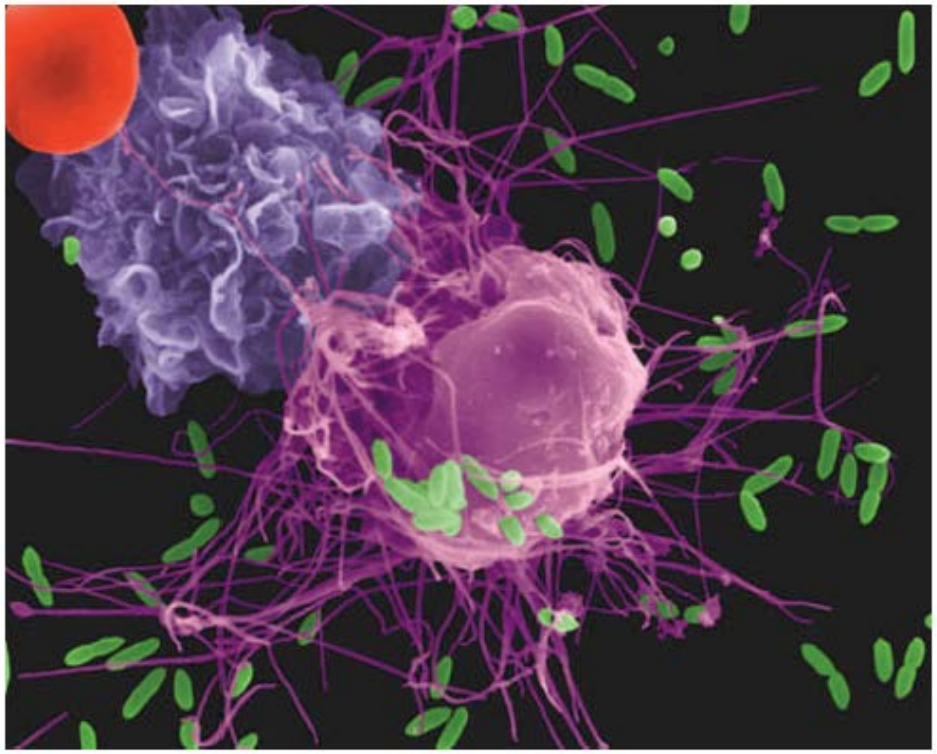
Acute and chronic inflammation



Sarah Beck, DVM

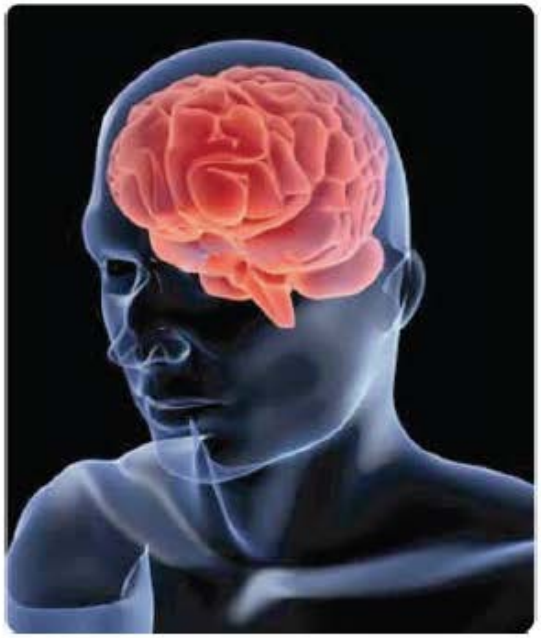
sbeck8@jhmi.edu

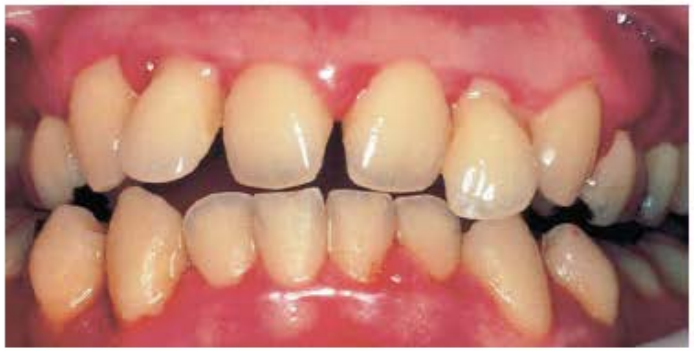
Outline

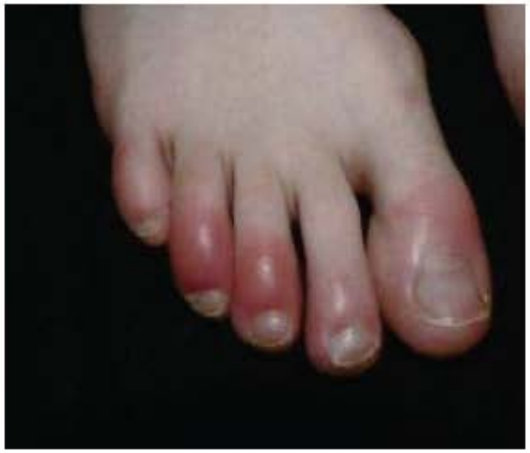
- Introduction to inflammation
- Acute inflammation
  - Clinical examples of acute inflammation
- Chronic inflammation
  - Clinical examples of chronic inflammation
- Leukocyte activation and mechanisms of microbial killing
- Chemical mediators of inflammation

Inflammation

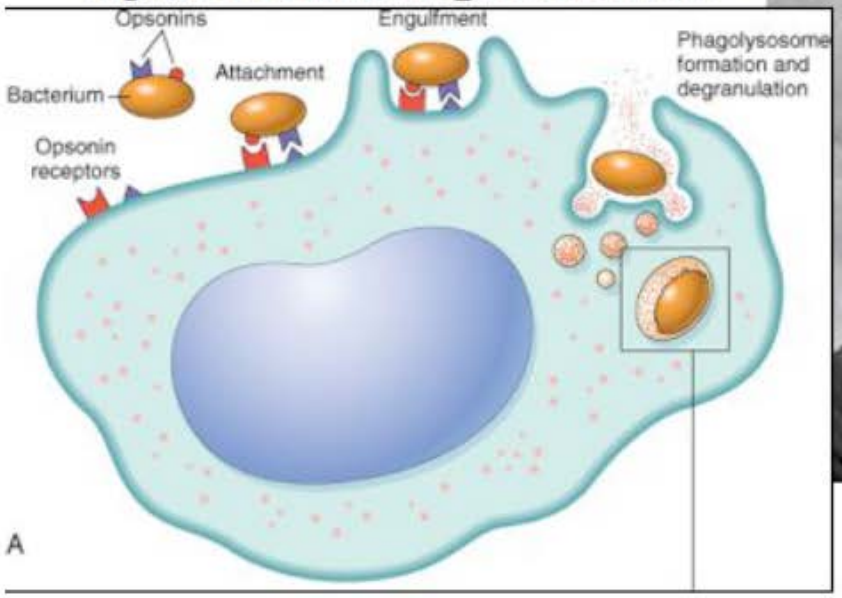
Inflammare
(Latin: to set on fire)



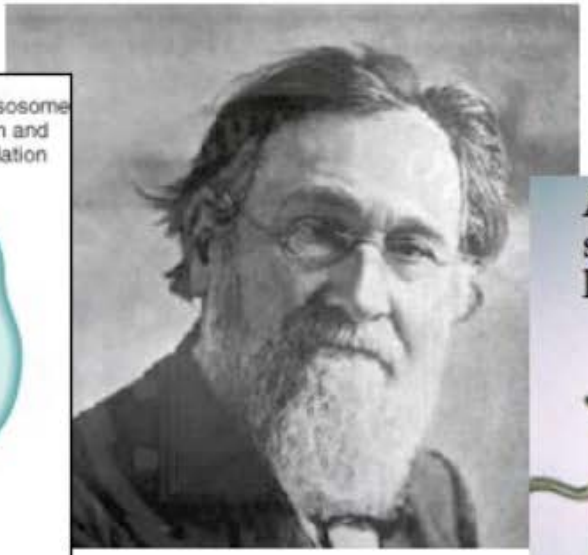




Phagocytosis:
To bring phagocytic cells to the injured area to engulf bacteria



Elie Metchnikoff



Nobel Prize 1908 for his is work on phagocytes. He discovered the process of phagocytosis (ingestion of rose thorns by amebocytes of starfish larvae as a major component of inflammation).

Metchnikoff shared the Nobel prize with **Paul Erlich**, who recognized the role of serum factors, mainly antibodies, as a critical factor in the defense against microorganisms

Inflammation

- A protective response involving host cells, blood vessels and proteins
  - Goals are:
    - eliminate the initial cause of cell injury
    - Remove necrotic cells and tissue
    - Initiate the process of repair
- Also a potentially harmful process
  - Components of inflammation that are capable of destroying microbes can also injury bystander normal tissue

Inflammation

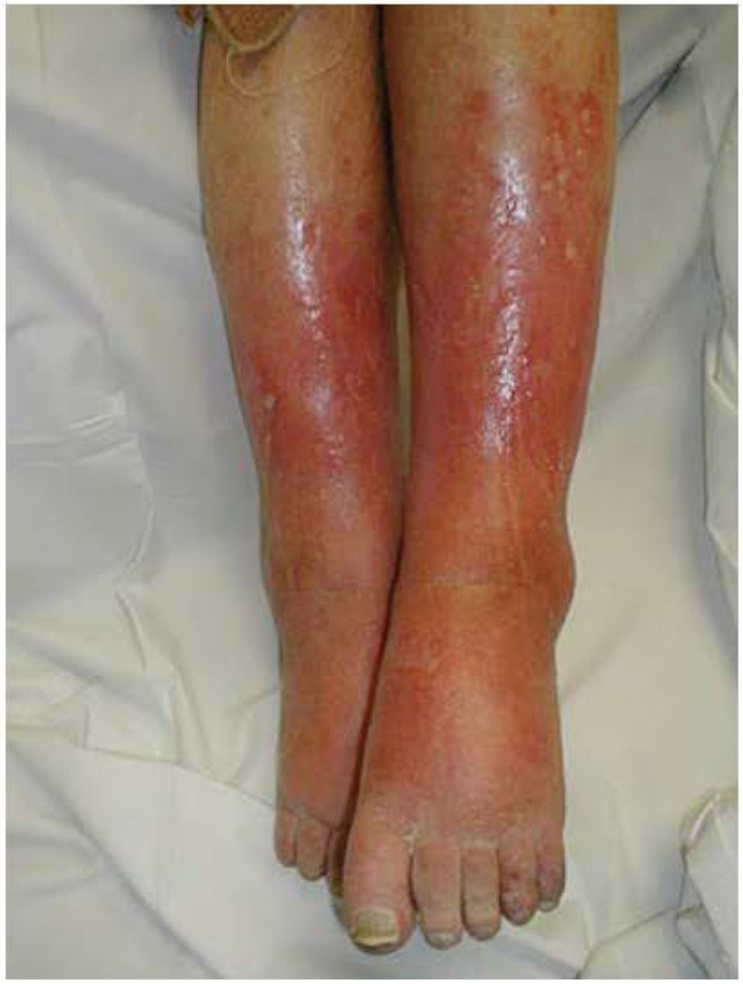
- Components of the inflammatory process include white blood cells and plasma proteins
  - Normally present in the blood
  - The inflammatory reaction's goal is to bring these to the site of infection and/or tissue damage
- Inflammation is induced by chemical mediators produced by damaged host cells
  - Cytokines and other mediators
- Inflammation is normally controlled and self-limited

Excess inflammatory reactions

- Inappropriate inflammatory response when there are no foreign substances to fight off leads to **autoimmunity**

- Inflammatory process must be **tightly regulated** by the immune system to avoid excessive tissue damage and spillover to normal tissue

Cardinal signs of inflammation



Cellulitis: Severe bilateral inflammation and swelling of the legs

- Heat (calor)
- Redness (rubor)
- Swelling (tumor)
- Pain (dolor)
  - Celsus, *De Medicina*
  - Roman encyclopedia of medicine, >2000 years ago
- Loss of function
  - Rudolf Virchow ("father of modern pathology")
  - Late 19th century

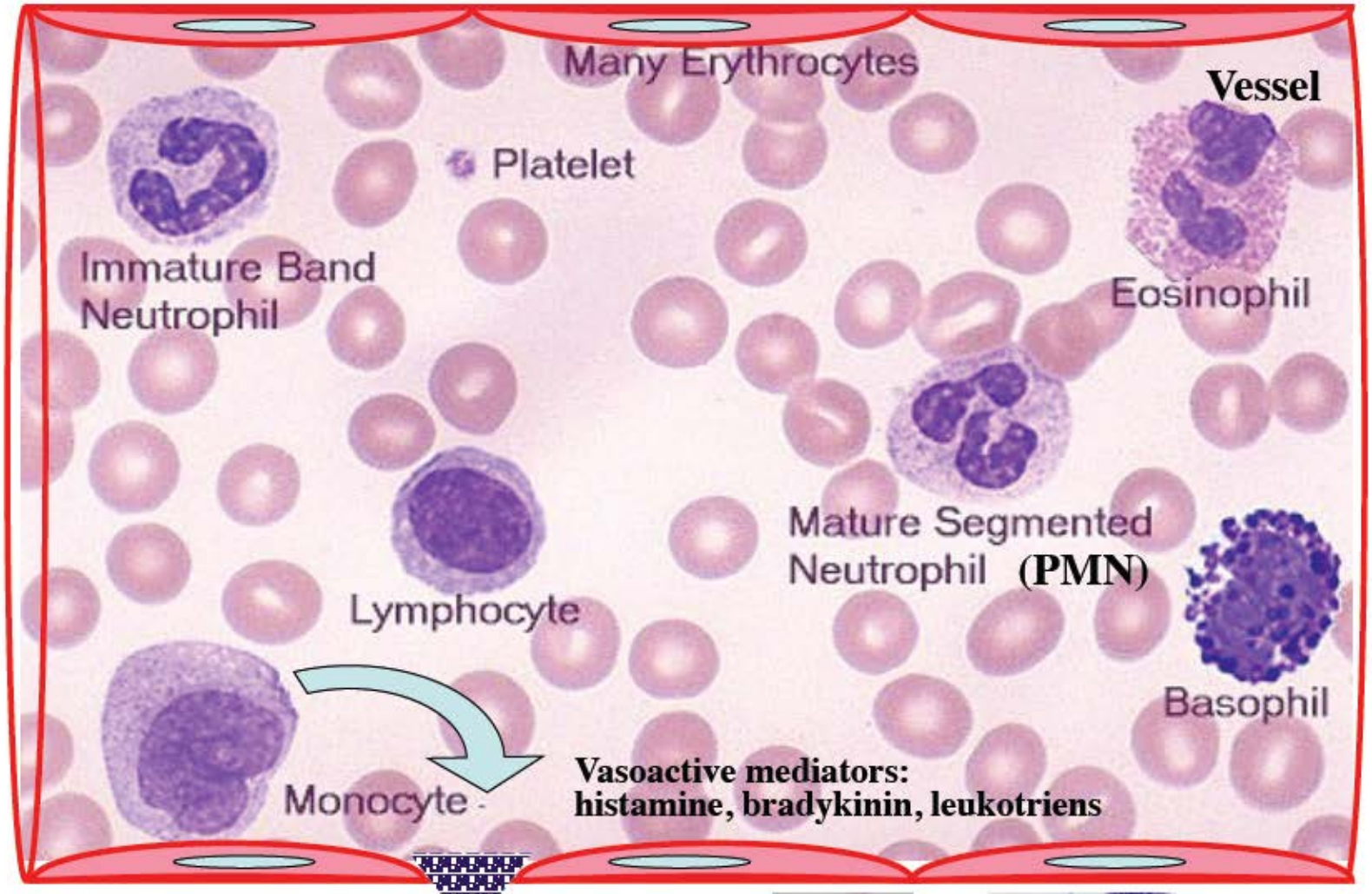
Cells

Platelets
Granulocytes (PMNs, Mast, etc)
Monocyte/Macrophages
Lymphocytes
Fibroblasts

Proteins

Complement, Pentraxins, MBL, Ficolins
Coagulation
Kininogens
Proteoglycans

Cells involved in inflammation



Components of acute and chronic inflammation

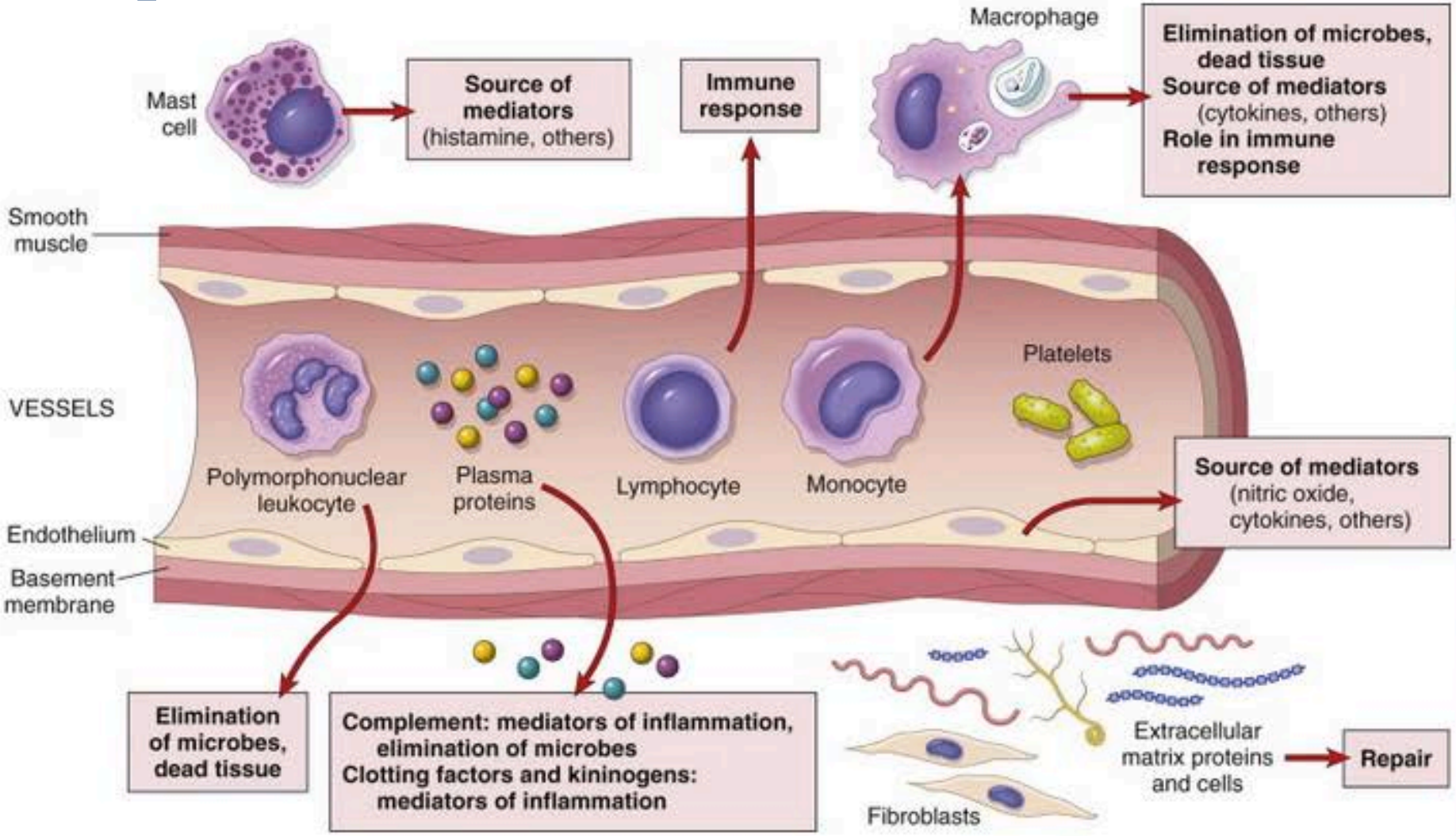


Figure 2–1

The components of acute and chronic inflammatory responses and their principal functions. The roles of these cells and molecules in inflammation are described in this chapter.

