XXX	XXX	XXX			
Protasglandins, leukotrienes	XXX	XXX			XXX	XXX
Nitric Oxide	XXX					
Chemokines				XXX		
Cytokines			XXX		XXX	XXX
Byproducts of						
Complement activation		XXX	XXX	XXX		
Congulation, eg: fibrin, thrombin			XXX	XXX		
Collagen degradation				XXX		
Uniquely Microbial Products						
Bacterial lipopolysaccharide			XXX			
N-formylated peptides				XXX		

Acute Inflammatory Response: Vasodilatation

- Relaxation of vascular smooth muscle
- Arterioles, capillaries, and venules
- Effects: local blood volume increases

(erythema and warmth!) leukocytes drift along slowly and collide more often against vessel walls

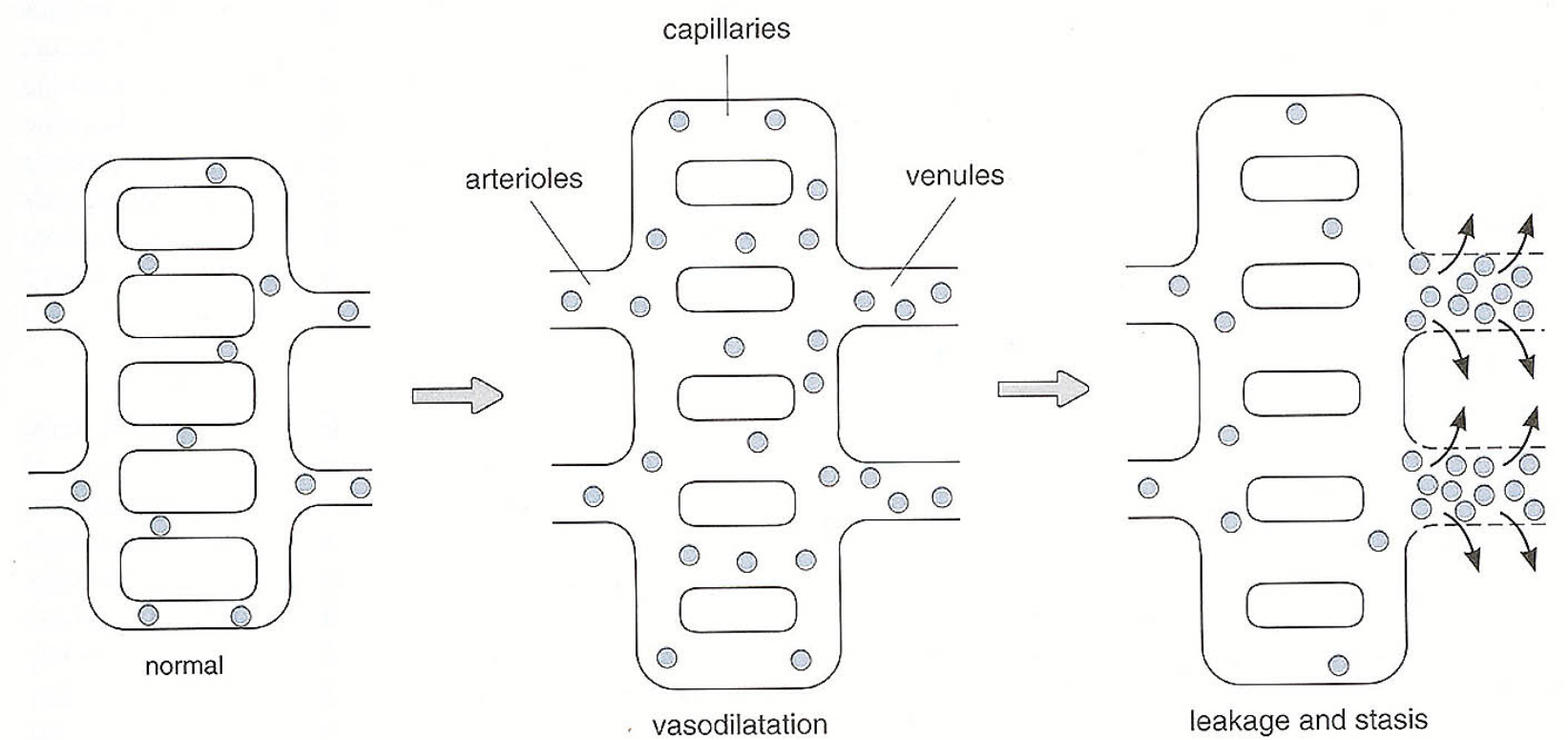
Vasodilatation



The Inflammatory Response: Increased Permeability

- Endothelial cells retract
- Only in post-capillary venules
- Effects: protein-rich fluid leaks out of vessel and into tissue (edema) sludging of blood cells
- Benefits: dilute foreign substances, release serum immune proteins, increase lymphatic drainage

Vasodilatation & Vascular Leakage

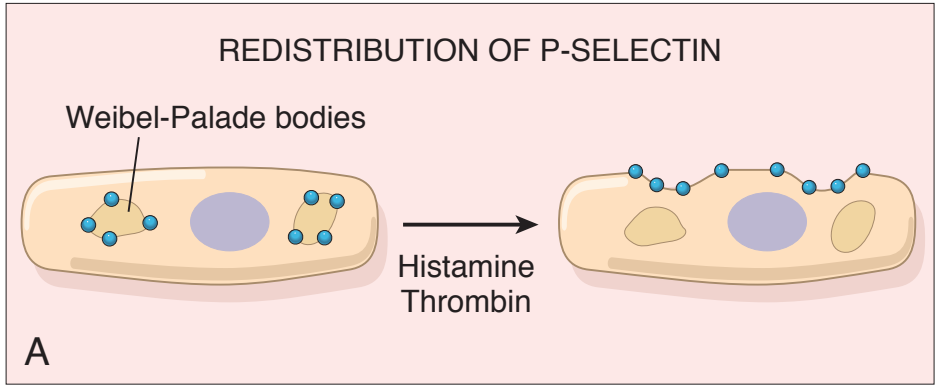


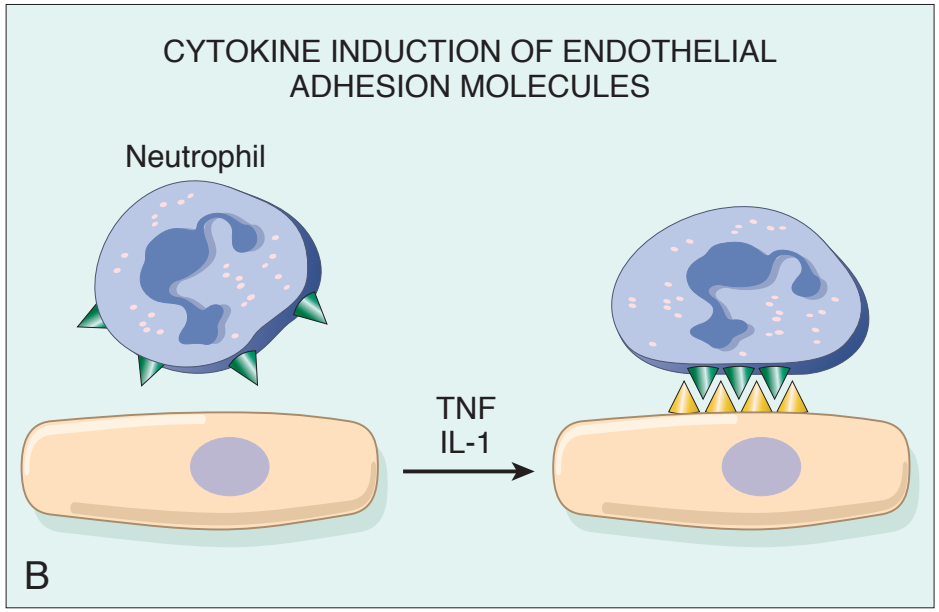
Vasodilatation and vascular leakage. Vasodilatation affects arterioles, capillaries, and venules. Leakage results from endothelial retraction that occurs only in postcapillary venules.

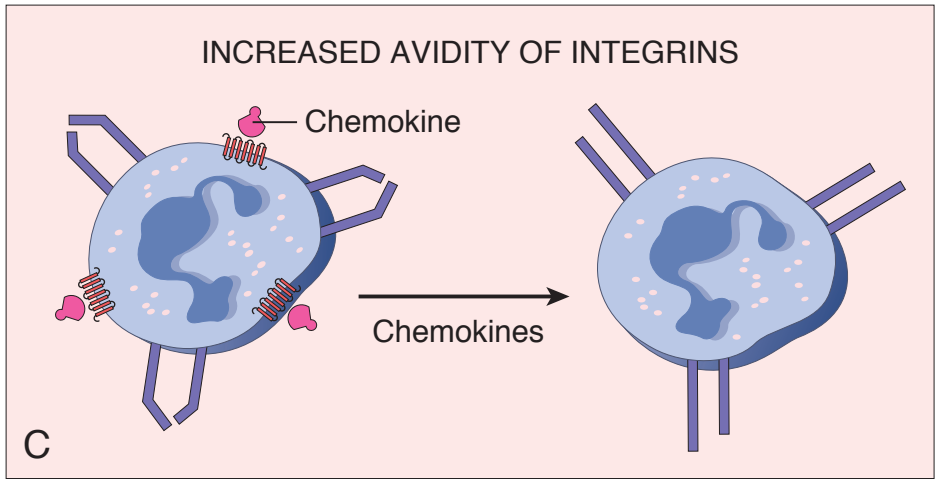
Acute Inflammatory Response: Endothelial Cell Activation

- Only in post-capillary venules
- Histamine, many other inflammatory mediators
- Activated endothelial cells in the post-capillary venules begin to express surface proteins that bind to other proteins on leukocyte surfaces: selectins bind to glycoproteins ICAM, VCAM bind to integrins
- Effect: Activated endothelium is “sticky” for leukocytes!

Adhesion Molecules







The Inflammatory Response: Leukocyte Chemoattraction

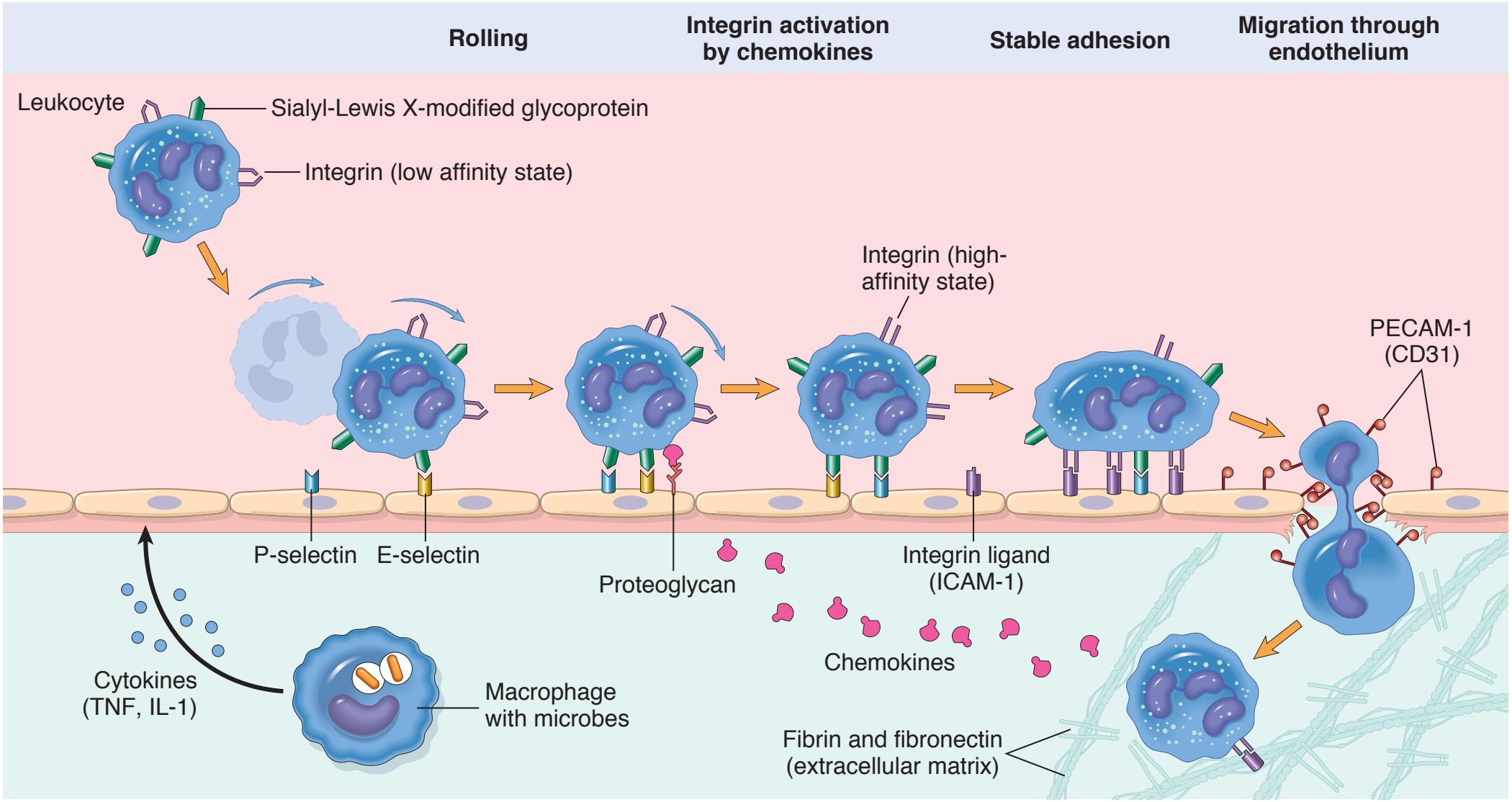
Inflamed tissues attract leukocytes because:

- WBCs drift slowly through, bumping along vessel walls
- Activated endothelial cells express selectins that bind WBC surface
- Some of the inflammatory mediators produced by distressed/injured tissue act as leukocyte chemotactic factors!

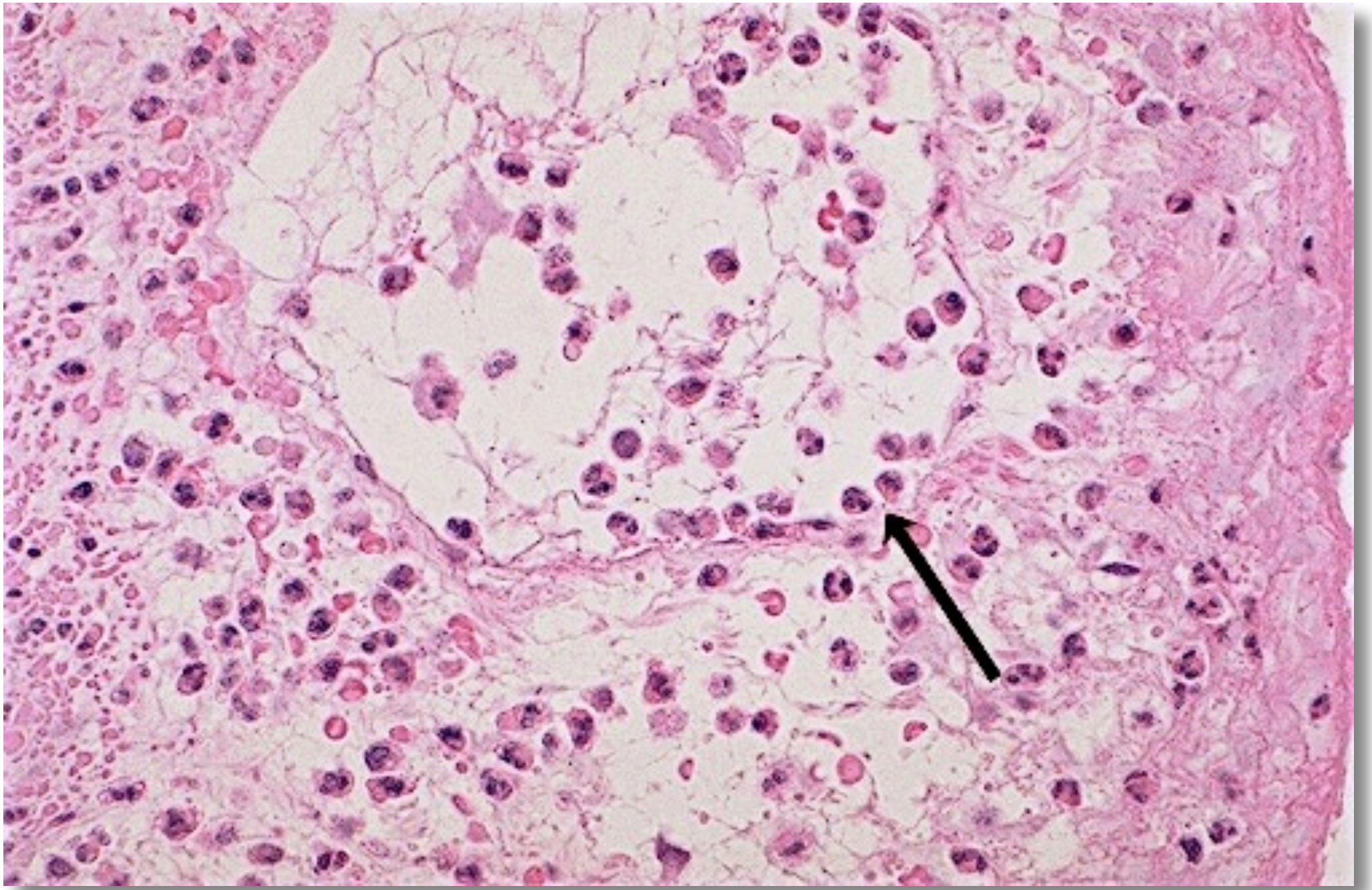
Leukocyte Chemotactic Factors:

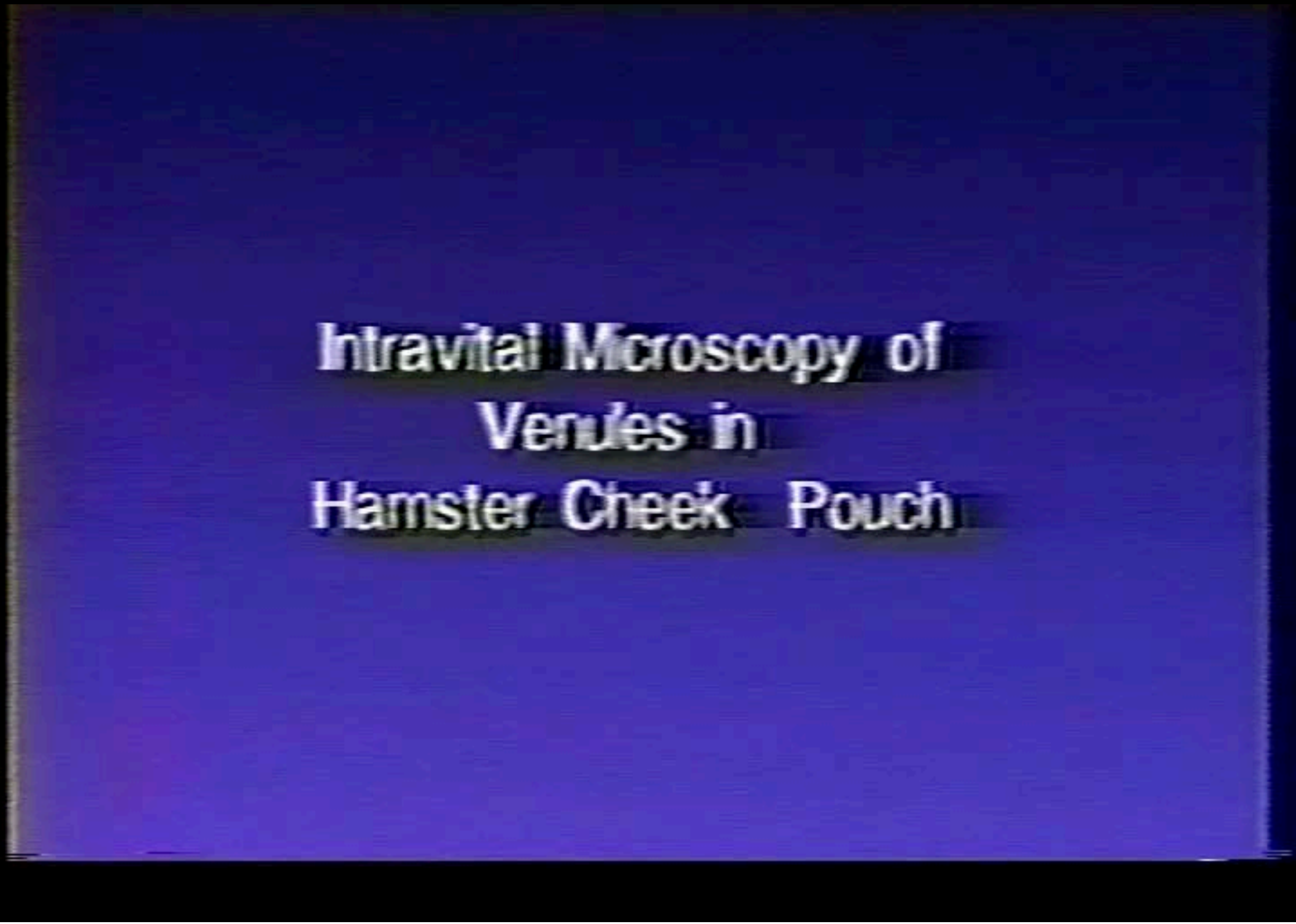
- Chemokines
- Collagen or fibrin debris
- Complement byproducts - C3a, C5a
- Unique microbial molecules - N-formylated peptides