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Acute vs. Chronic inflammation

Table 2–1
Features of Acute and Chronic Inflammation

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

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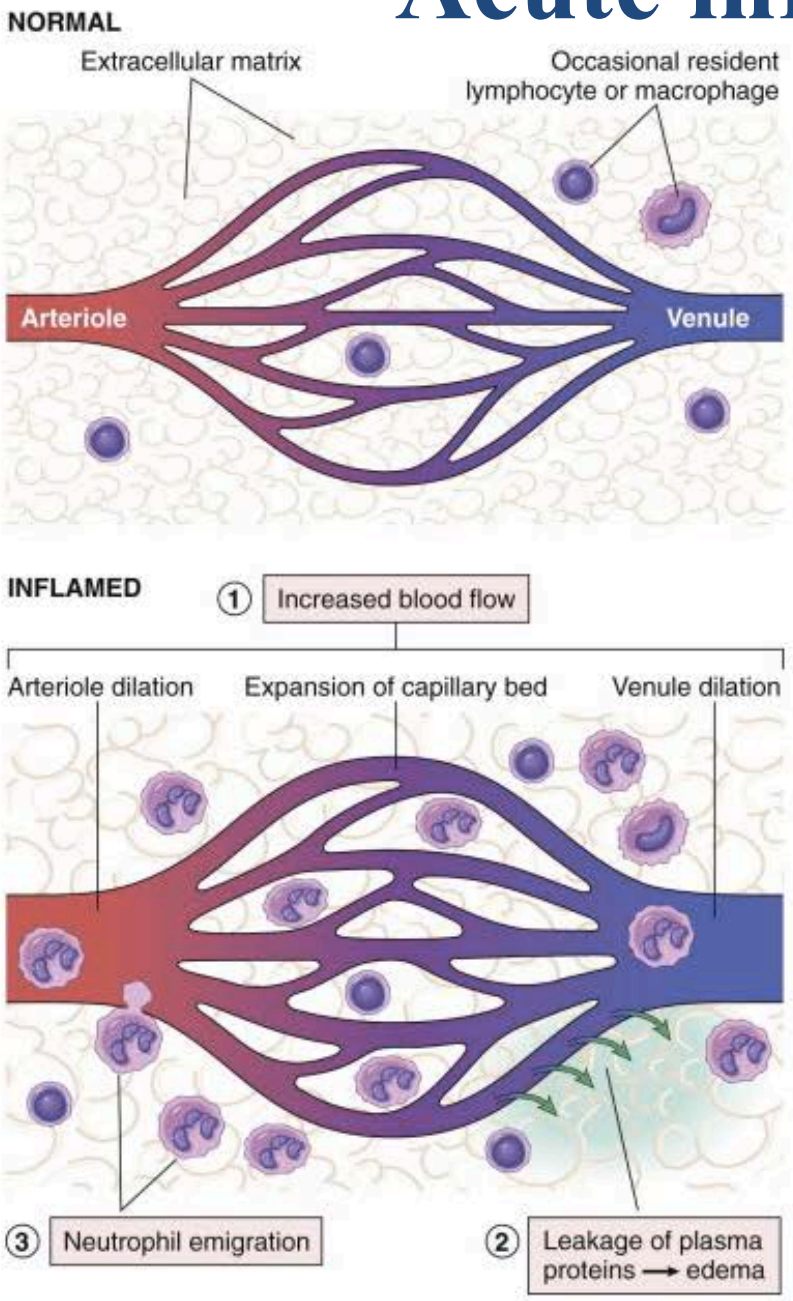
Acute inflammation

Stimuli for Acute Inflammation

- **Infections** (bacterial, viral, fungal, parasitic) & microbial toxins
- Tissue **necrosis**: ischemia, trauma, physical or chemical injury (e.g., thermal injury; irradiation; some environmental chemicals)
- **Foreign bodies** (splinters, dirt, sutures)
- **Immune reactions** (aka hypersensitivity reactions)

Acute inflammation



- Main components:
  - Vascular changes
    - Vasodilation
    - Vascular permeability
    - Increased adhesion of white blood cells
  - Cellular events
    - Cellular recruitment and activation of neutrophils (polymorphonuclear leukocytes)

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Acute Inflammation

1. **Vasodilation:**
   - The reactions of blood vessels
   - Alterations in vascular caliber (diameter)
     - Causes decrease in blood pressure
2. **Vascular leakage and edema**:
   - The accumulation of fluid and proteins of plasma in the extravascular tissues (interstitium)
3. **Leukocyte emigration** to extravascular tissues
   A. Margination and rolling
   B. Activation and adhesion
   C. Transmigration

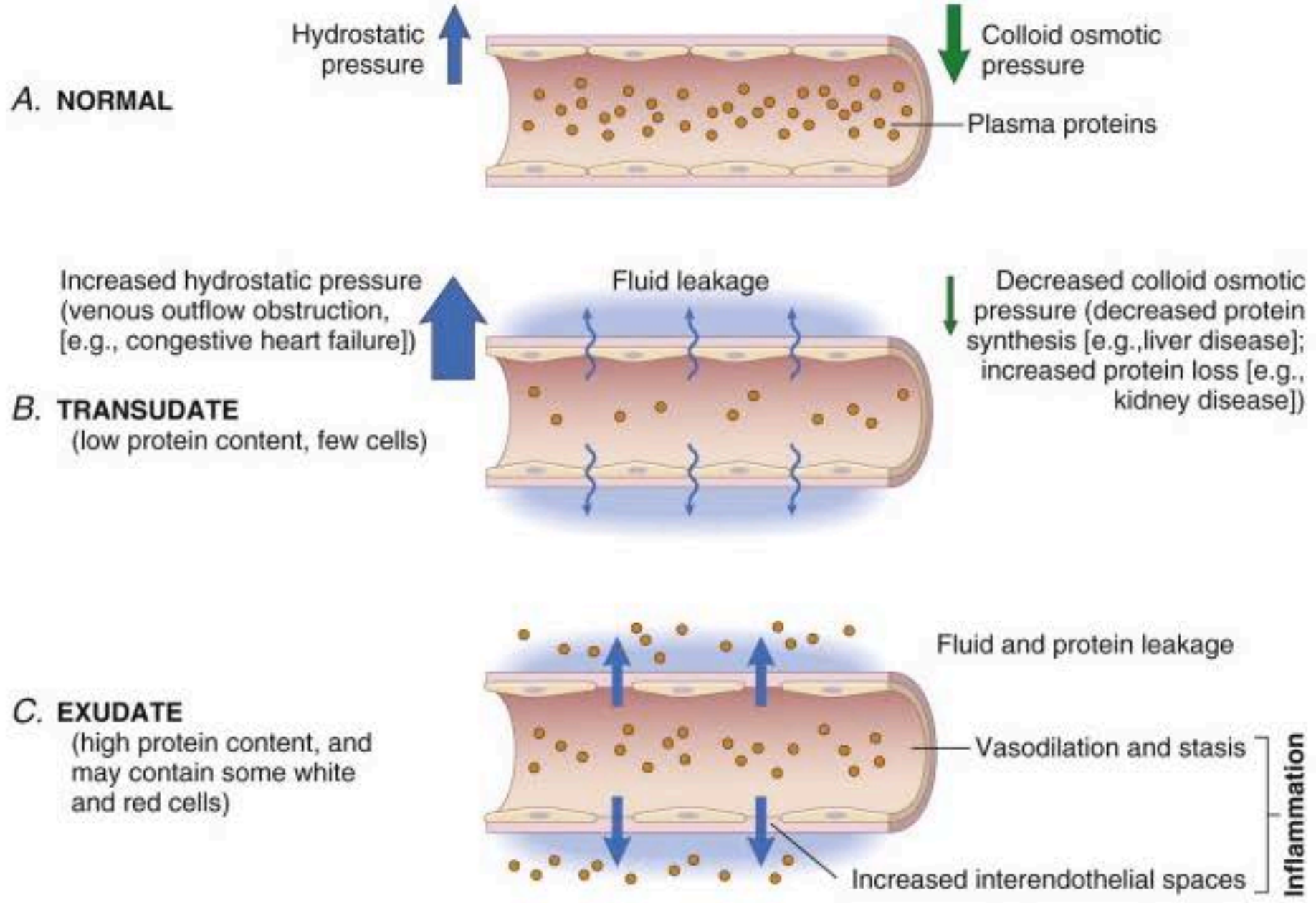
1. Vasodilation

- Change in vessel **flow**
  - NO, histamine➔vascular smooth muscle➔ vasodilation➔increased blood flow (heat & redness)
  - Stasis: slowed blood flow, hyperviscosity
  - Margination of circulating leukocytes & endothelial activation

- Followed by increased permeability of the vasculature
  - Formation of an early **transudate** (protein-poor filtrate of plasma) gives way to **exudate** (protein-rich filtrate) into extracellular tissues

2. Vascular leakage and edema

- Change in vessel permeability
  - Histamines, bradykinins, leukotrienes cause endothelial cell contraction that widens intercellular gaps of venules
  - Outpouring of protein-rich fluid (exudate) into the extracellular tissues leads to:
    - Reduction of intravascular osmotic pressure
    - Increase in extravascular/interstitial osmotic pressure
  - Increase of interstitial osmotic pressure leads to edema (water and ions)



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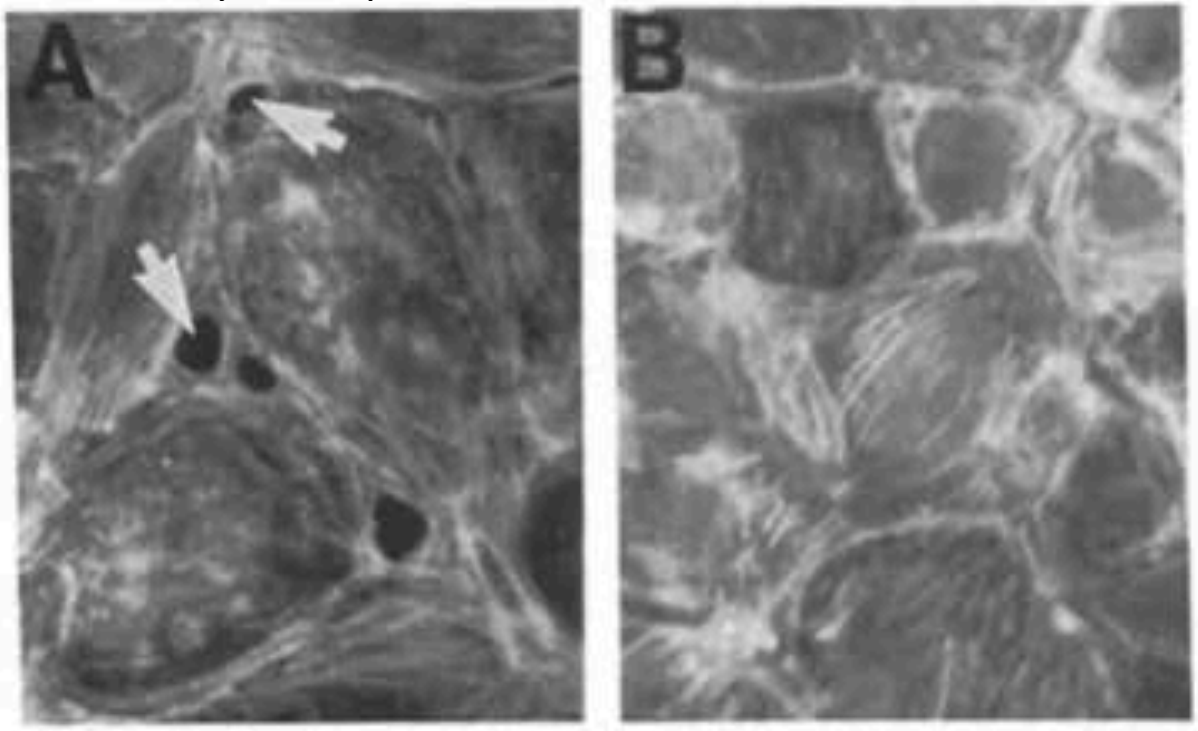
Transient Perturbation of Endothelial Integrity Induced by Natural Antibodies and Complement

By Soheyla Saadi* and Jeffrey L. Platt‡

*From the *Department of Surgery, and the ‡Department of Pediatrics and Immunology, Duke University, Durham, North Carolina 27710*

Antibody + complement

Serum alone



Gap formation in monolayers of porcine endothelial cells induced by the combination of antibody and complement

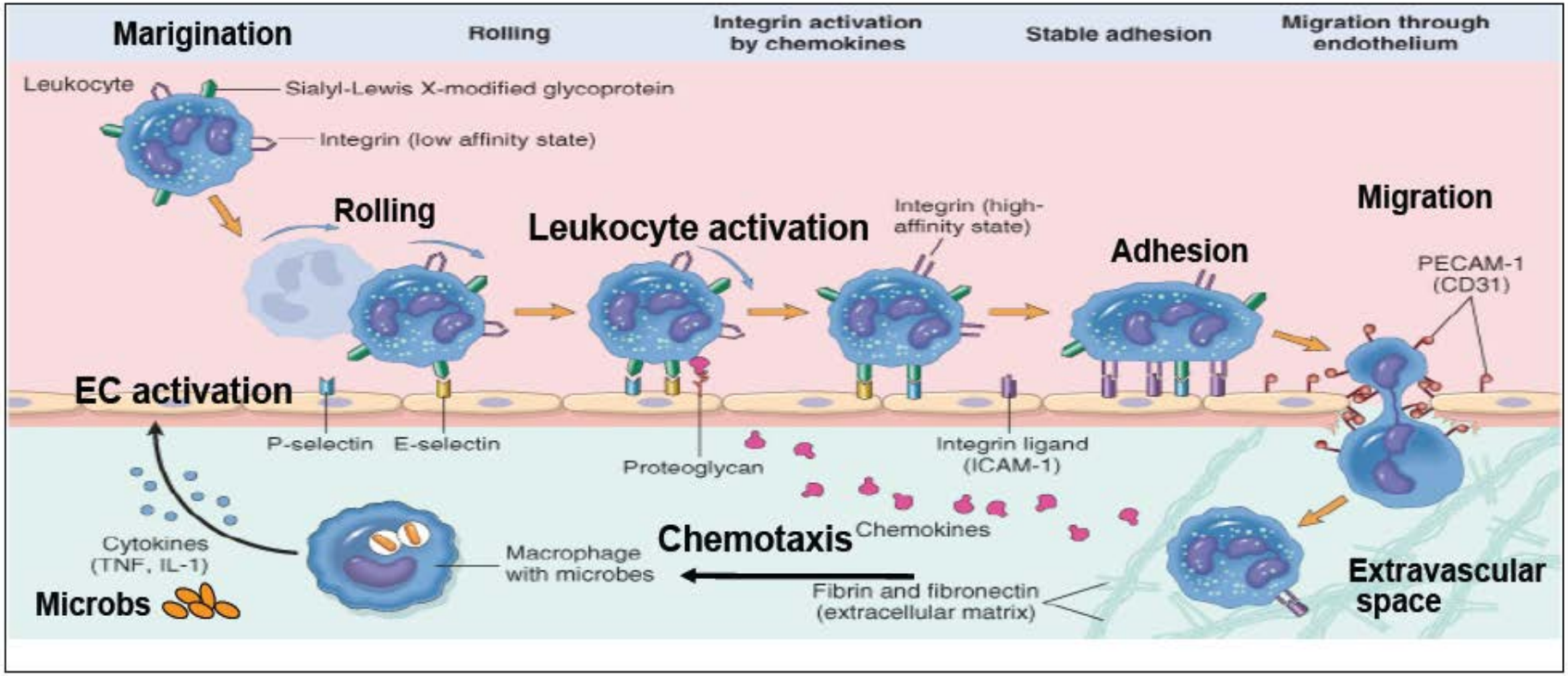
3. Leukocyte emigration to extravascular tissues

Leukocytes leave the vasculature through the following sequence of events:

A. margination and rolling

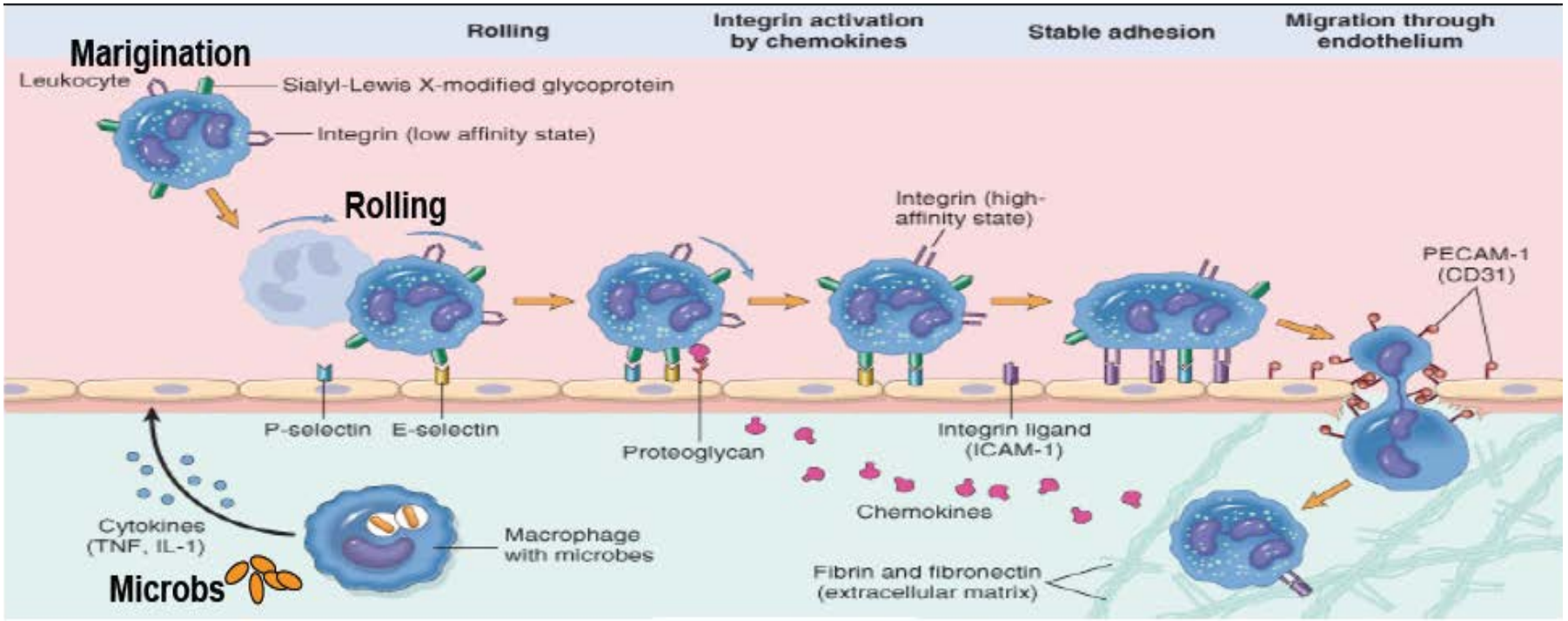
B. activation and adhesion

C. transmigration



A. Margination and Rolling

- Fluid (**exudate**) leaves the vessel, leukocytes **"marginate"** along the endothelial surface
- In the process of **"rolling"** individual and then rows of leukocytes tumble slowly along the endothelium, adhere through surface **adhesion molecules on endothelial** cells and their complementary **ligands on leukocytes**