Margination and Adhesion



Margination

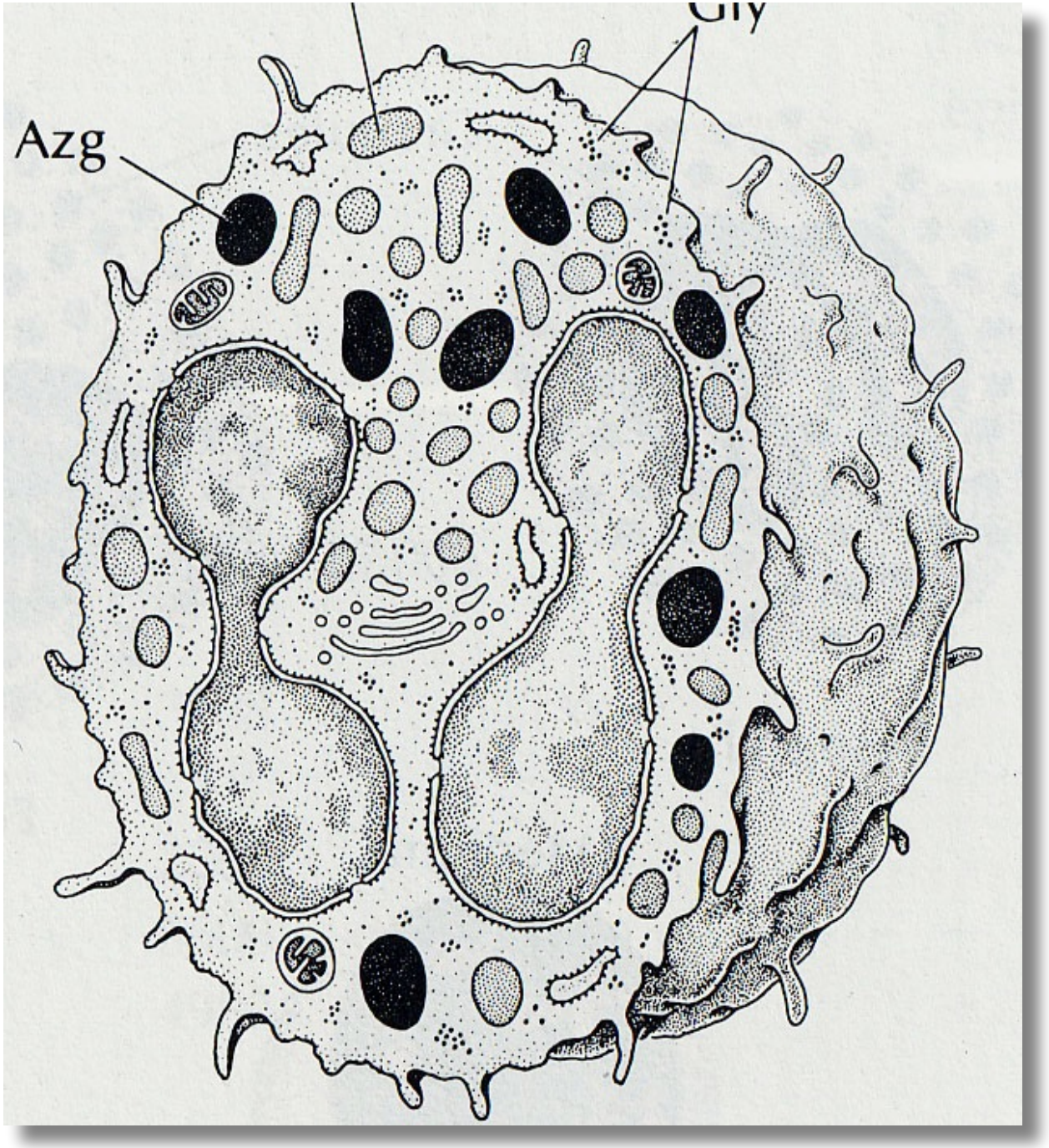



Intravital Microscopy of
Venules in
Hamster Cheek Pouch

Neutrophils in the Acute Inflammatory Response

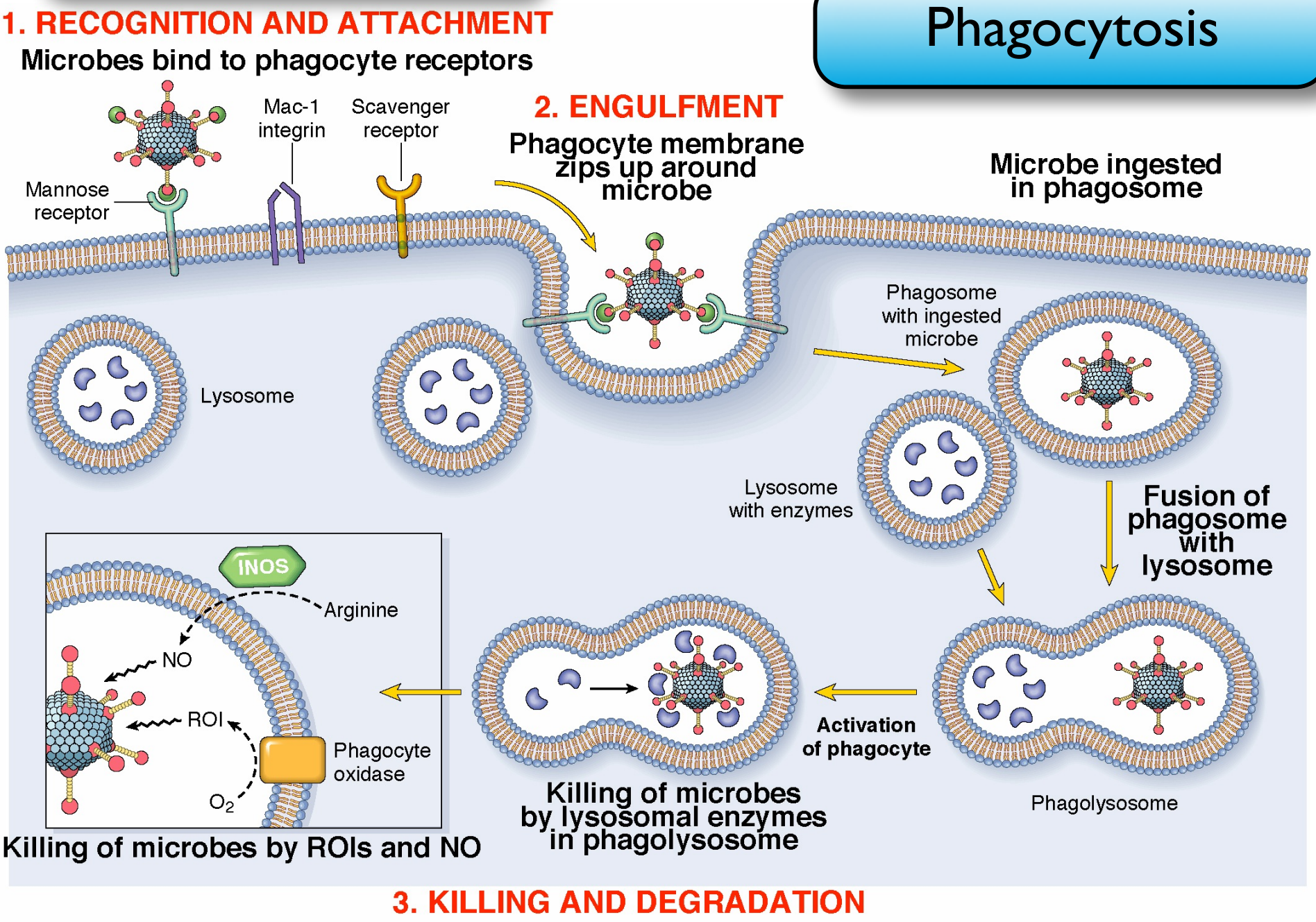
- Neutrophils = polymorphonuclear leukocytes, PMNs
- First leukocytes to arrive and have a short lifespan in the extravascular space (24-48 hrs) followed by monocytes becoming macrophages

Neutrophil



Opsinization

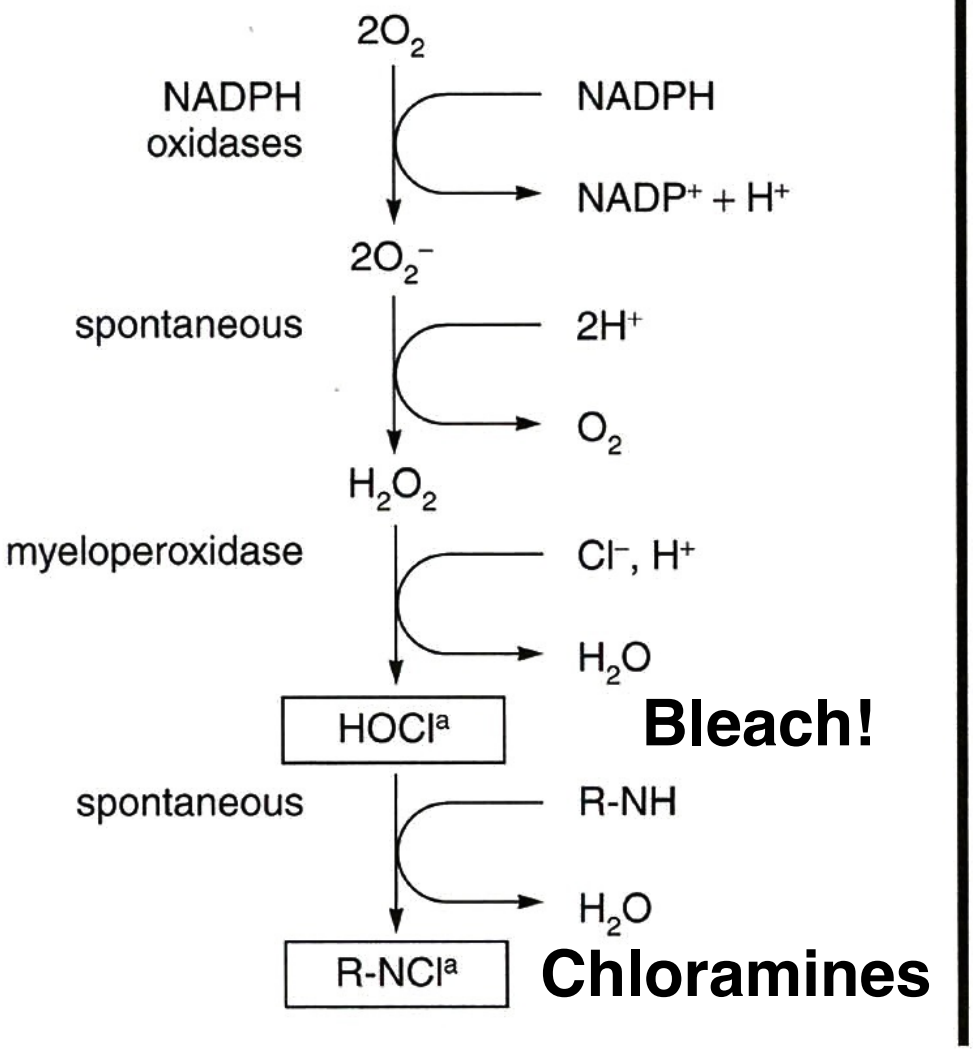
Phagocytosis

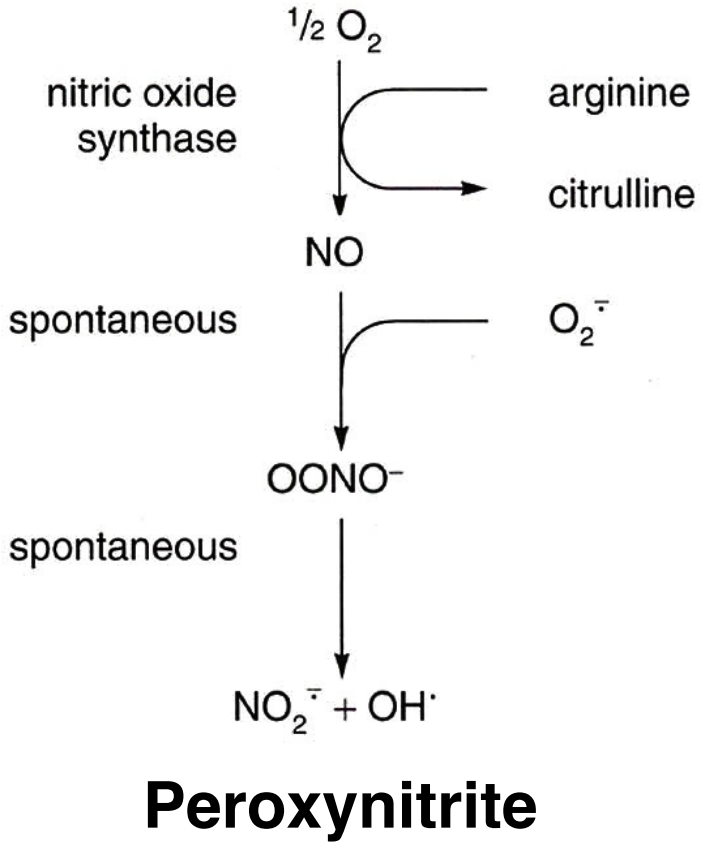


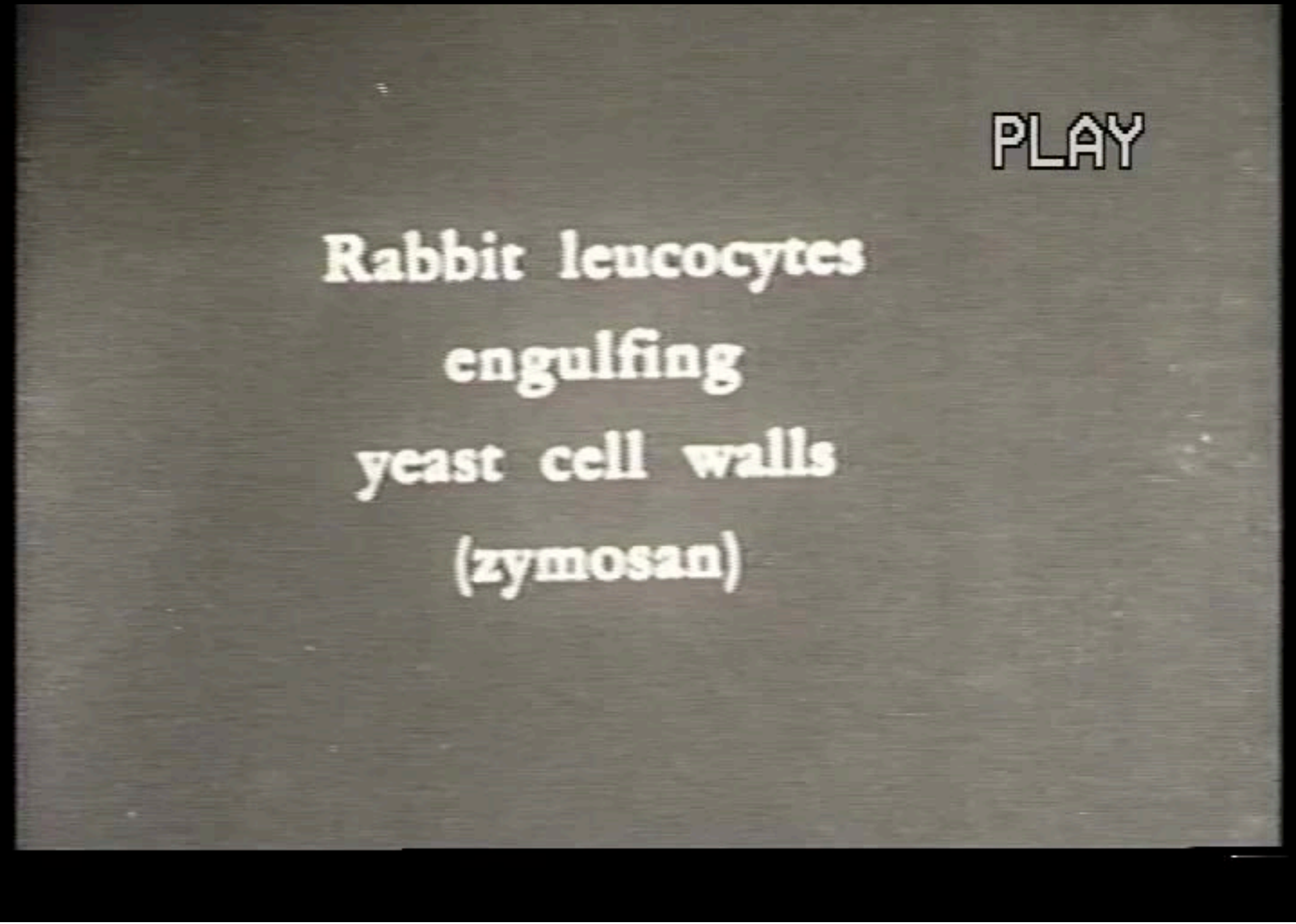
How Neutrophils Kill Microbes:

- Microbicidal Proteins
  - Alpha-defensins
  - Lysozyme
  - Lactoferrin
  - Proteases
  - Vitamin B12 binding protein
- Acid
- Oxidation