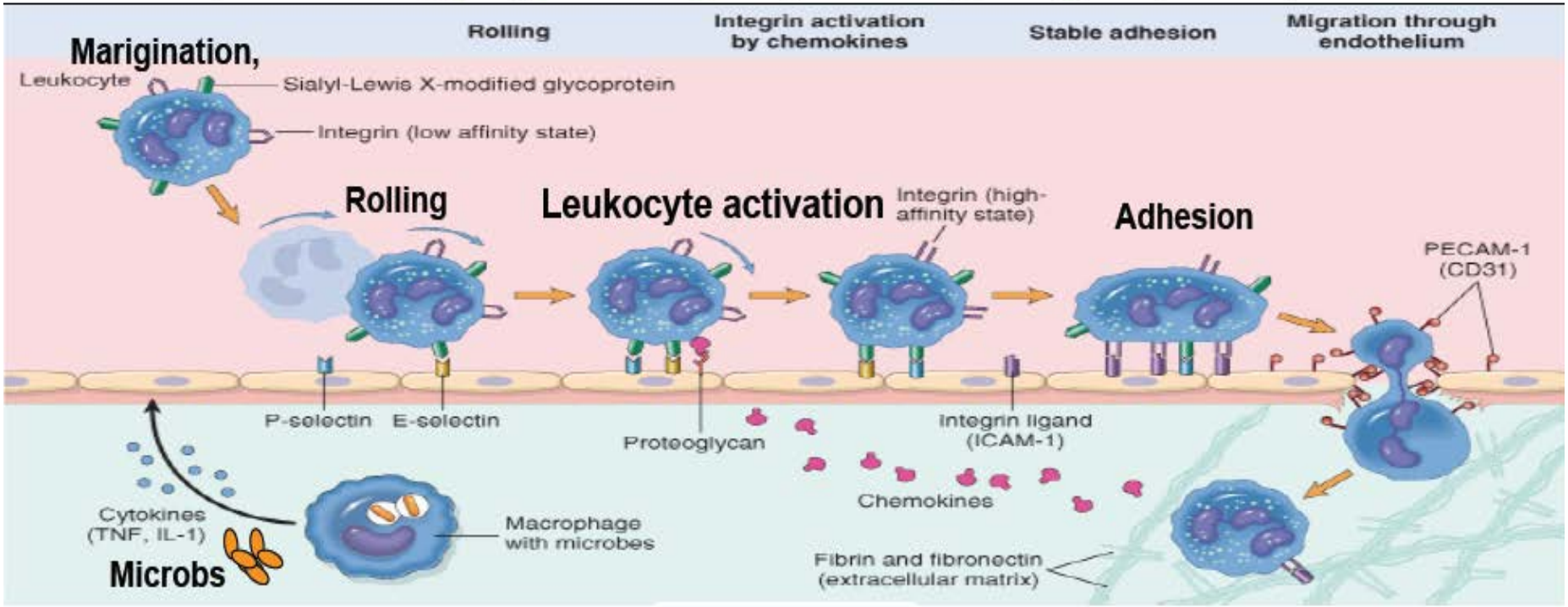


B. Activation and Adhesion

Adhesion is mediated by selectin family (adhesion molecules)

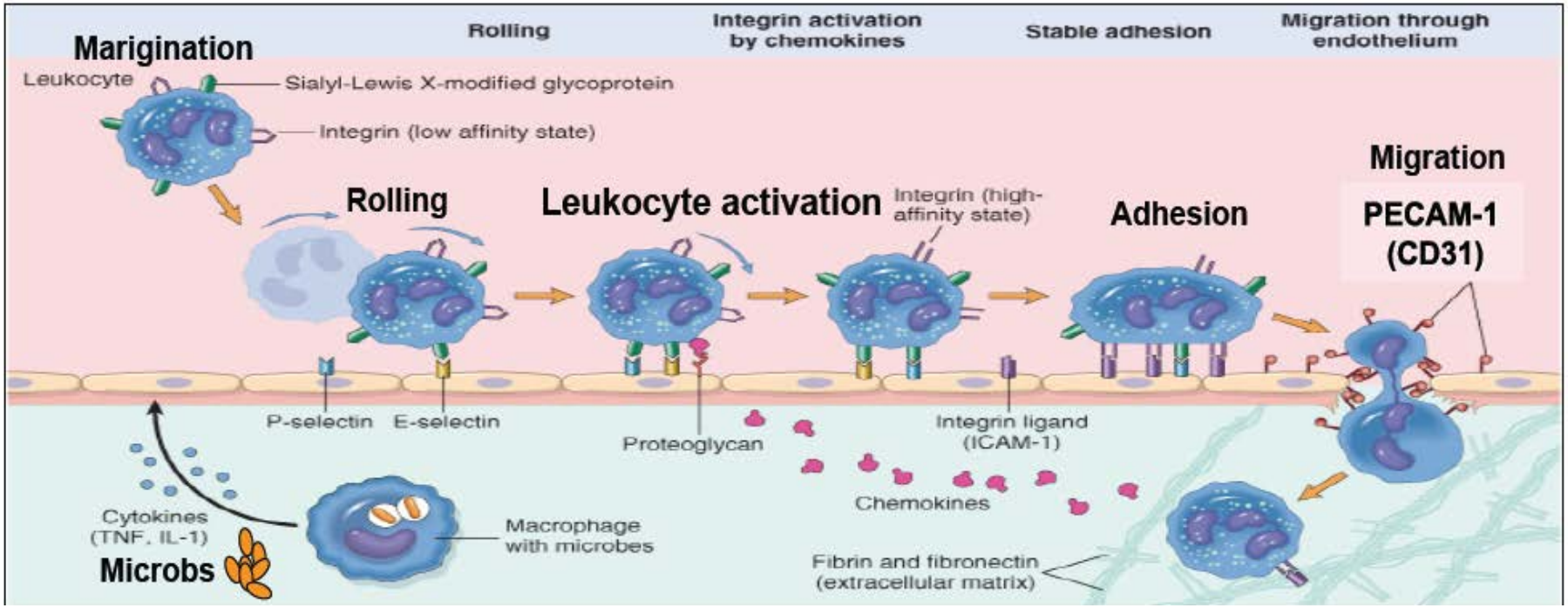
- **E-selectin** (endothelium)
- **P-selectin** (platelets, endothelium)
- **L-selectin** (leukocytes)

Selectins that are upregulated on endothelium by cytokines (TNF-α, IL-1) at injury sites bind leukocyte surface molecules (*i.e.*, **Sialyl-Lewis X modified GP, P-selectin glycoprotein ligand(PSGL-1), integrins, CD34**)

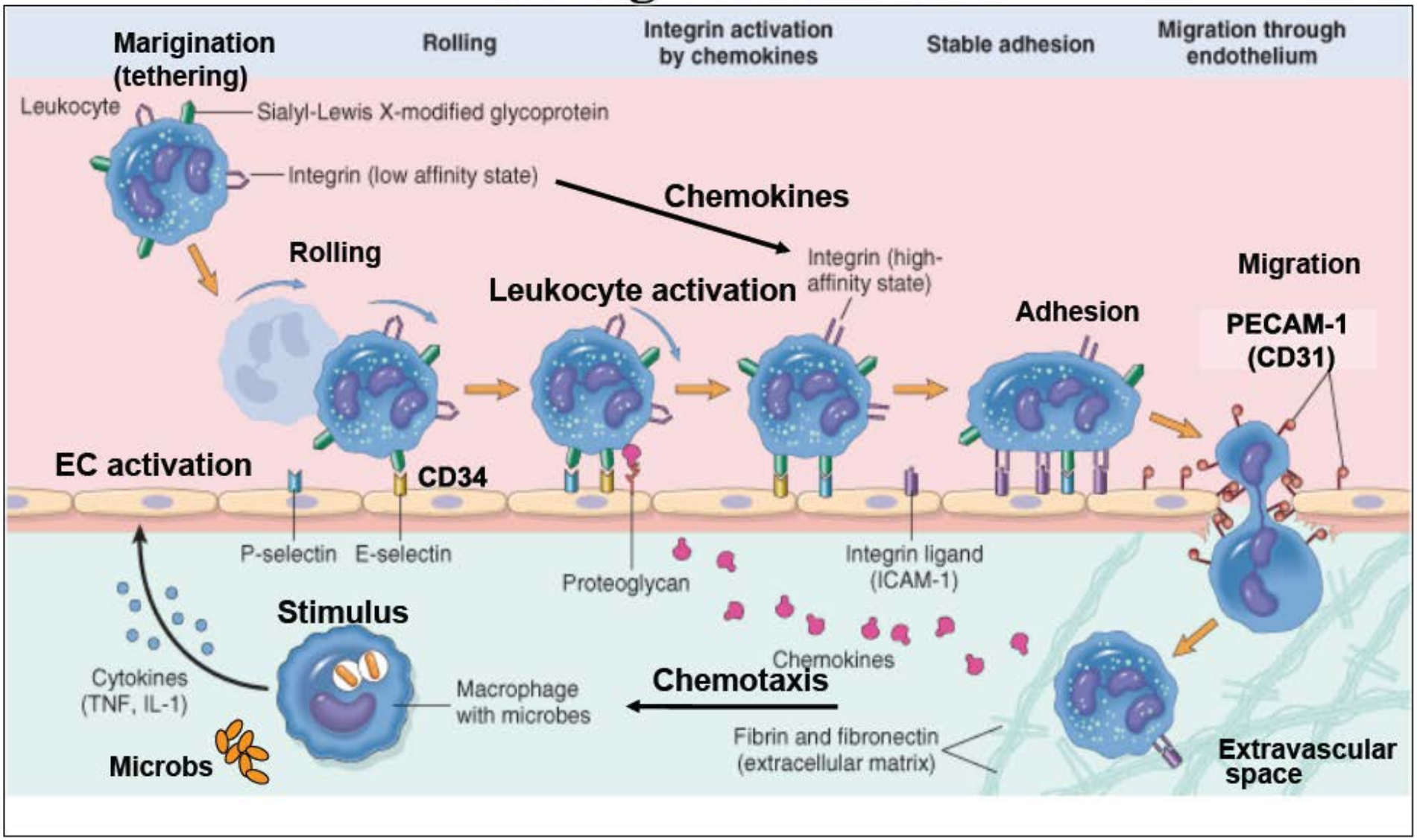


C. Transmigration (diapedesis)

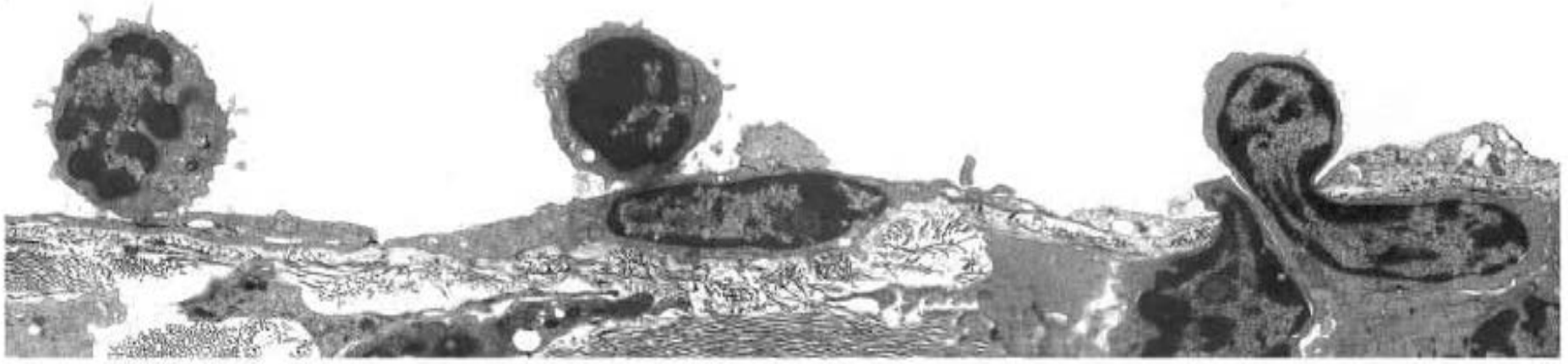
- Occurs after firm adhesion within the system of venules and capillaries via **PECAM –1 (CD31)** (platelet-endothelial cell adhesion molecule) on endothelial cells, neutrophils, monocytes/macrophages, lymphocytes
- Upregulation of endothelial cell ligands (integrins) for adhesion molecules results in activation/adhesion of different populations of leukocytes (monocytes, lymphocytes, *etc*)



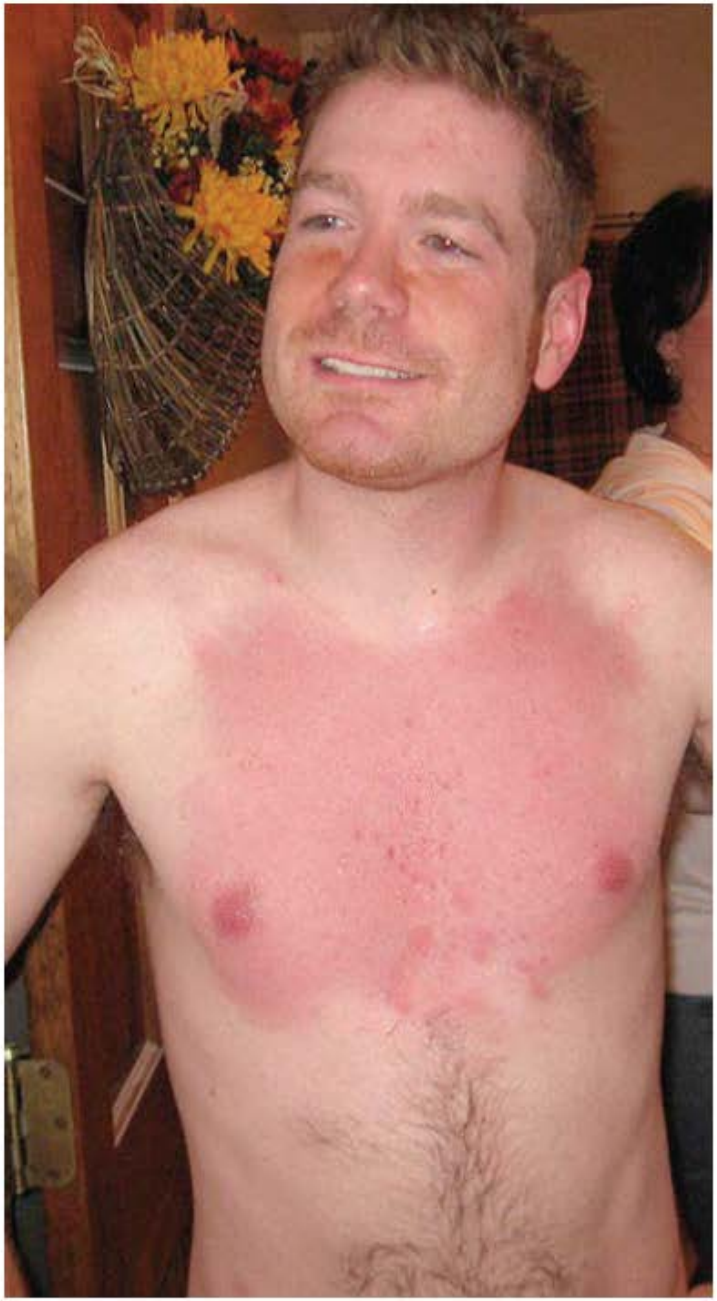
The multistep process of leukocyte migration through blood vessels



The multistep process of leukocyte migration through blood vessels



Clinical Examples of Acute Inflammation



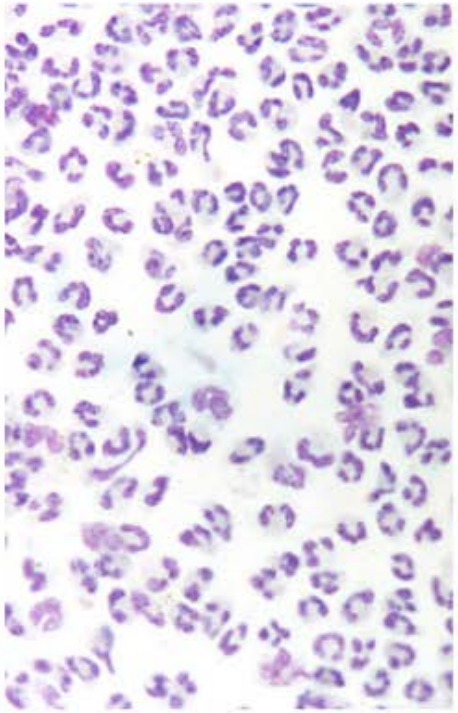
Acute skin inflammation

- skin reacts to harmful stimuli such as pathogens, damaged cells, or irritants.

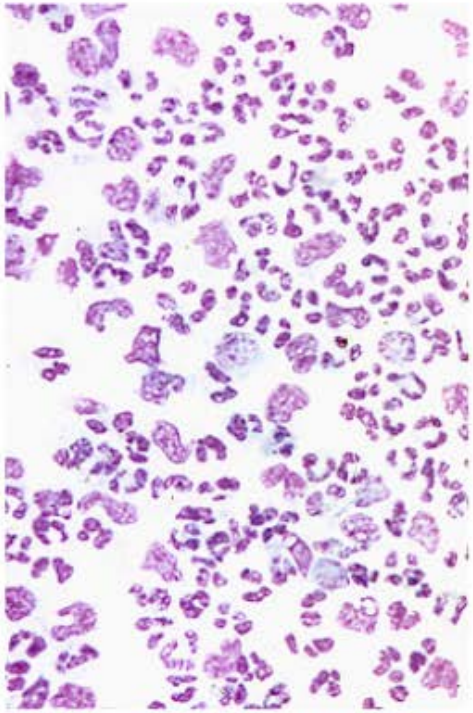
- Inflammation helps get rid of these harmful stimuli and initiates the skin tissue's healing process

- without inflammation, the skin will not heal.

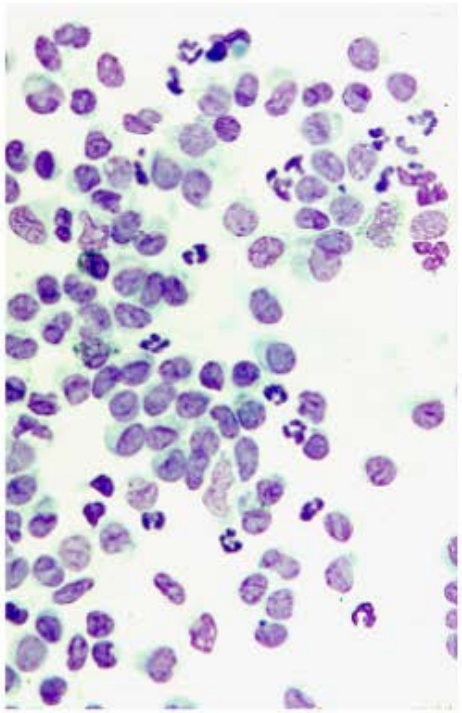
Time course of inflammatory cell infiltration in the skin



2h

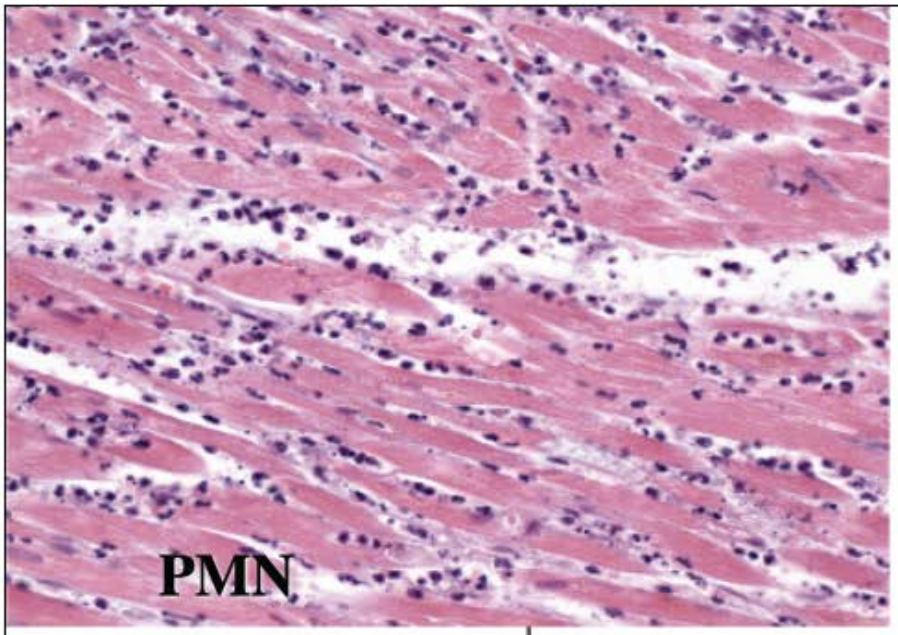


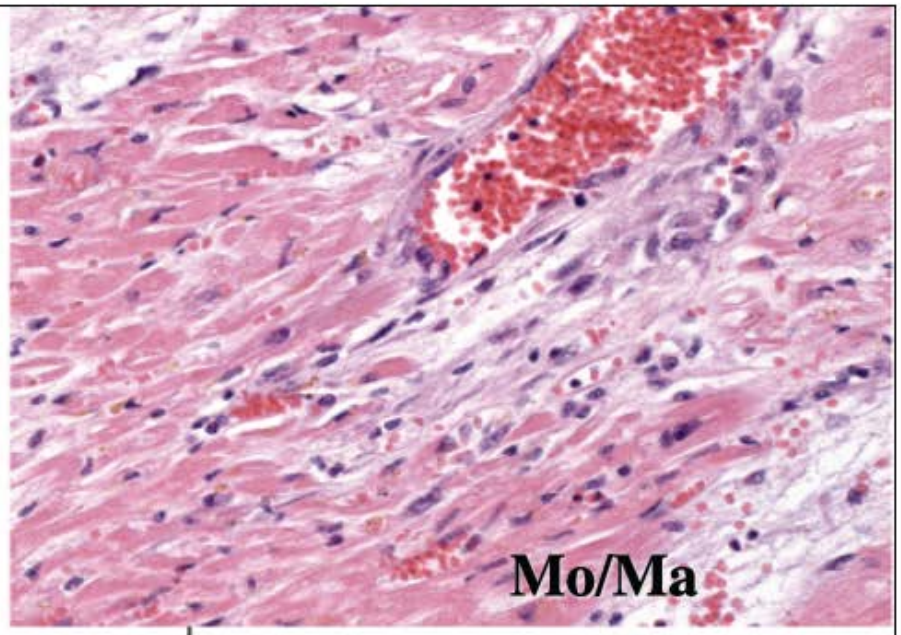
6h



48h

Acute injury of infarcted myocardium

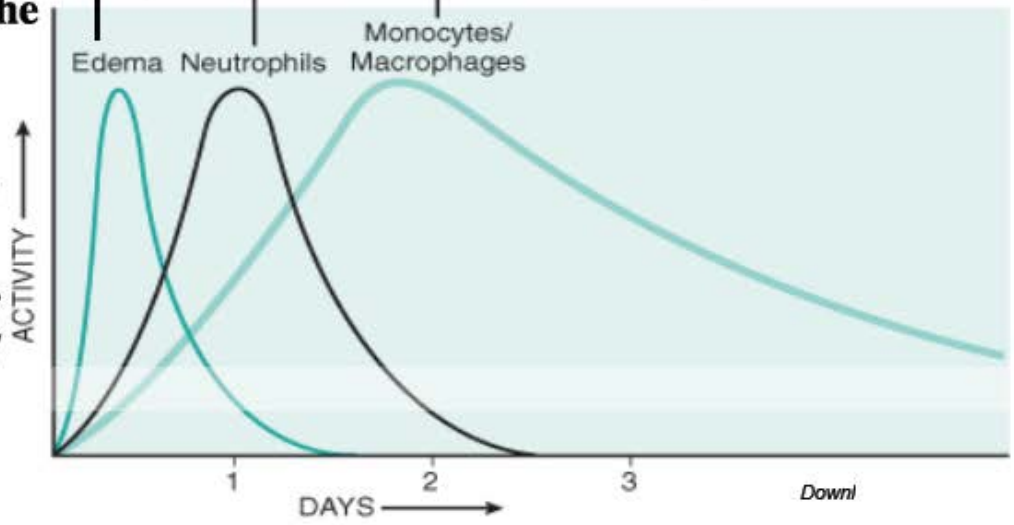




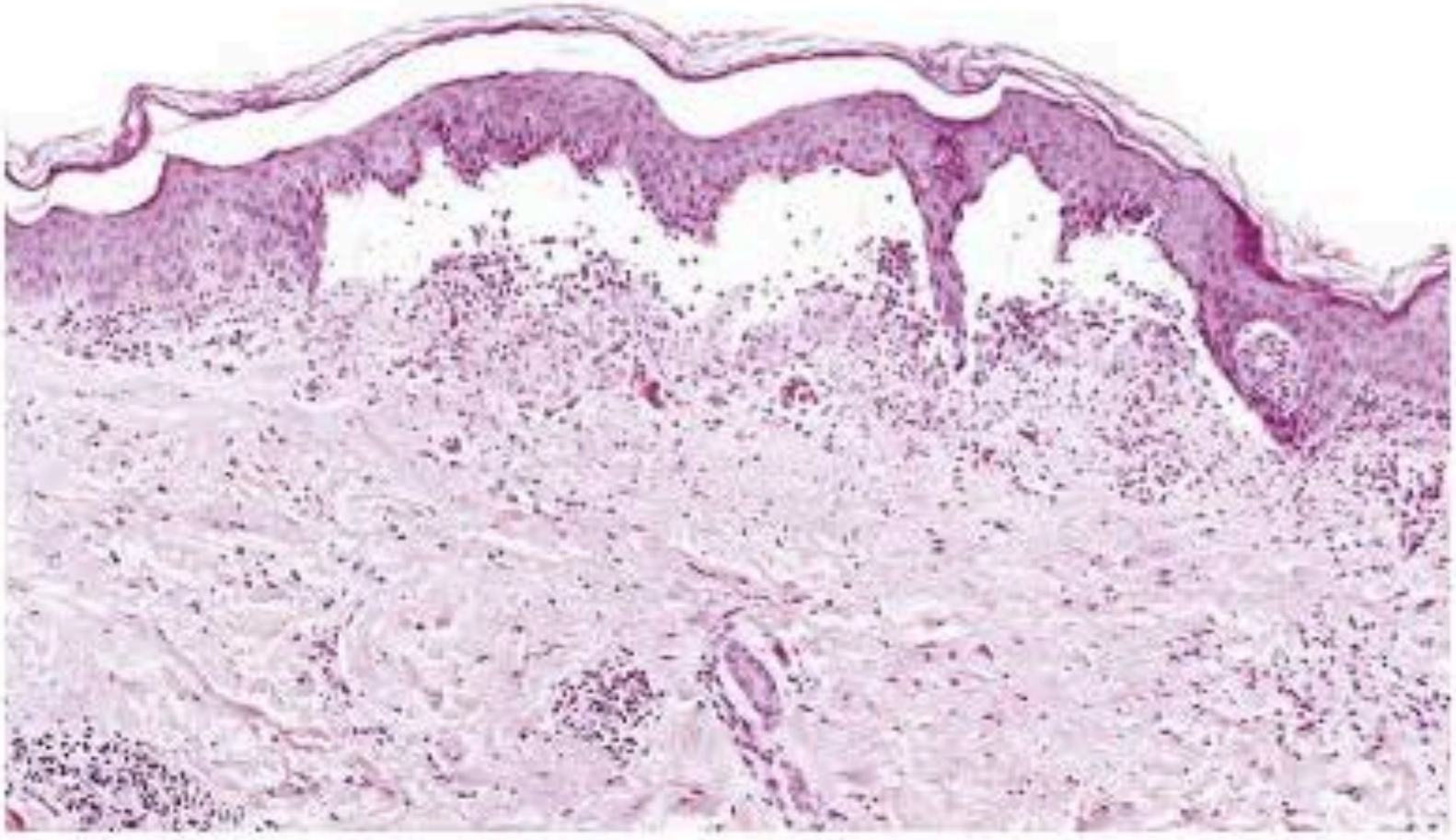
1. **Exudate** leaves the vessel

2. Increase of interstitial osmotic pressure

3. Accumulation of PMNs, then Mono/ Mac



Acute inflammation: skin blister



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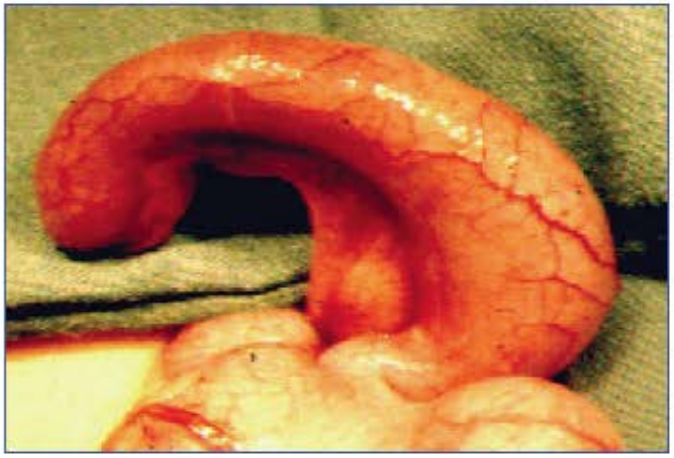
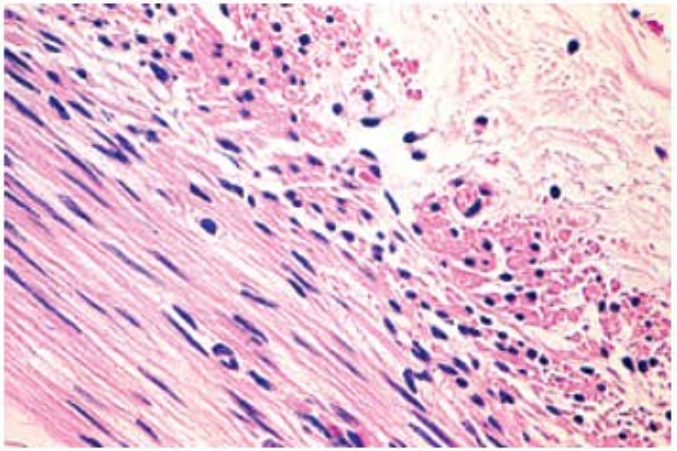
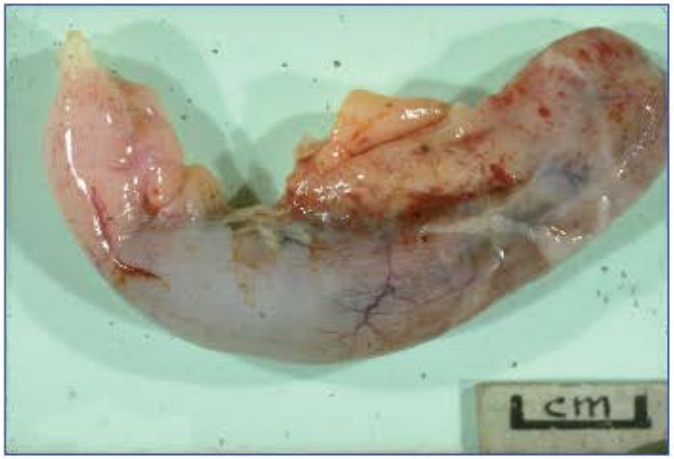
Acute Inflammation: Appendicitis

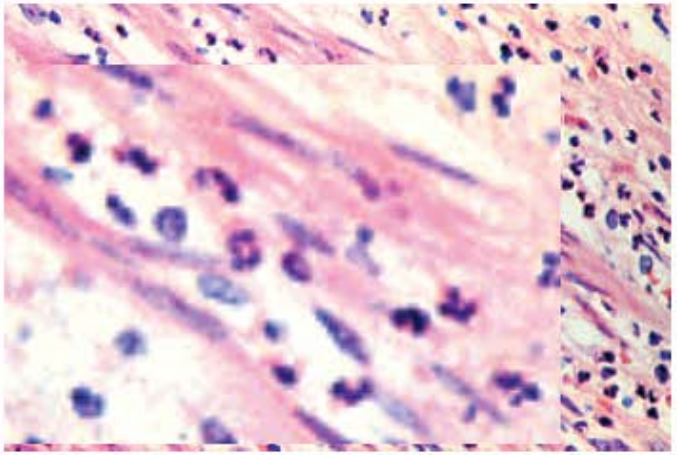


normal

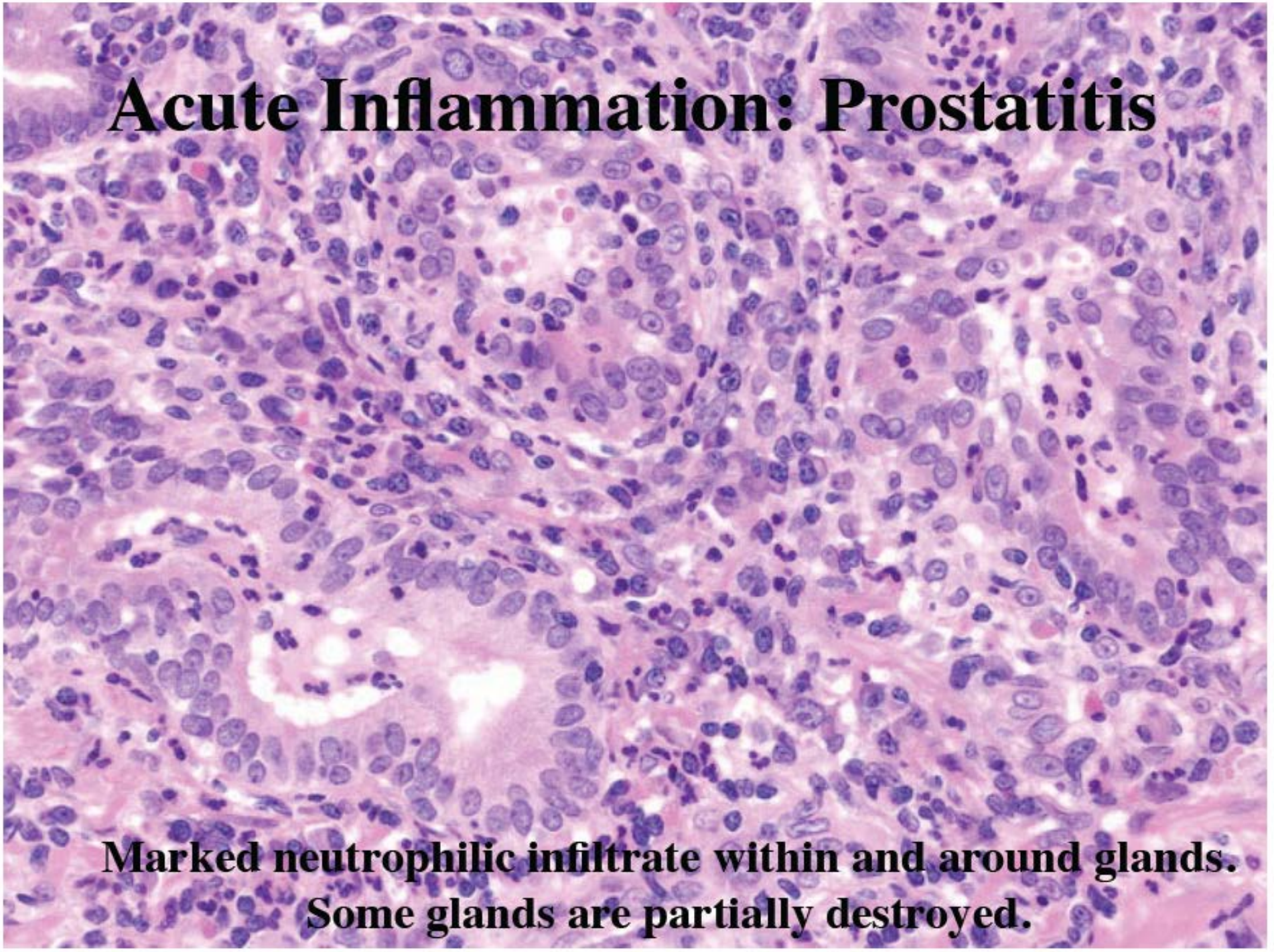




inflamed



Acute Inflammation: Prostatitis



Marked neutrophilic infiltrate within and around glands.
Some glands are partially destroyed.