Oxidative Killing

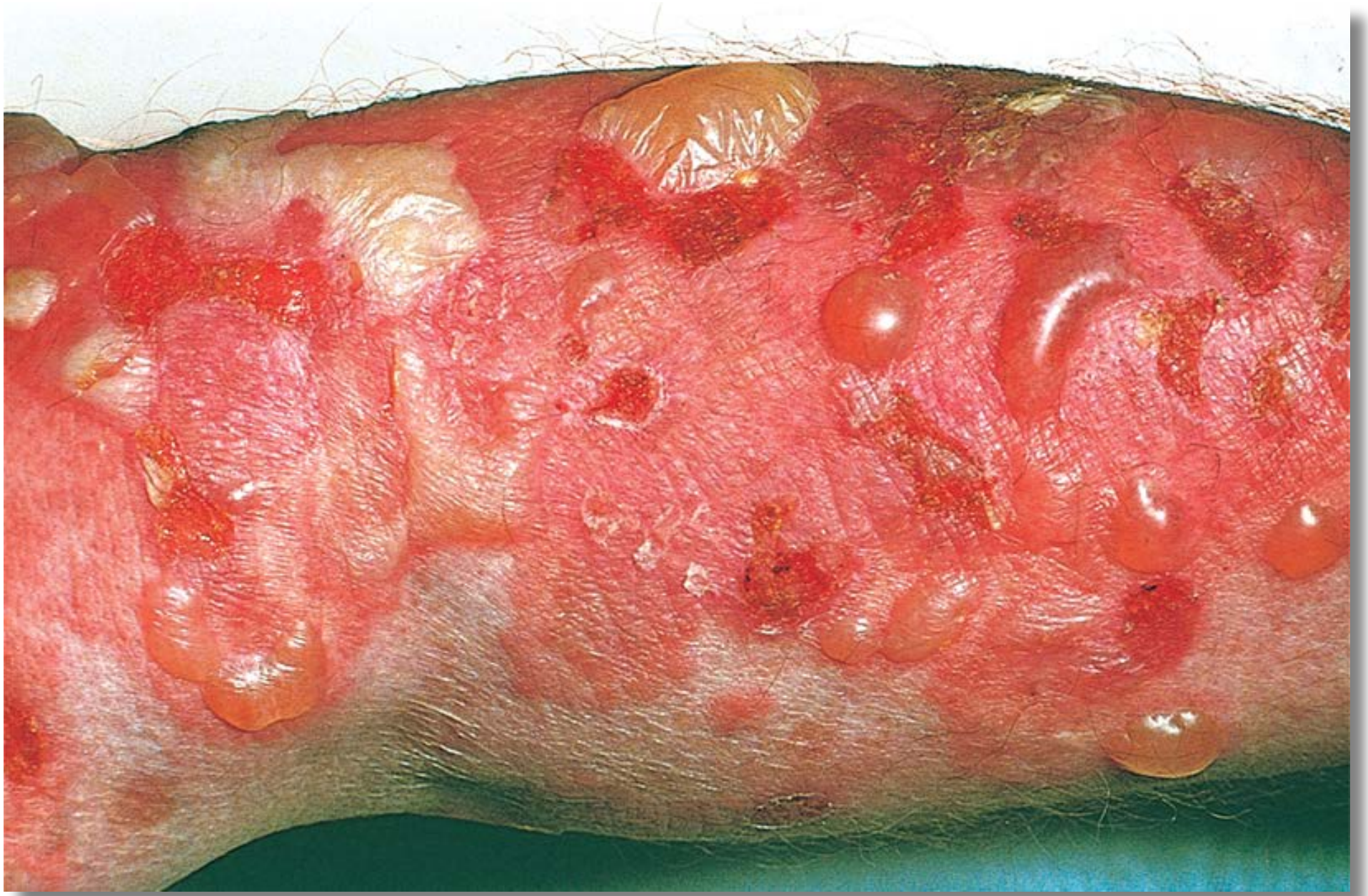





PLAY
Rabbit leucocytes
engulfing
yeast cell walls
(zymosan)