Acute inflammation: bacterial bronchopneumonia

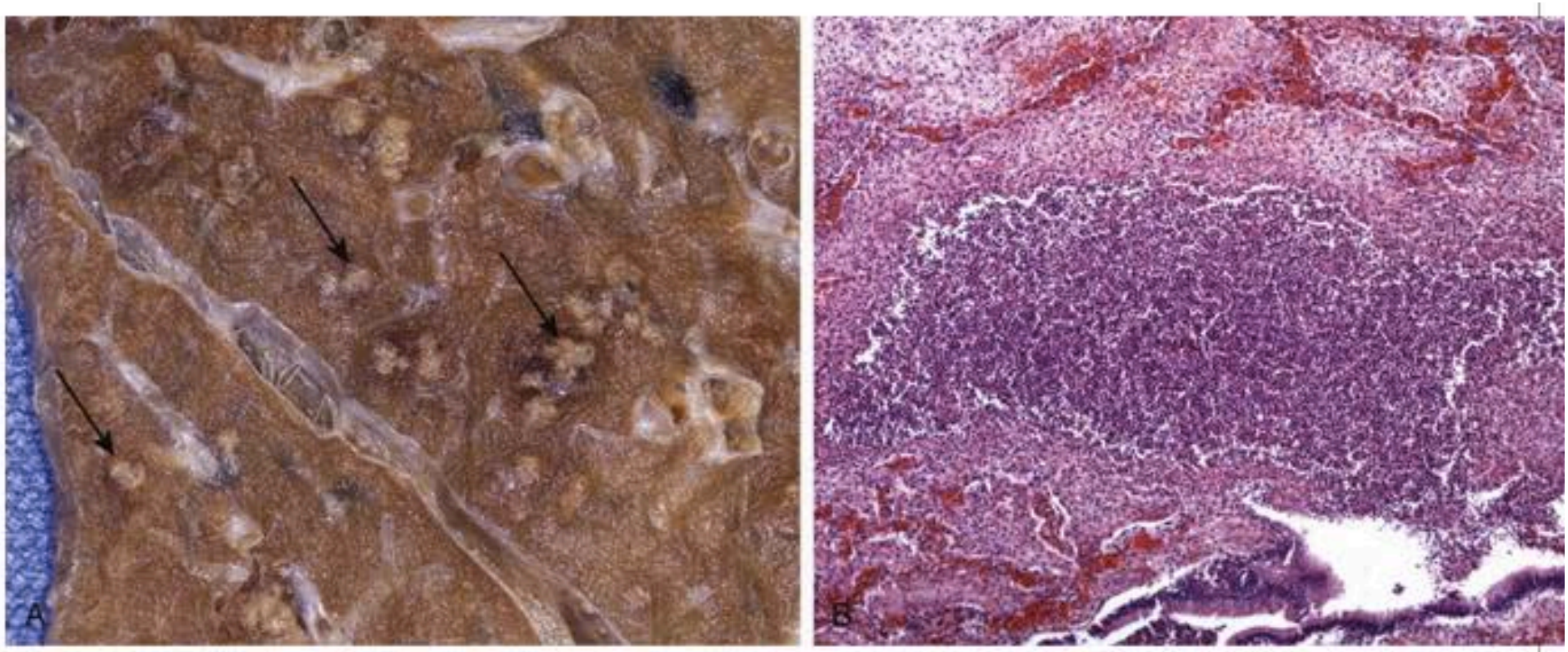


Figure 2–13 Purulent inflammation with abscess formation. A, Multiple bacterial abscesses in the lung (*arrows*) in a case of bronchopneumonia. B, The abscess contains neutrophils and cellular debris and is surrounded by congested blood vessels.

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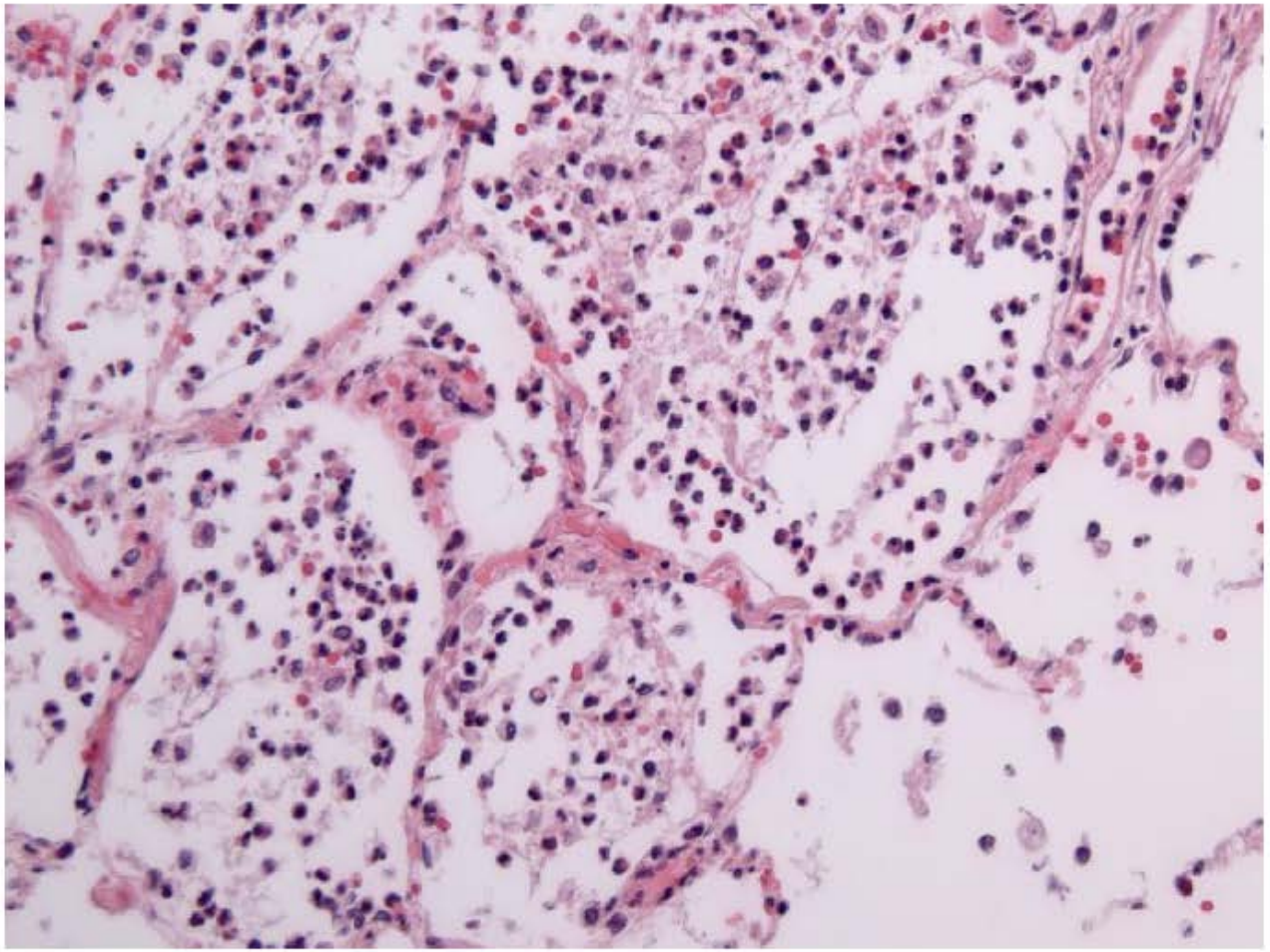
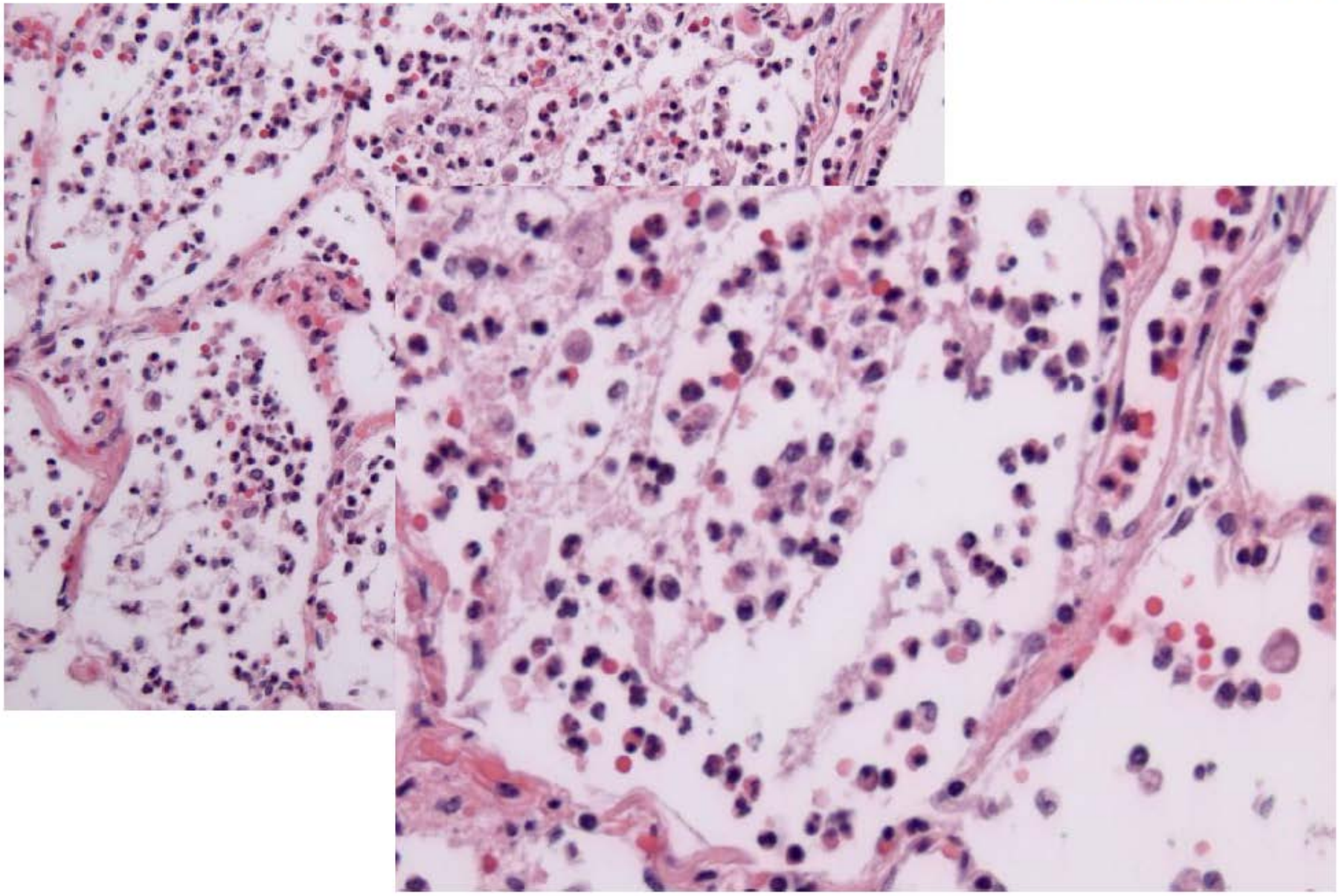
Acute Inflammation: Bacterial Pneumonia

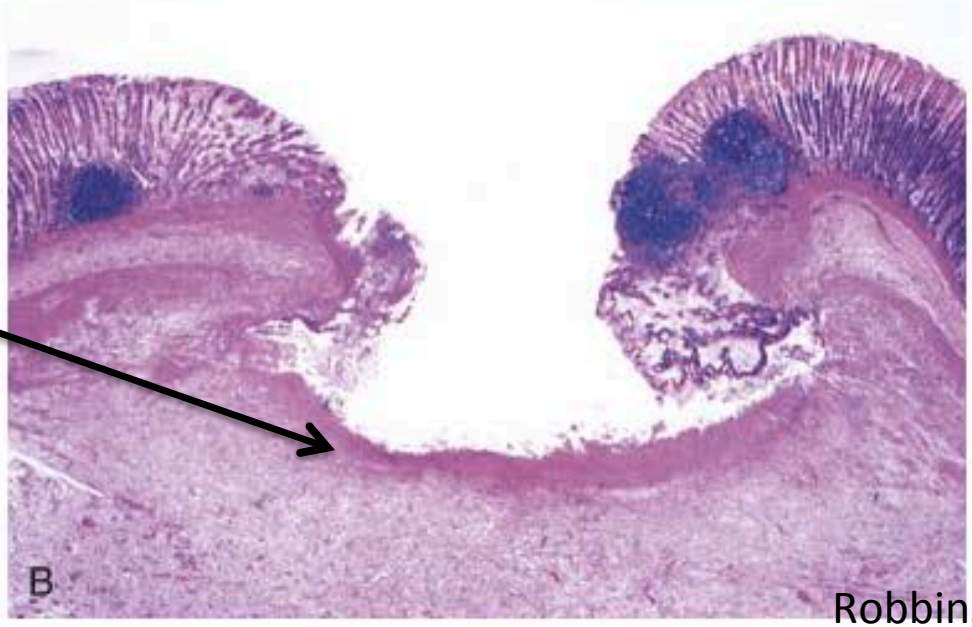


Acute Inflammation: Bacterial Pneumonia



Acute inflammation: chronic gastric ulcer

Chronic ulcer with an acute inflammatory exudate at the base



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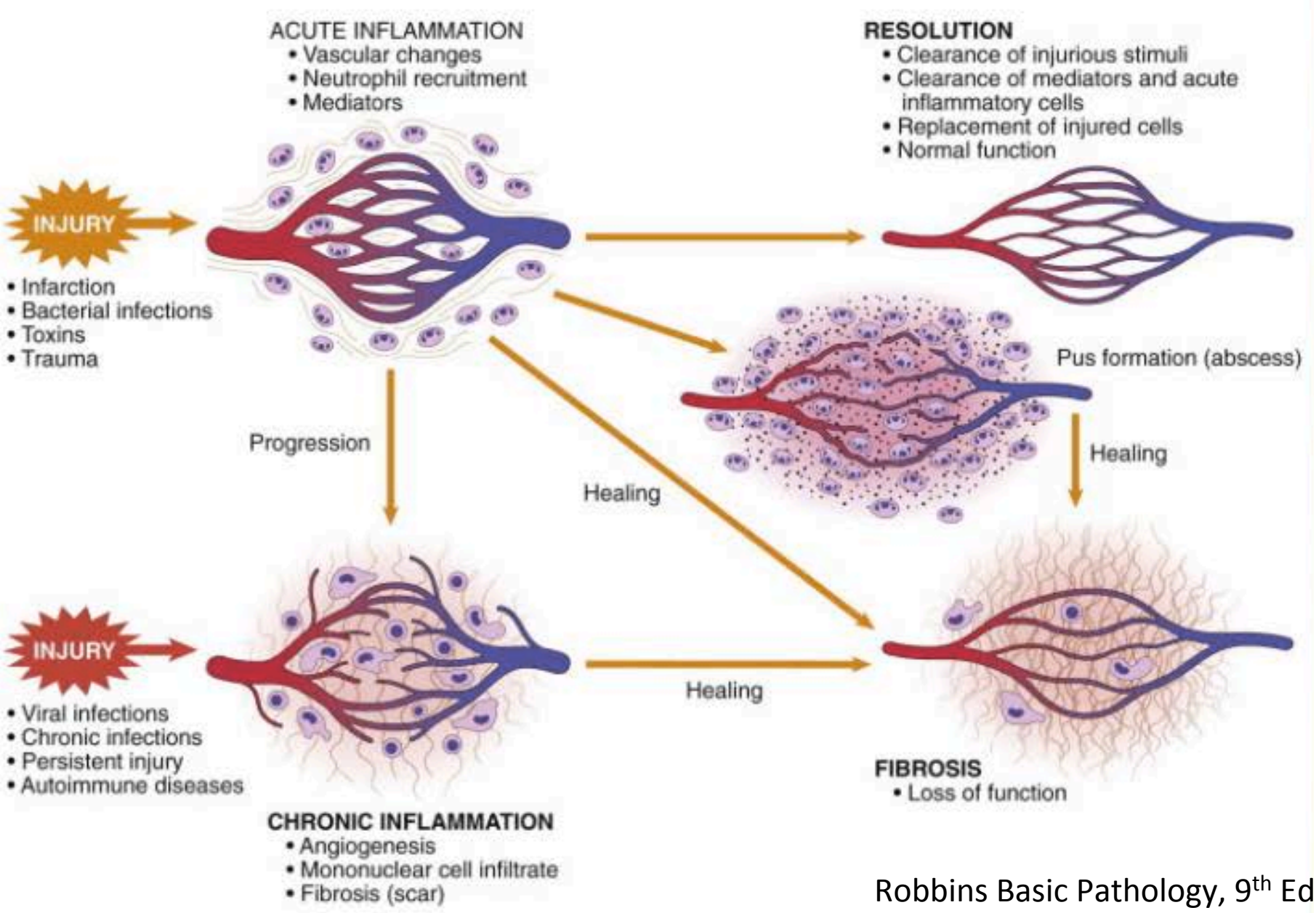
Outcomes of acute inflammation



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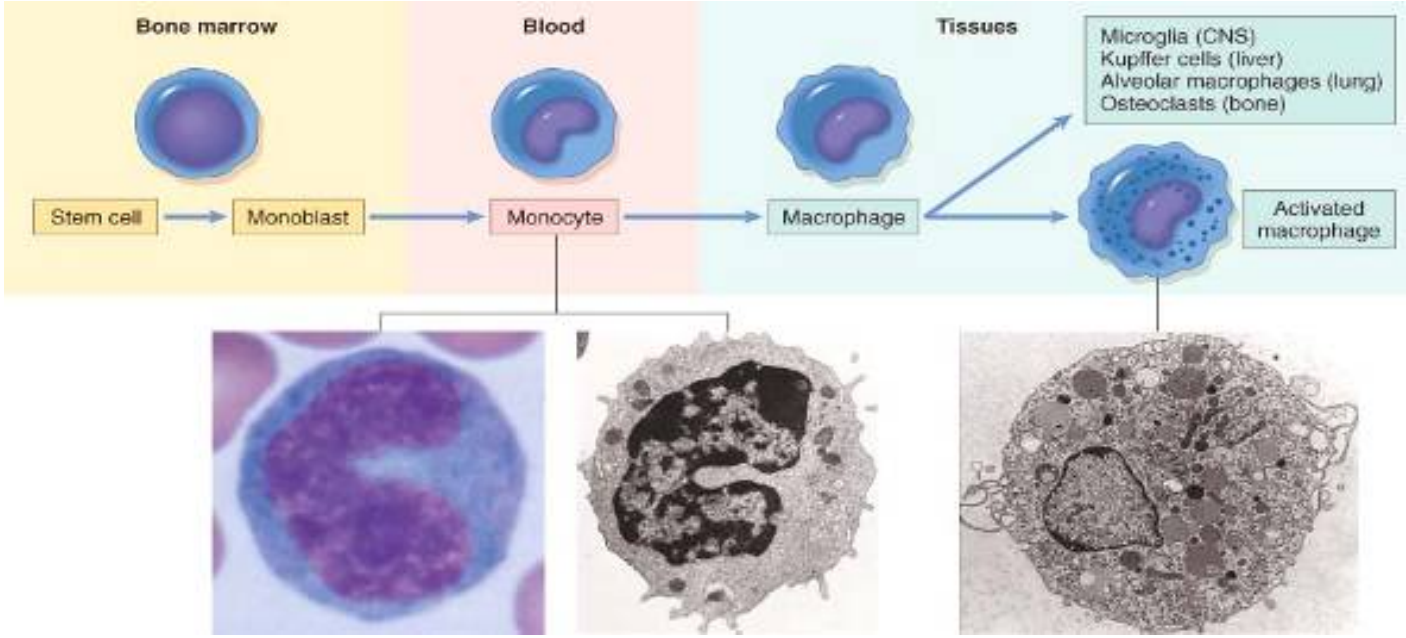
Chronic inflammation