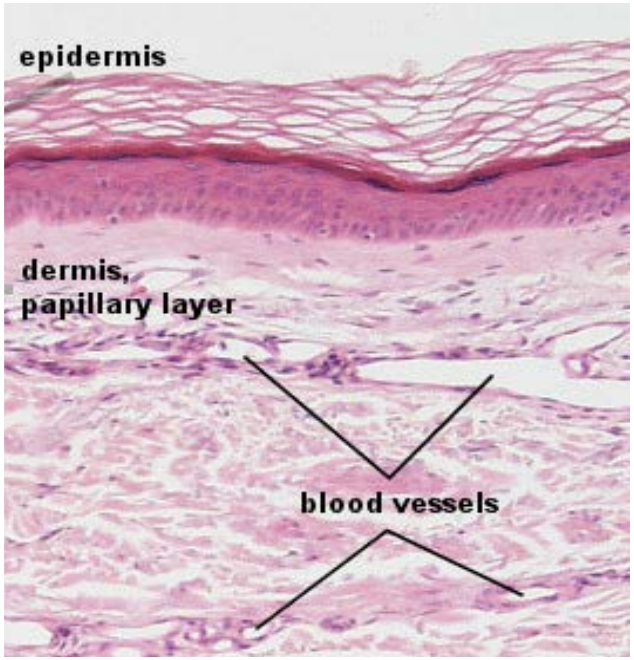
Morphology of Acute Inflammation

Serous Inflammation: Bullous Pemphigoid

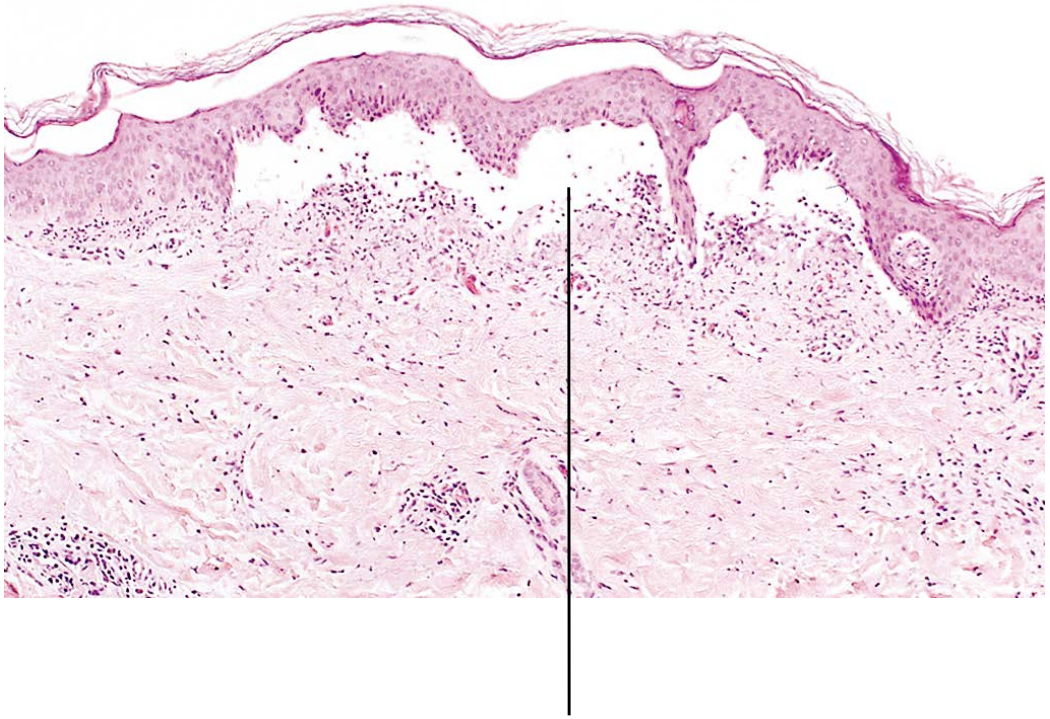


Serous Inflammation: Blister

Normal skin

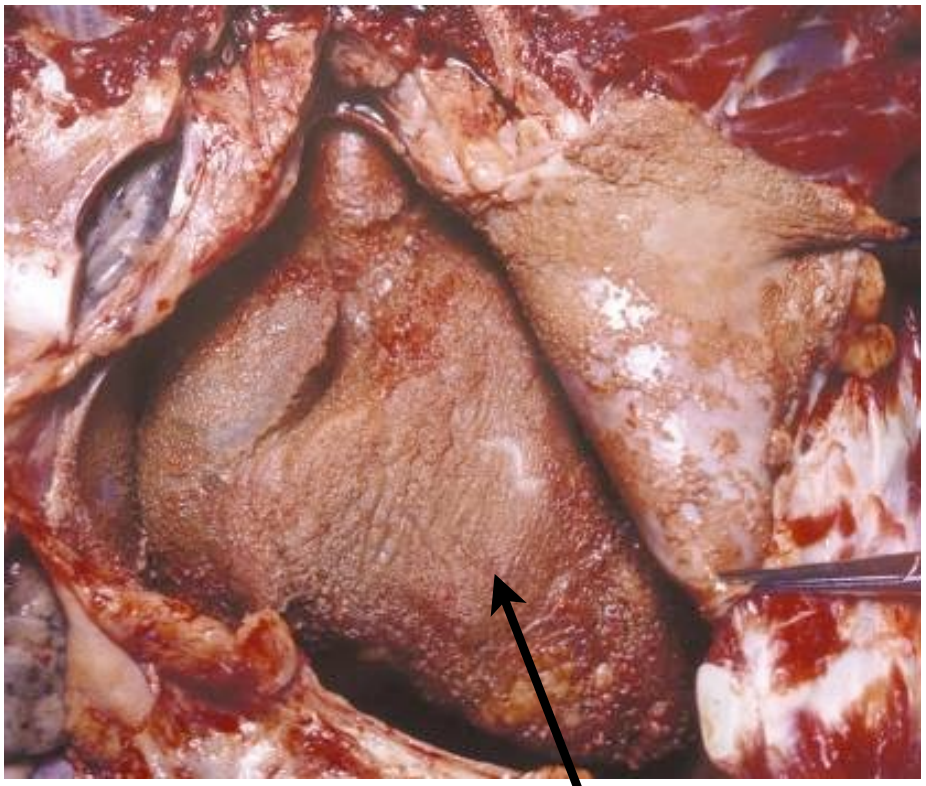


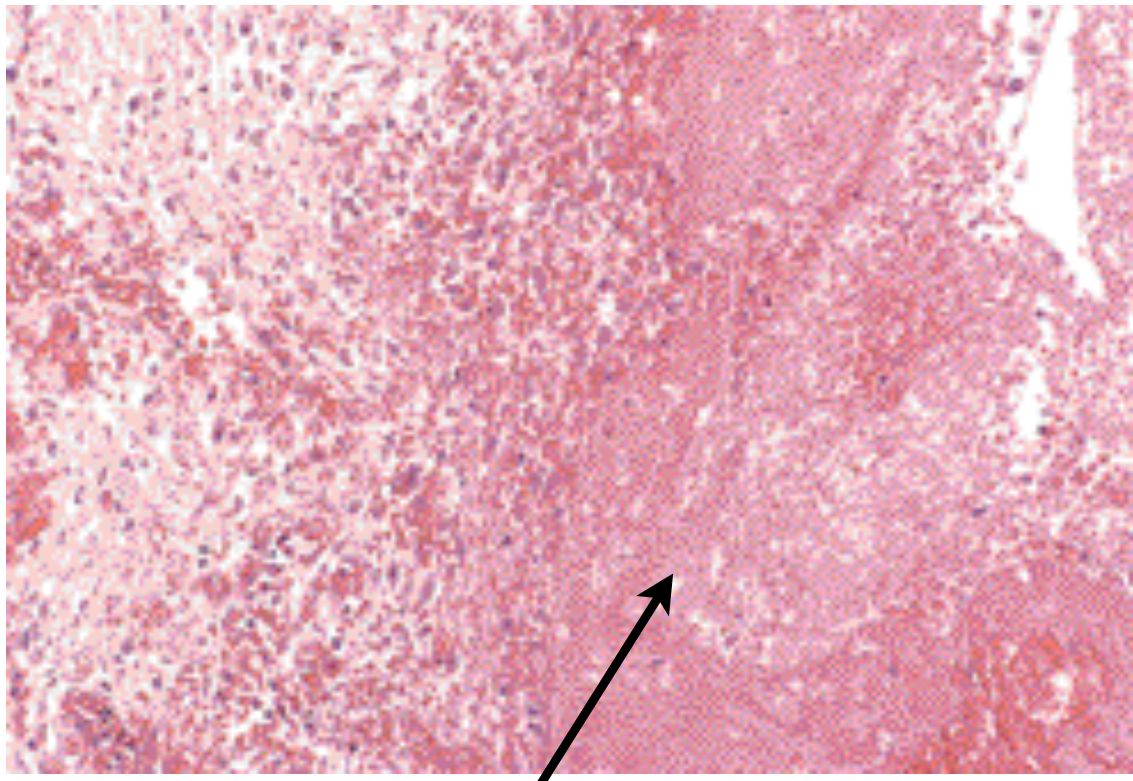
Inflammation



Blister

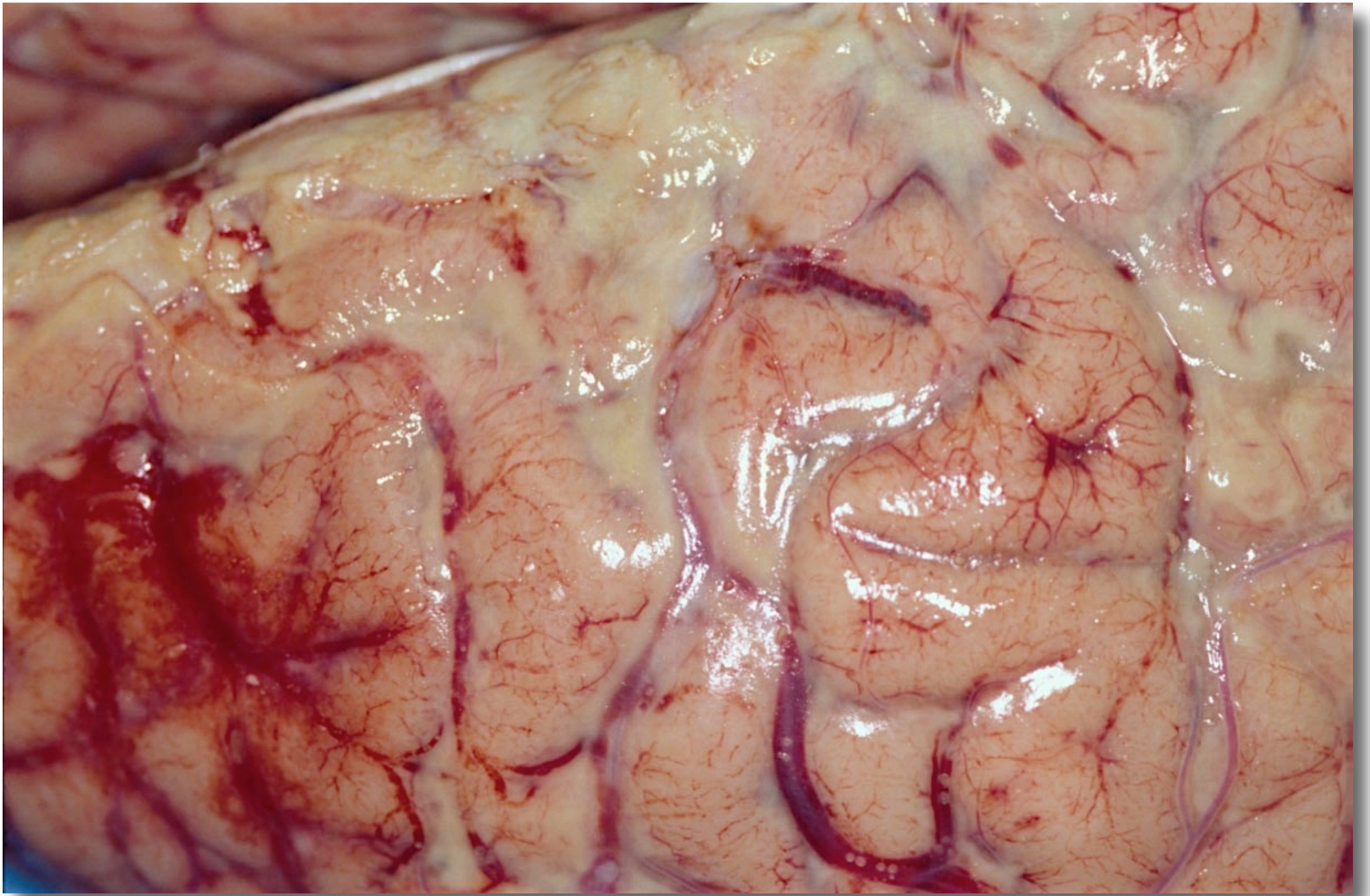
Fibrinous Inflammation: Fibrinous Pericarditis



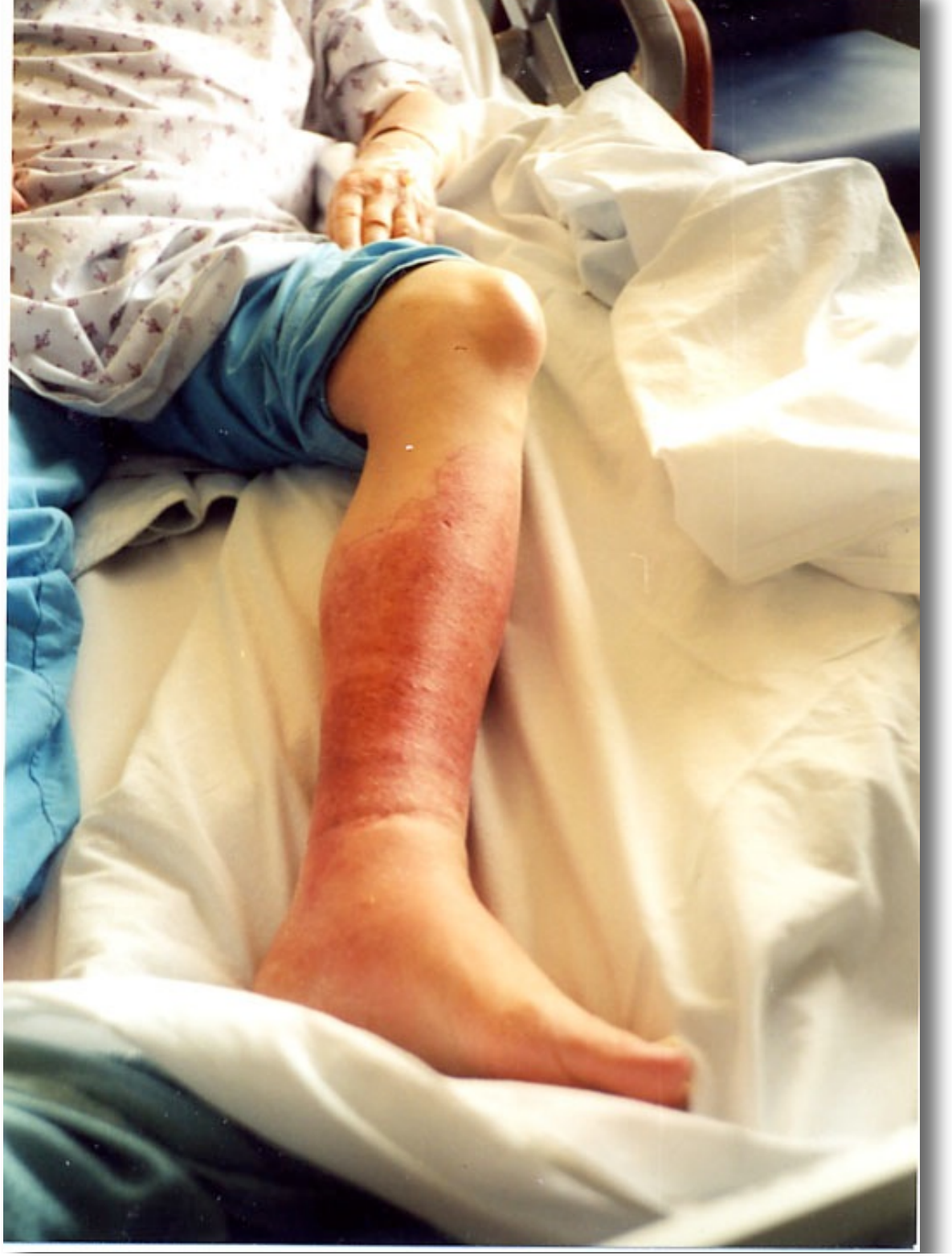


Fibrin deposition on pericardium

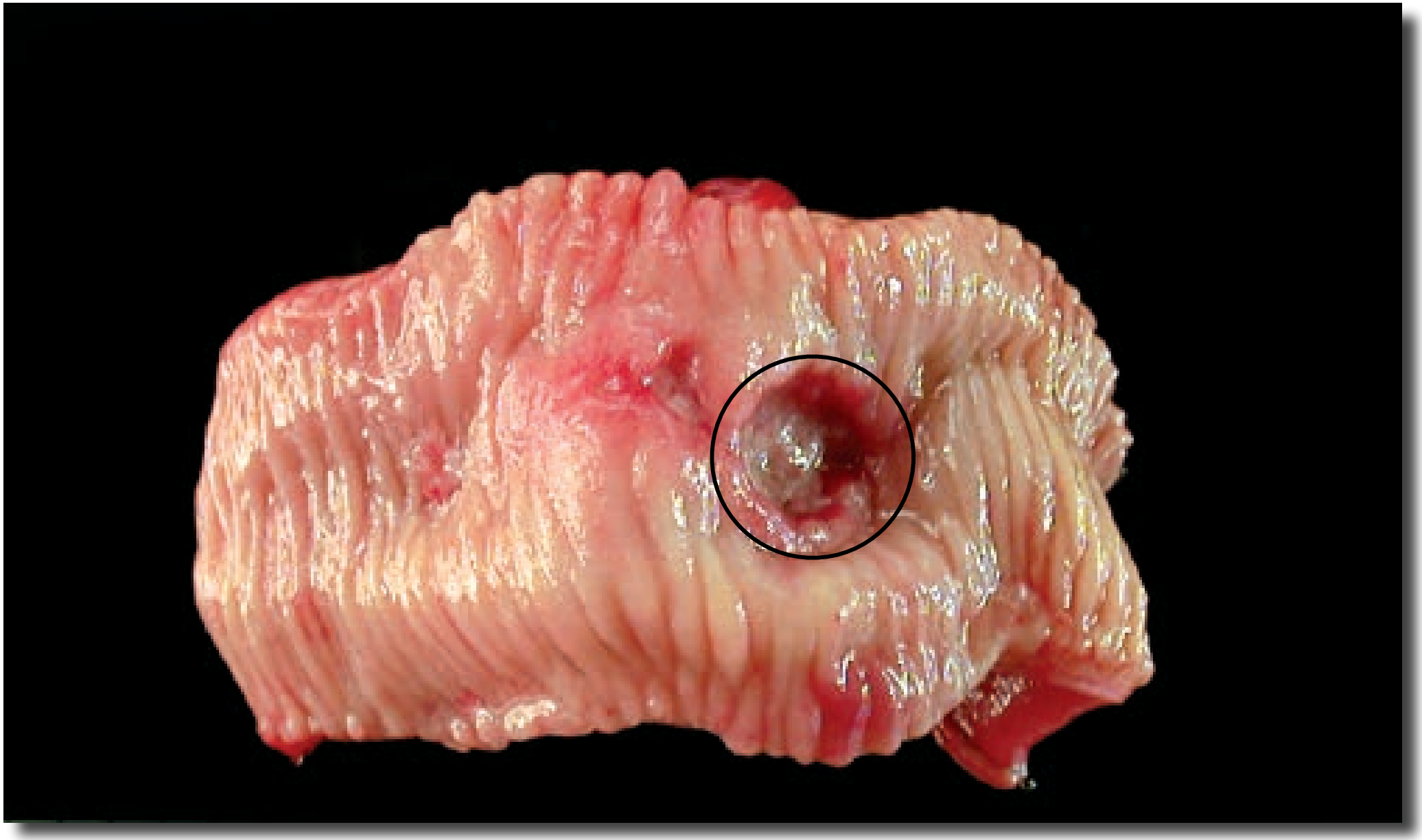
Purulent Inflammation: Acute Purulent Meningitis