Features of chronic inflammation

- Chronic inflammation = long duration
- Components:
  - Lymphocyte, plasma cell, macrophage (mononuclear cell) infiltration
  - Tissue destruction by inflammatory cells
  - Repair with fibrosis and angiogenesis (new vessel formation)



Acute vs. Chronic inflammation

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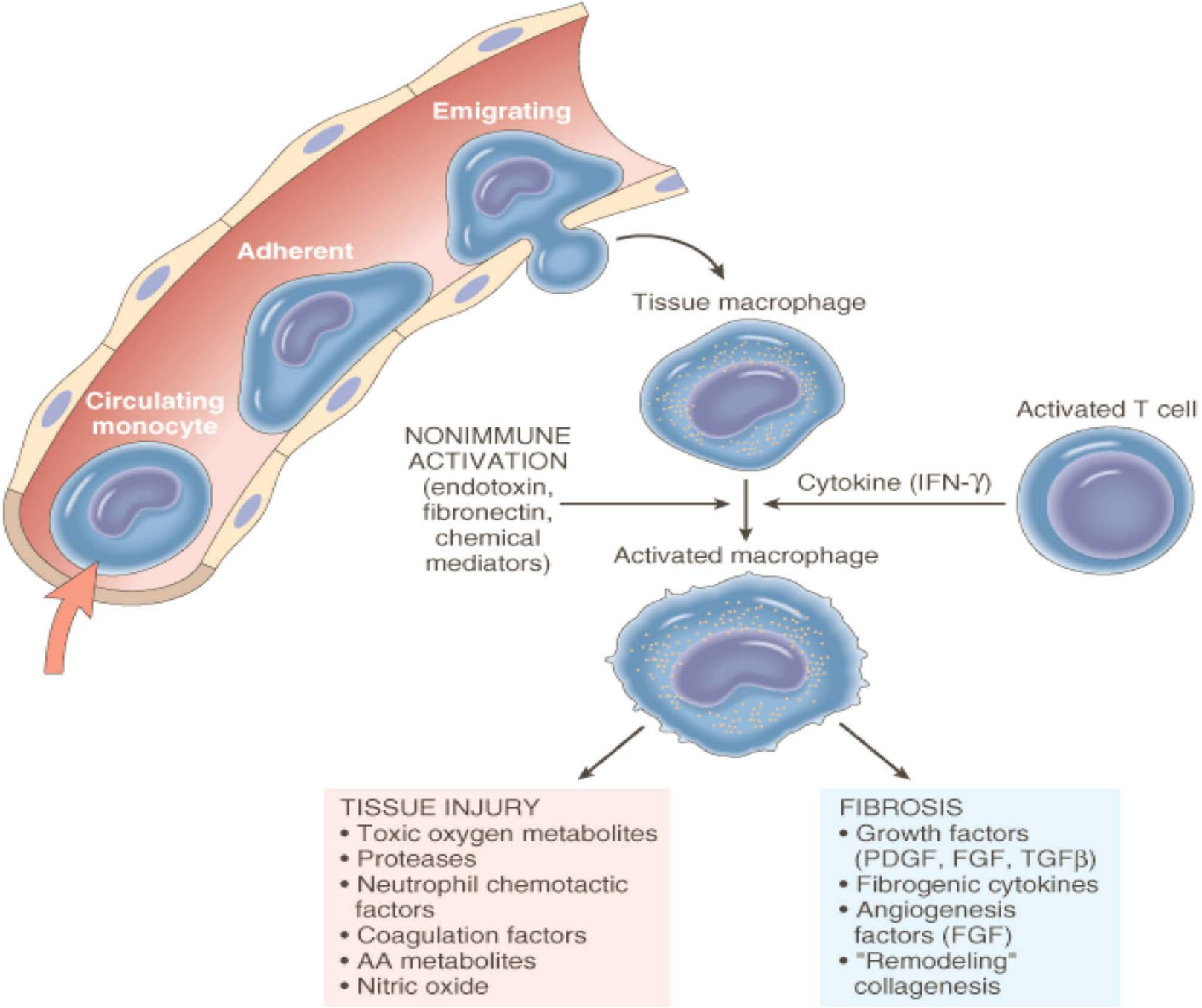
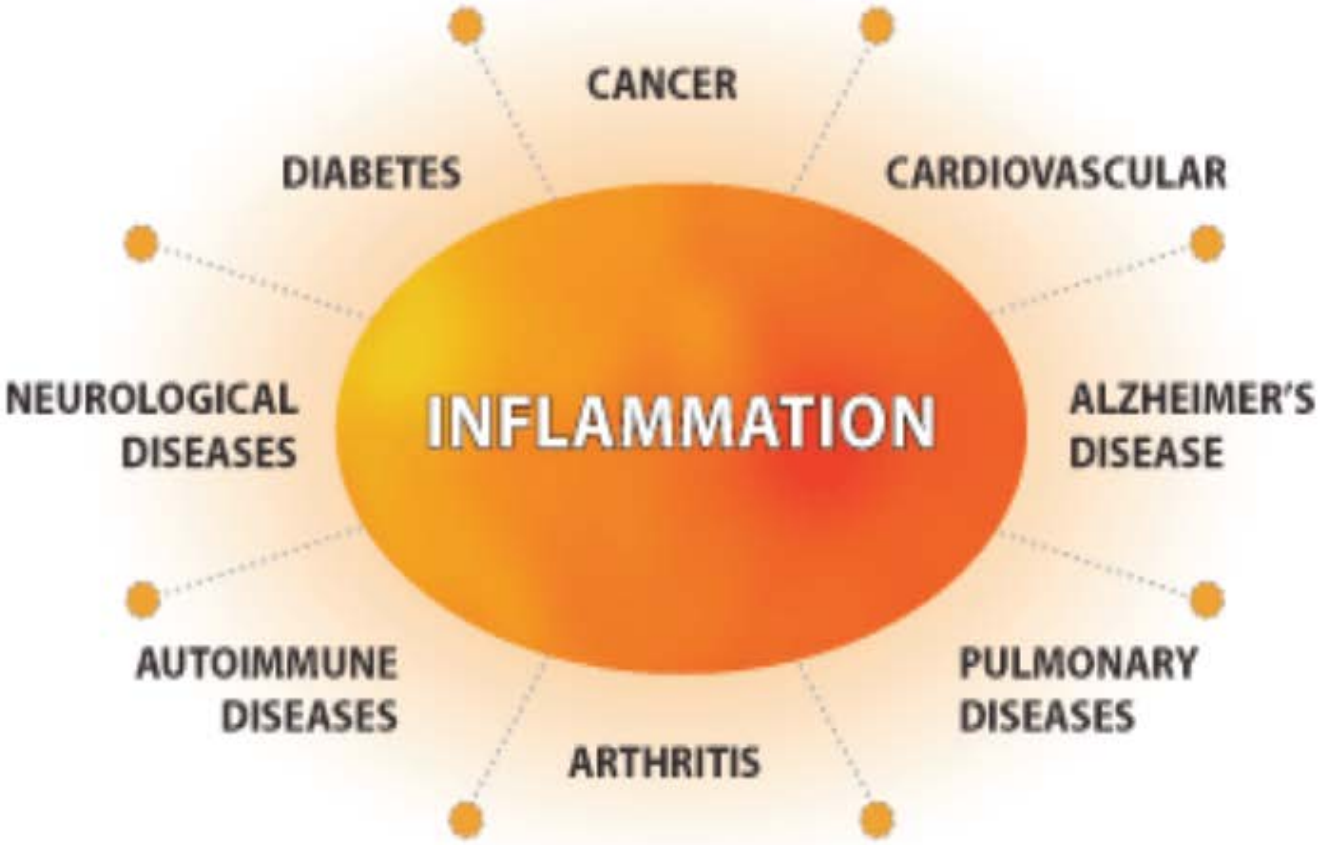

Emigrating
Adherent
Circulating monocyte
Tissue macrophage
Activated T cell
NONIMMUNE ACTIVATION (endotoxin, fibronectin, chemical mediators)
Cytokine (IFN-γ)
Activated macrophage
TISSUE INJURY
• Toxic oxygen metabolites
• Proteases
• Neutrophil chemotactic factors
• Coagulation factors
• AA metabolites
• Nitric oxide
FIBROSIS
• Growth factors (PDGF, FGF, TGFβ)
• Fibrogenic cytokines
• Angiogenesis factors (FGF)
• "Remodeling" collagenesis

Causes of chronic inflammation

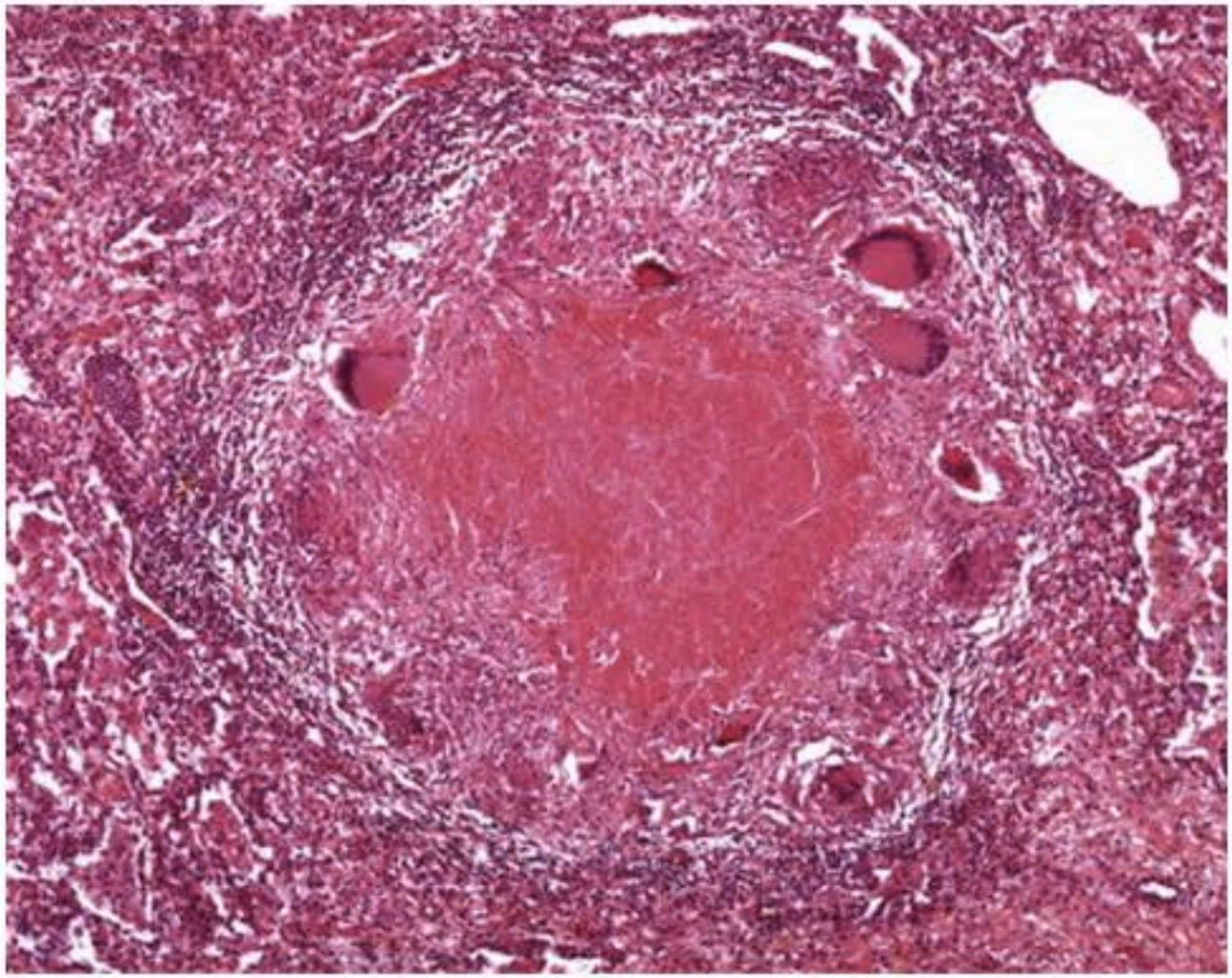
- **Persistent** injury or infection
  - Ulcer, tuberculosis
- **Prolonged** exposure to a toxic agent
  - Pulmonary silicosis (silica in the lung)
- **Autoimmune disease**—self-perpetuating immune reaction that results in tissue damage and inflammation
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Multiple sclerosis

Diseases with chronic inflammation



Clinical examples of chronic inflammation

Chronic inflammation: tuberculous granuloma

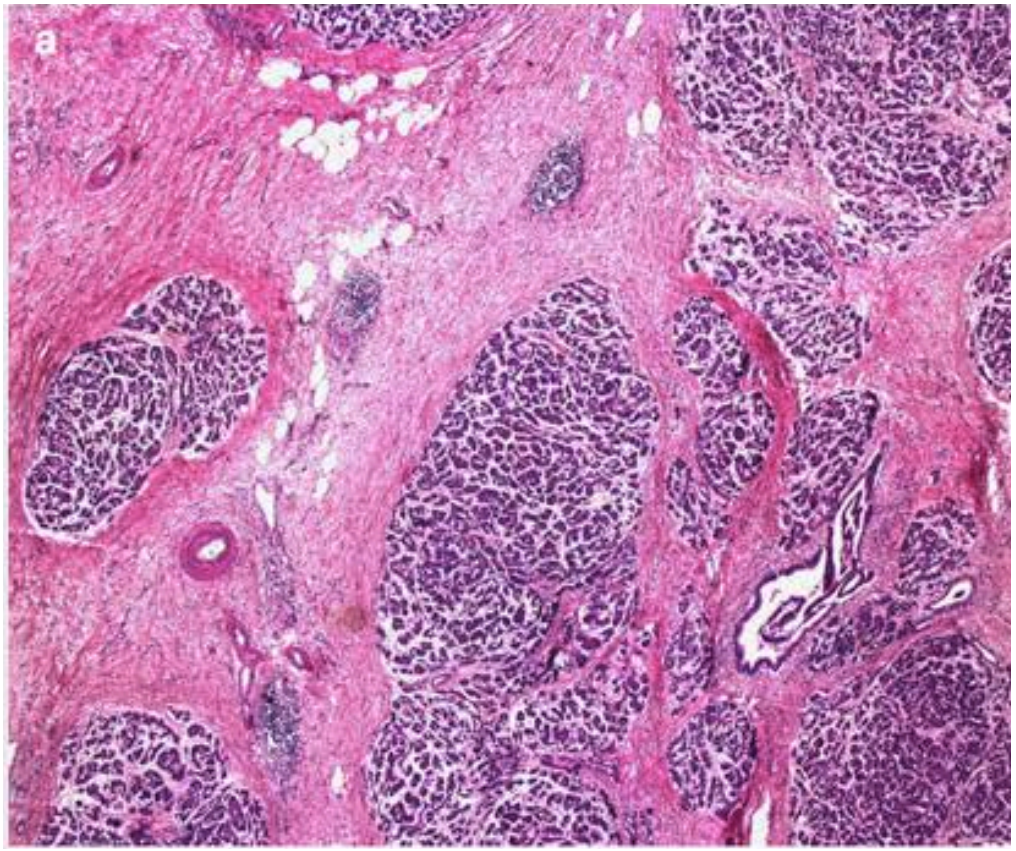


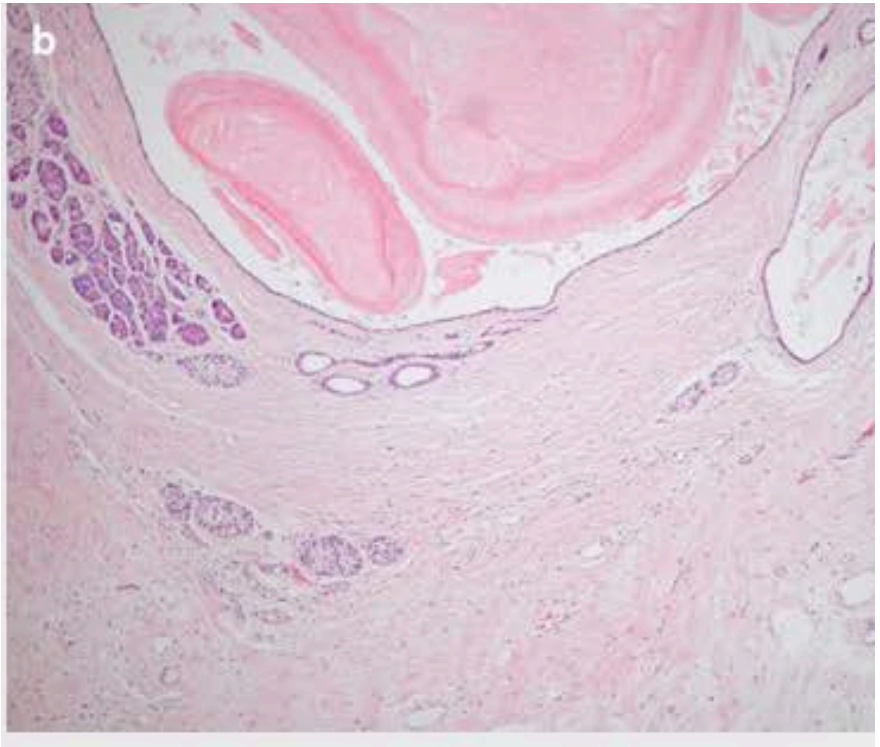
Features:

1. Central necrosis
2. Epithelioid macrophages
3. Langhans-type giant cells
4. Peripheral lymphocytes

Robbins Basic Pathology, 9th Ed.

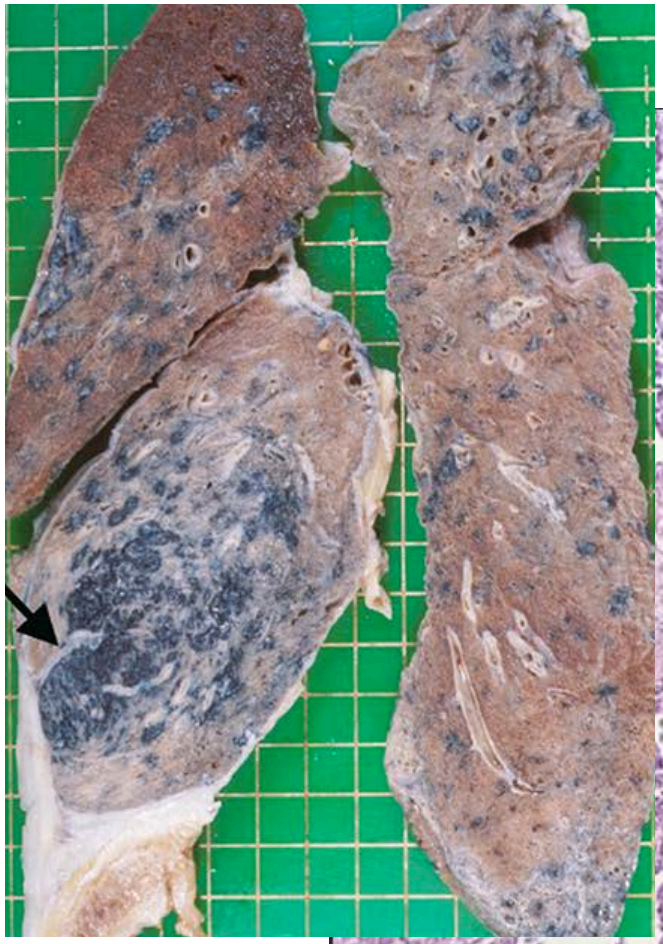
Chronic inflammation: chronic pancreatitis with fibrosis



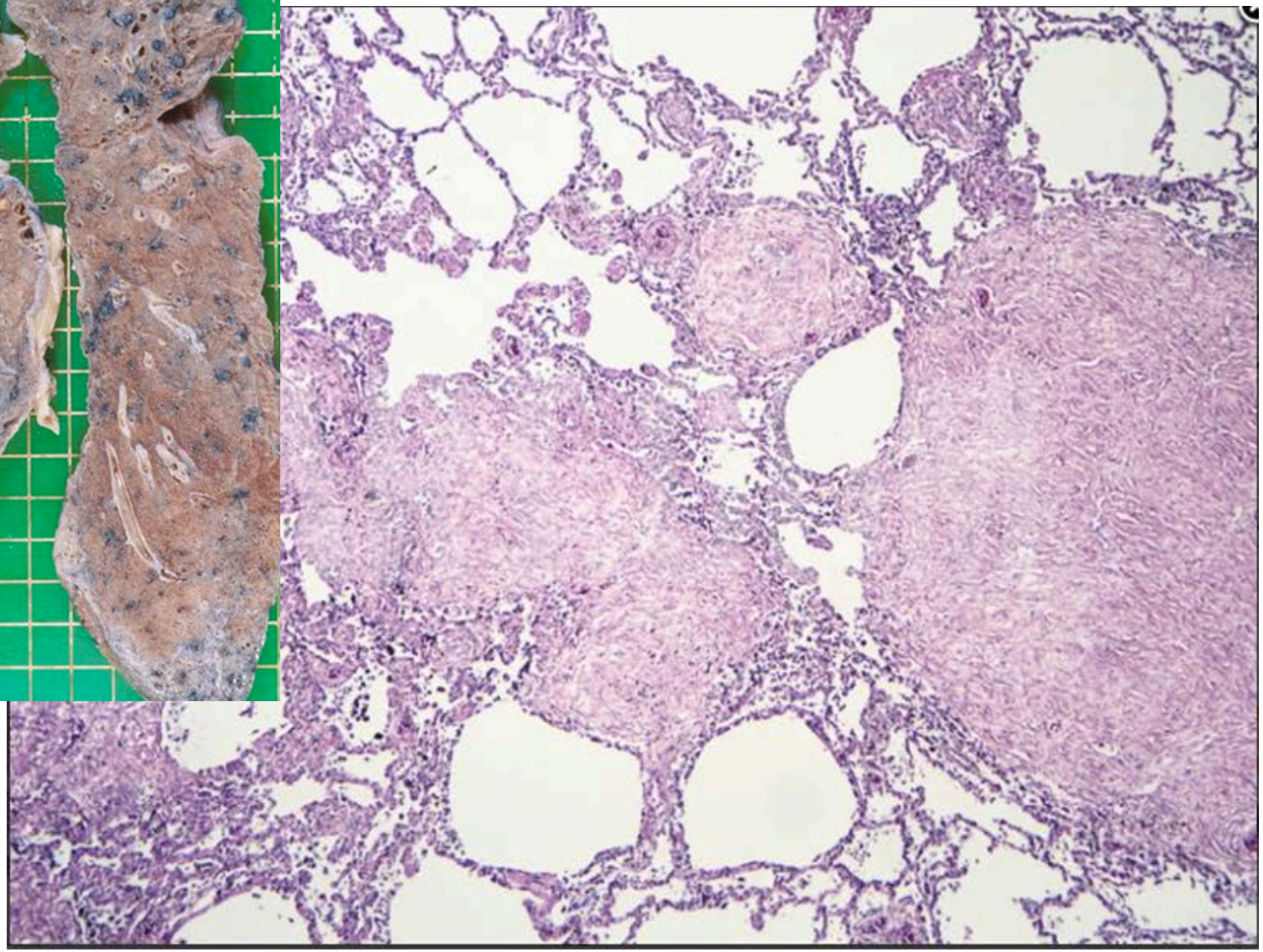


Klöppel, *Modern Pathology* (2007)

Chronic inflammation: pulmonary silicosis

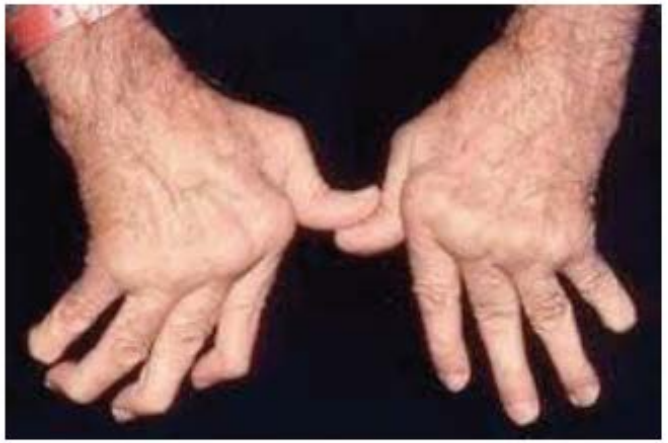


http://radiology.rsna.org/

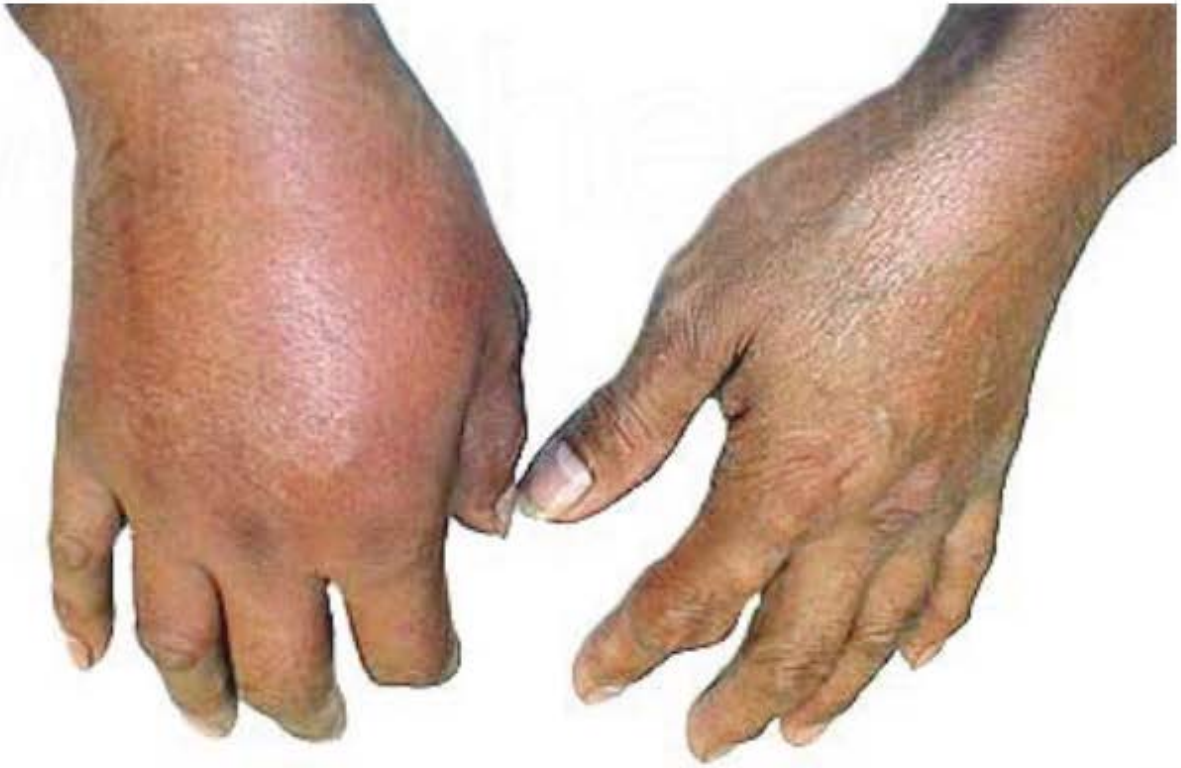


Rheumatoid Arthritis

- chronic, progressive inflammatory disorder
- caused by the **autoimmune** reactions
- attacks the small synovial joints of the hands and feet and can cause synositis and erosion of the cartilage of the joints



Inflammation of the skin caused by gout (form of arthritis): characterized by swelling and a smooth appearance of the skin caused by hyperuricemia



- Hyperuricemia is an excess of uric acid in the blood.
- Gout develops when tiny crystals of urate are deposited on the joints.
- Hyperuricemia may may occur without gout or any kidney related problems. This can later lead to further damage of the joints, decreased kidney function and later kidney stones.

Fat cells also produce inflammation molecules…

Leukocyte activation and mechanisms of microbial killing

Receptors involved in leukocyte activation

1. Toll-like receptors (TLRs)
2. Different seven-transmembrane G-protein-coupled receptors
3. Receptors for cytokines (e.g., IFN-γR)
4. Opsonins and their receptors
   - ➢Antibodies (specific opsonins recognized by FcγRs)
   - ➢Complement (mainly CR1 that recognizes breakdown products of C3 by either the classical or the alternative pathway)
   - ➢Plasma "early activation proteins": C-reactive protein (CRP), Serum amyloid protein (SAP), fibronectin, fibrinogen; lectins: mannose binding lectin (MBL)

Cytokines & Chemokines

Cytokines

- small proteins that modify the interactions between cells (15-30 kD)
- produced by activated lymphocytes and macrophages, also by endothelium, epithelium, connective tissue

Chemokines

- small proteins (8-10 kD) that act primarily as chemoattractants for specific types of leukocytes (chemotaxis)