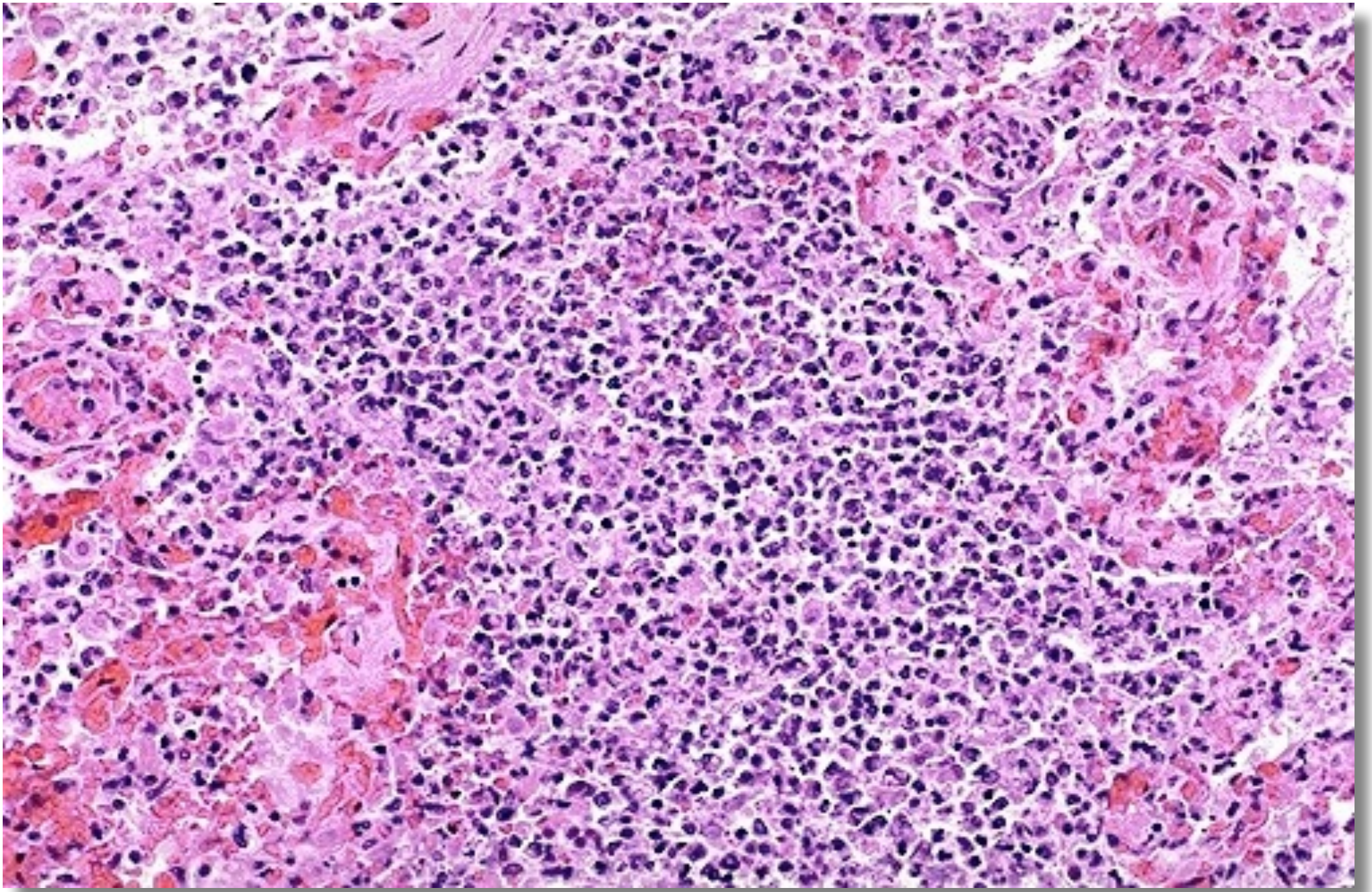
Acute Cellulitis



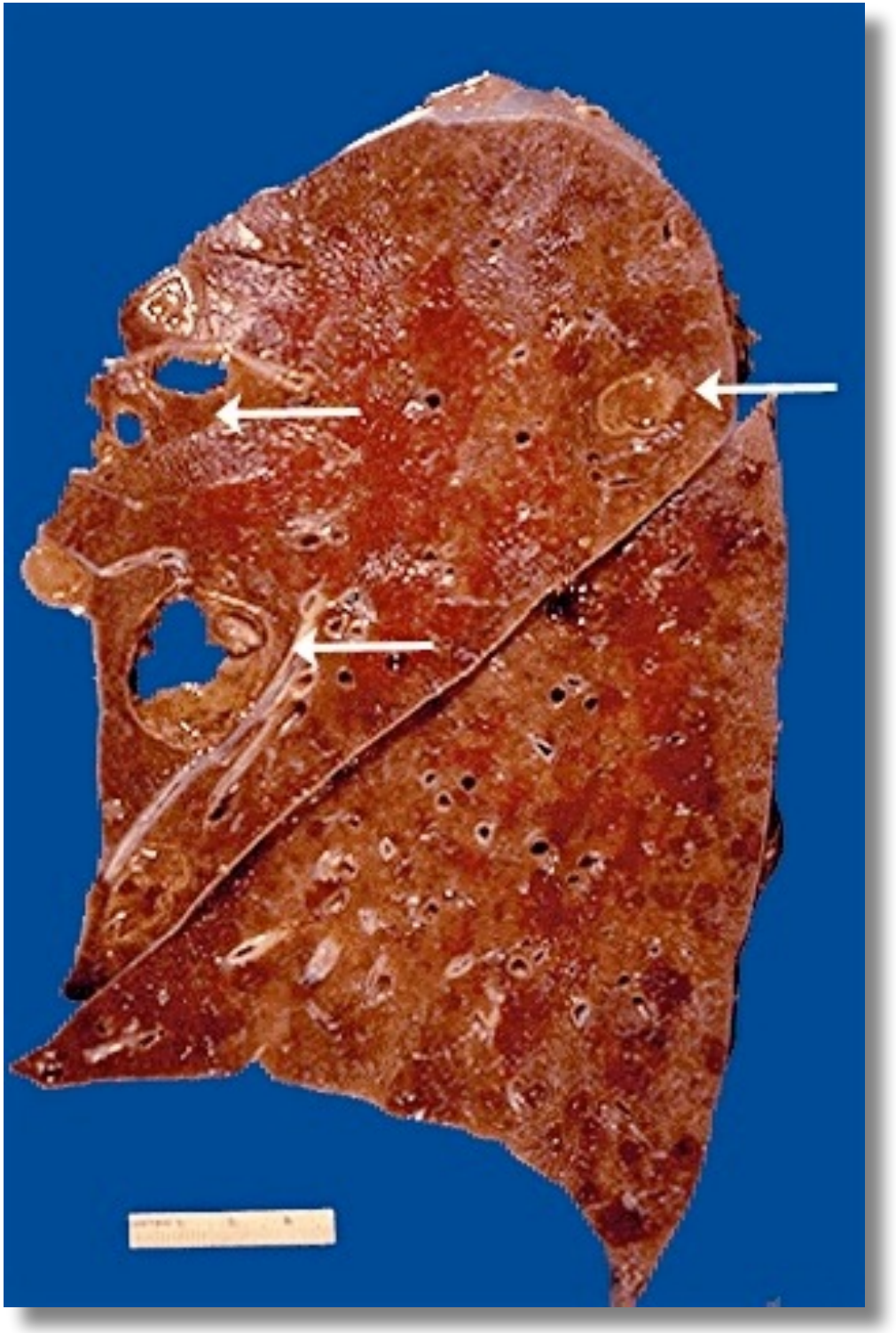
Chronic Duodenal Ulcer



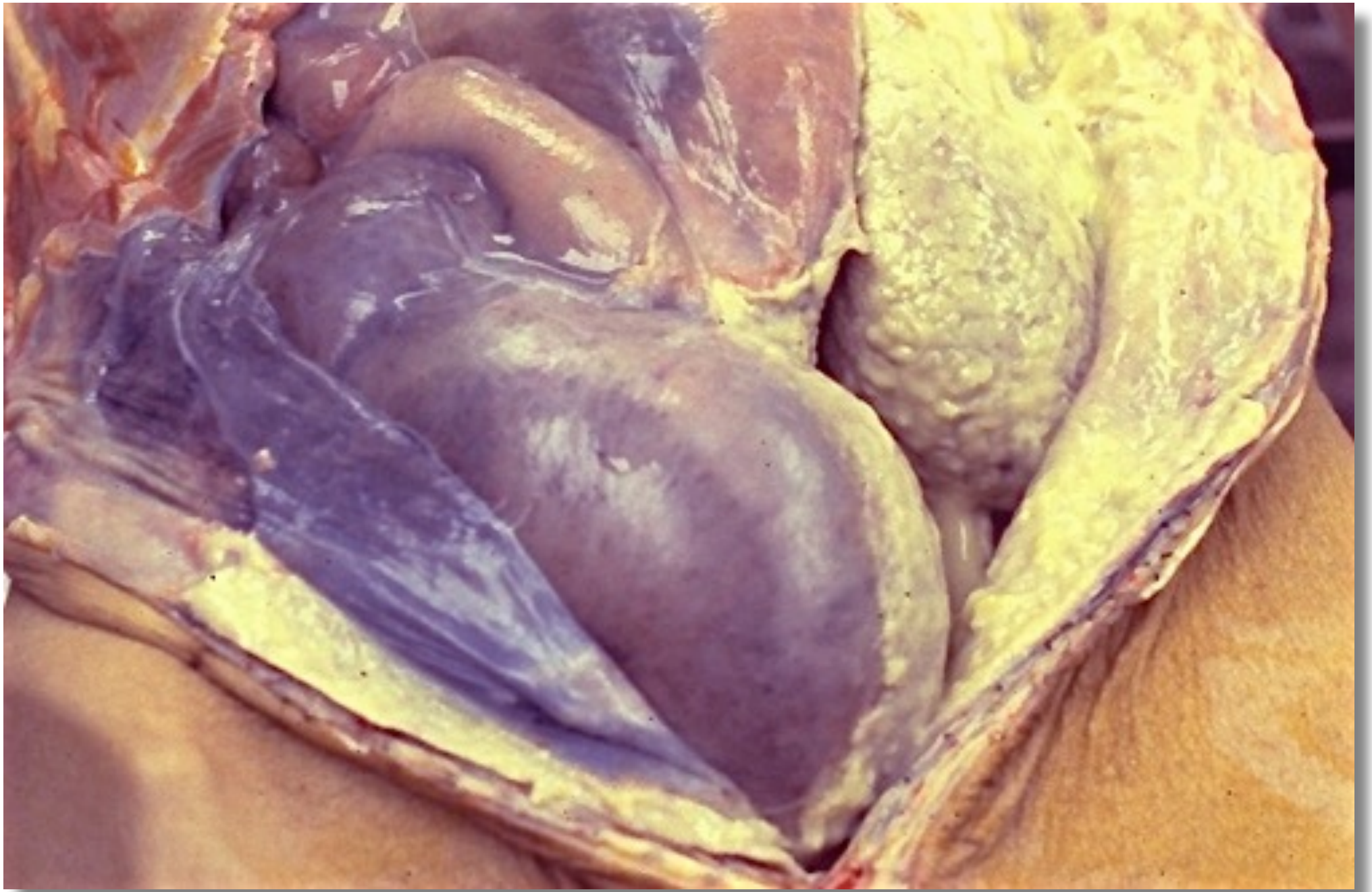
Early Lung Abscess



Lung Abscesses



Empyema



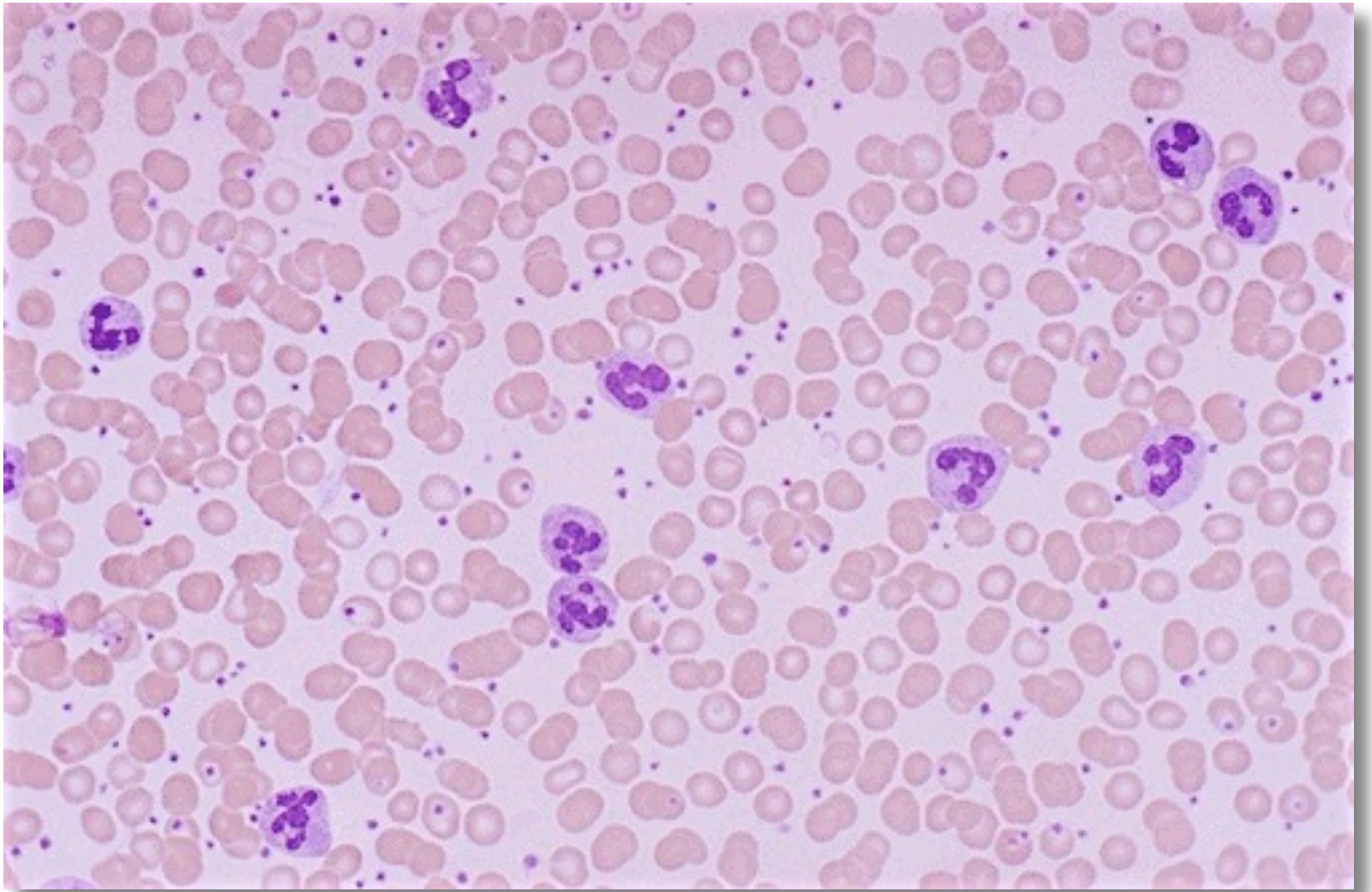
Local Manifestations

- Cardinal signs of inflammation
  - Redness — ***rubor***
  - Swelling (edema) — ***tumor***
  - Warmth — ***calor***
  - Pain — ***dolor***
  - Loss of function

Systemic Manifestations

- Fever (IL-1, TNF, prostaglandins)
- Left-shift
- “Acute phase response”
- Septic shock

Polymorphonuclear Leukocytosis



Actions of the Cytokines TNF and IL-1

Bacterial products, immune complexes, toxins, physical injury, other cytokines

↓

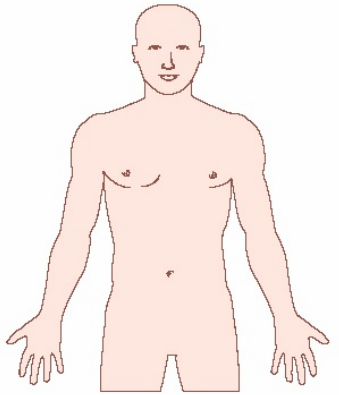
MACROPHAGE (and other cell) ACTIVATION

↓

IL-1 / TNF

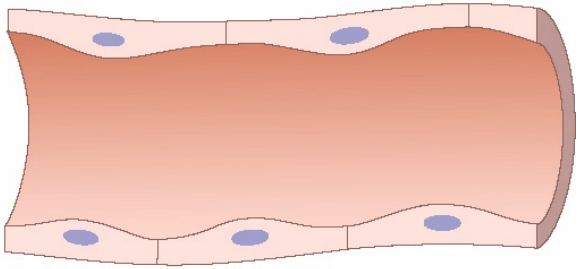
ACUTE-PHASE REACTIONS

Fever
↑Sleep
↓Appetite
↑Acute-phase proteins
Hemodynamic effects (shock)
Neutrophilia



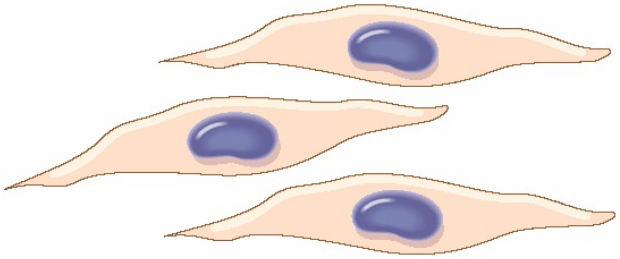
ENDOTHELIAL EFFECTS

↑Leukocyte adherence
↑PGI synthesis
↑Procoagulant activity
↓Anticoagulant activity
↑IL-1, IL-8, IL-6, PDGF



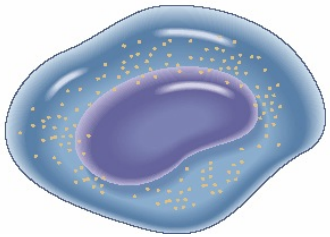
FIBROBLAST EFFECTS

↑Proliferation
↑Collagen synthesis
↑Collagenase
↑Protease
↑PGE synthesis



LEUKOCYTE EFFECTS

↑Cytokine secretion (IL-1, IL-6)



Outcomes of Acute Inflammation