Leukocyte activation

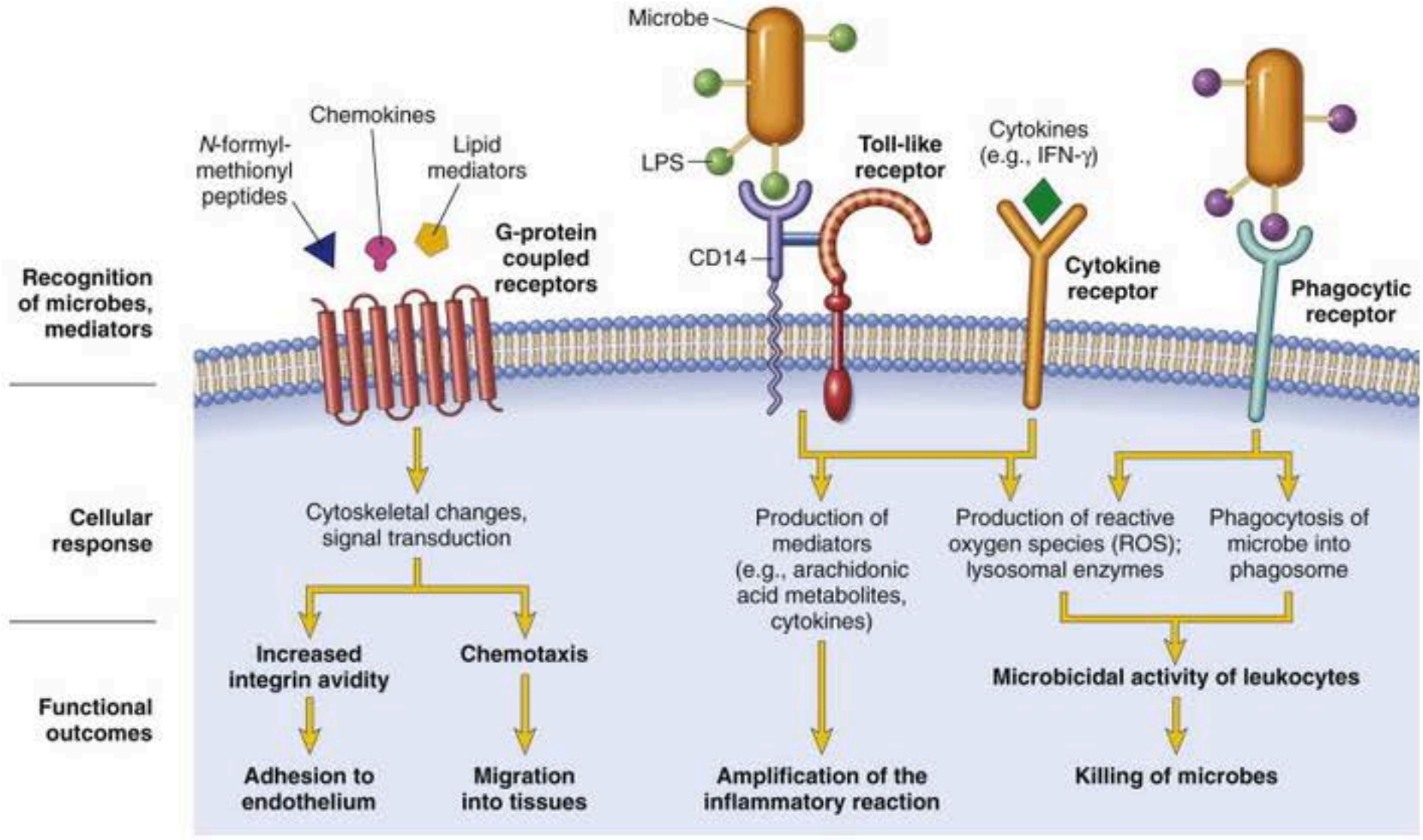


Figure 2–7

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Phagocytosis

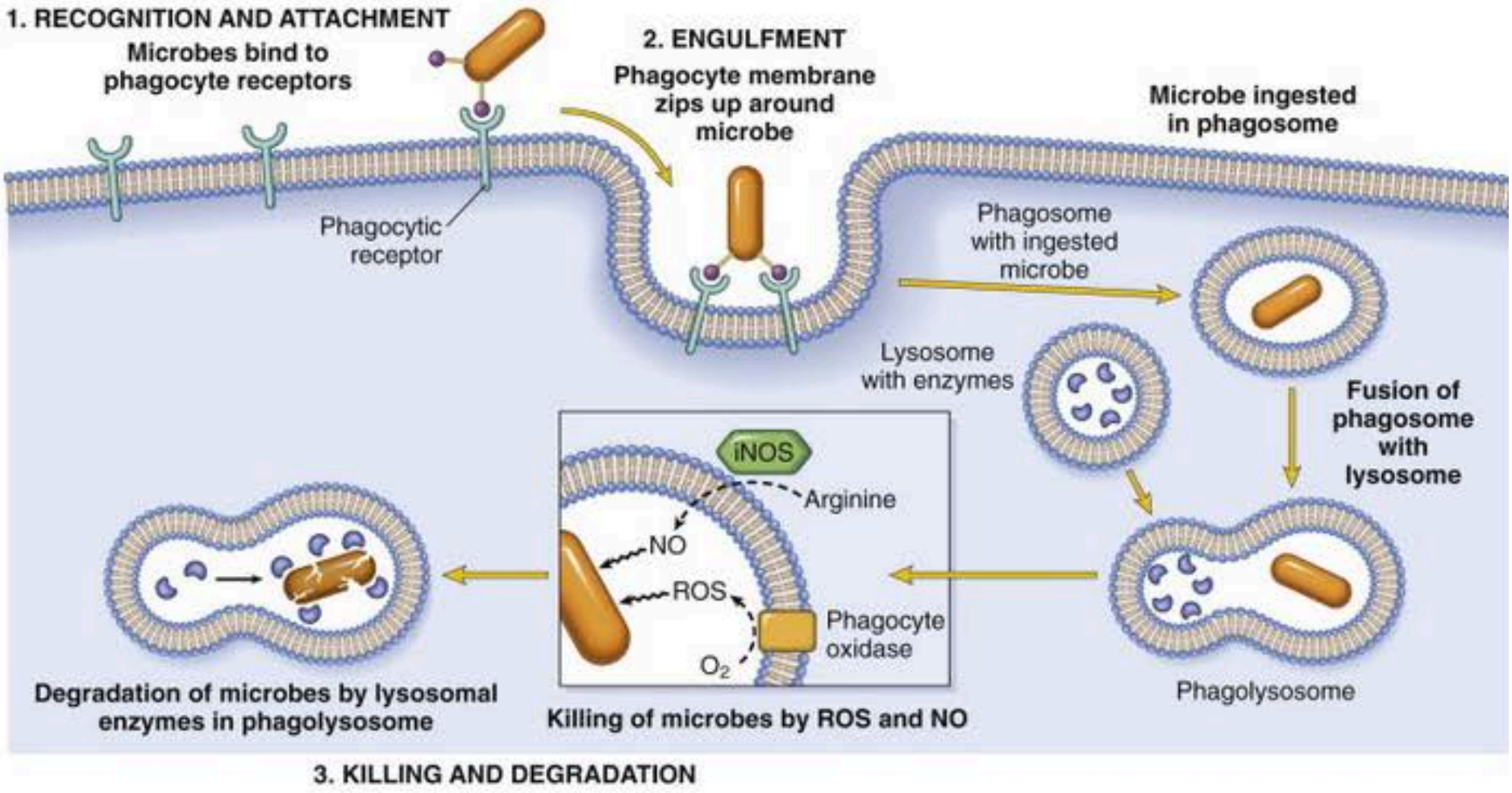

Figure 2–8

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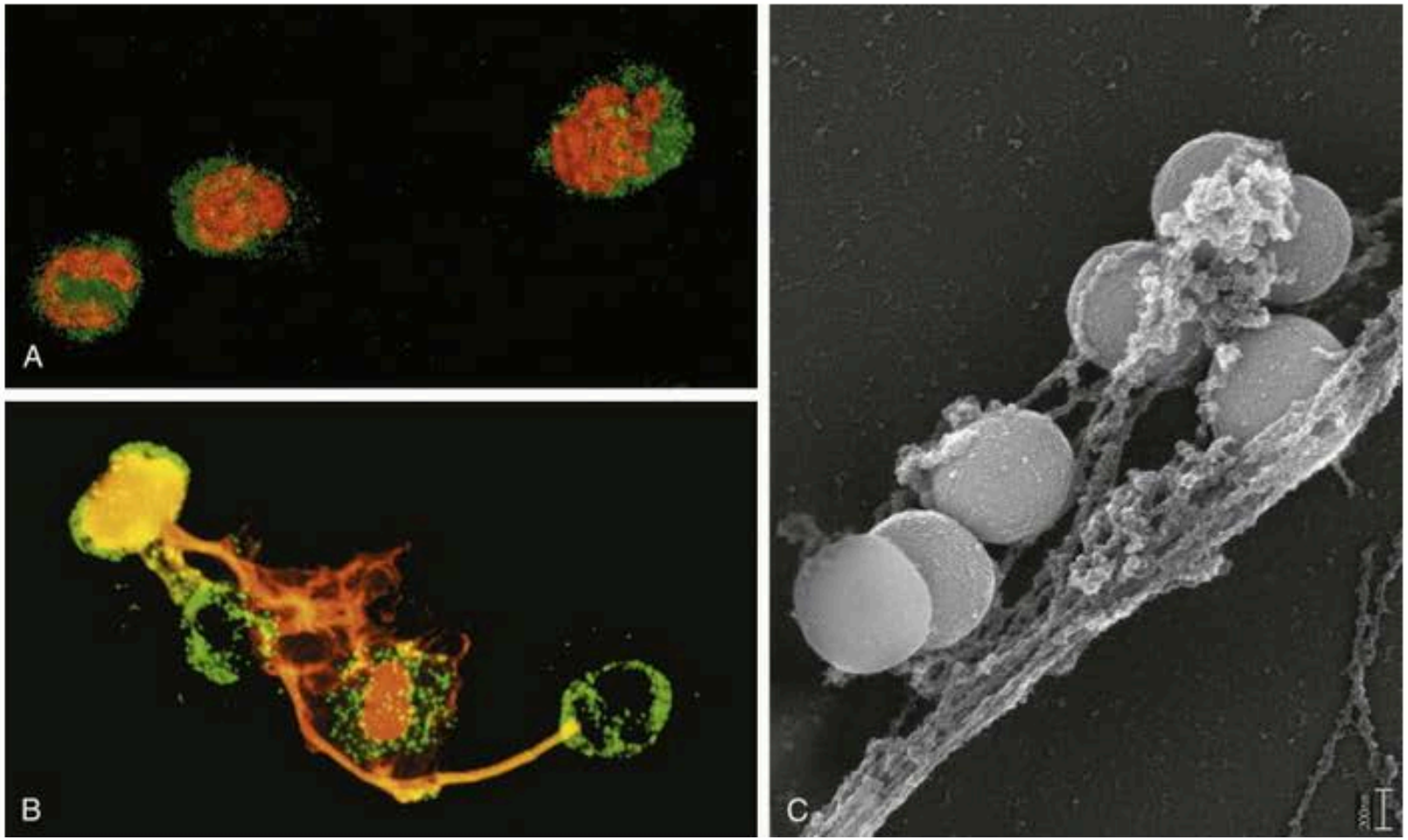
Neutrophil extracellular traps (NETs)



- Extracellular fibrillar networks that are produced by neutrophils in response to infectious pathogens and inflammatory mediators
  - contain a framework of **nuclear chromatin** with embedded granule proteins, such as **antimicrobial peptides** and **enzymes**

Robbins Basic Pathology, 9th Ed.

Chemical mediators of inflammation

Chemical mediators

- **Source** of chemical mediators:
  - May be produced locally by cells at the site of inflammation
  - may be derived from circulating inactive precursors (typically synthesized by the liver) that are activated at the site of inflammation
- **Cell-derived mediators:**
  - normally sequestered in intracellular granules
  - rapidly secreted upon cellular activation or are synthesized de novo in response to a stimulus
- **Plasma protein–derived mediators:**
  - complement proteins, kinins
  - circulate in an inactive form
  - typically undergo proteolytic cleavage to acquire their biologic activities.

Chemical mediators

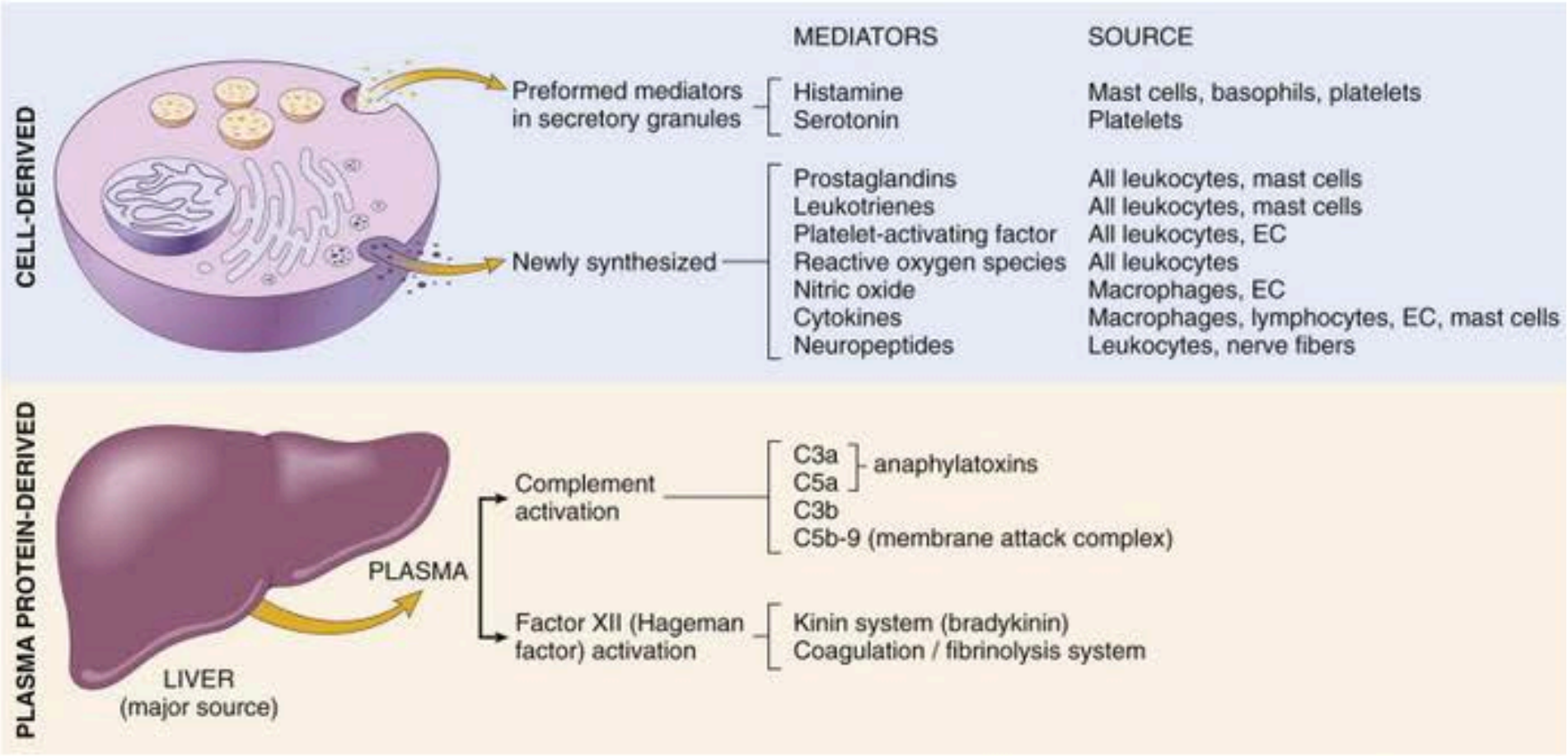


Figure 2–15 Mediators of inflammation. The principal cell-derived and plasma protein mediators are shown. EC, endothelial cells.

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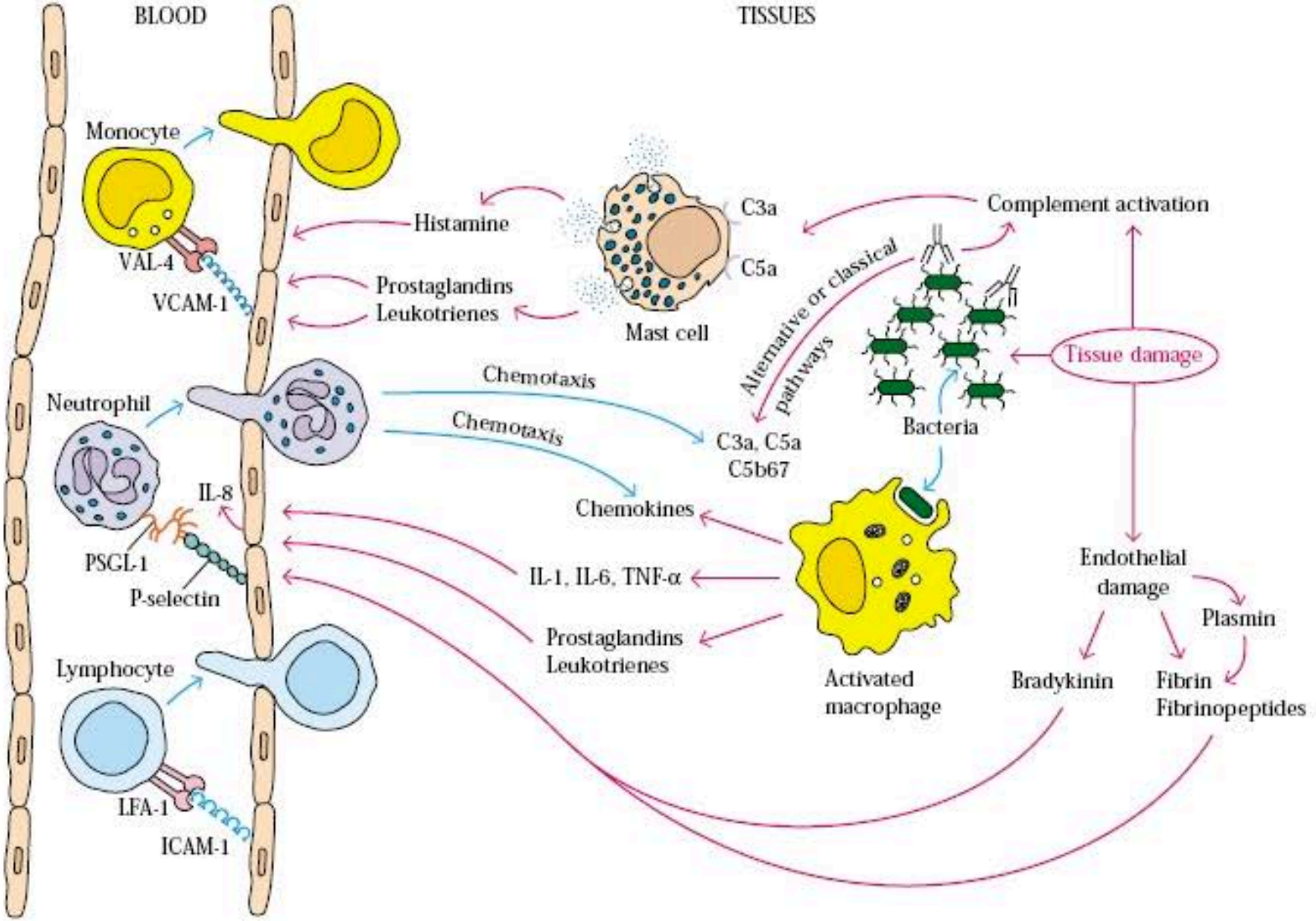
Chemical mediators



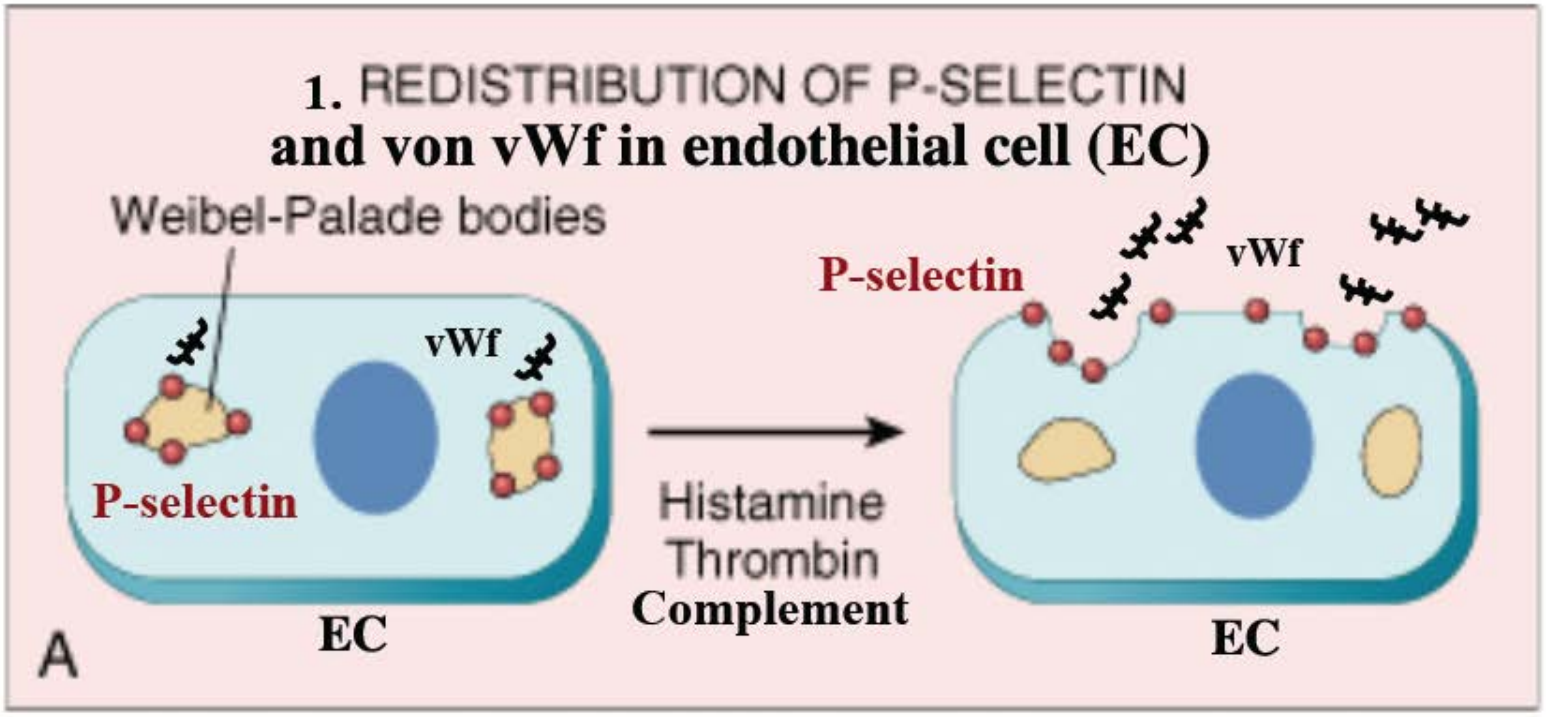
http://wenliang.myweb.uga.edu/

Mechanisms of increasing leukocyte-endothelial adhesion

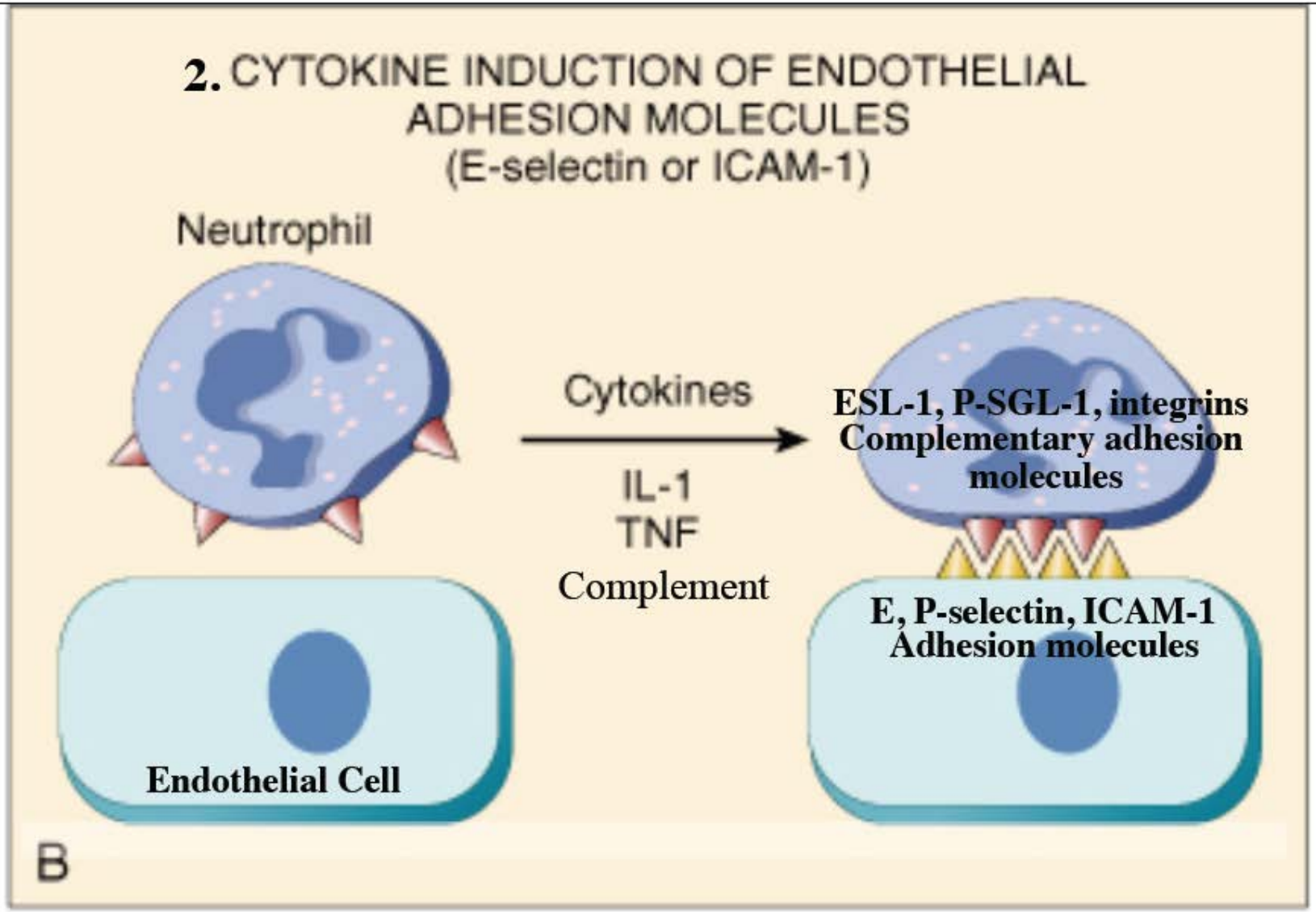
1. **Redistribution of P-selectin & vWf**
2. **Cytokine activation of endothelium**
3. **Increased binding avidity of integrins (adhesion molecules) expressed by leukocytes**

Robbins/Contran:

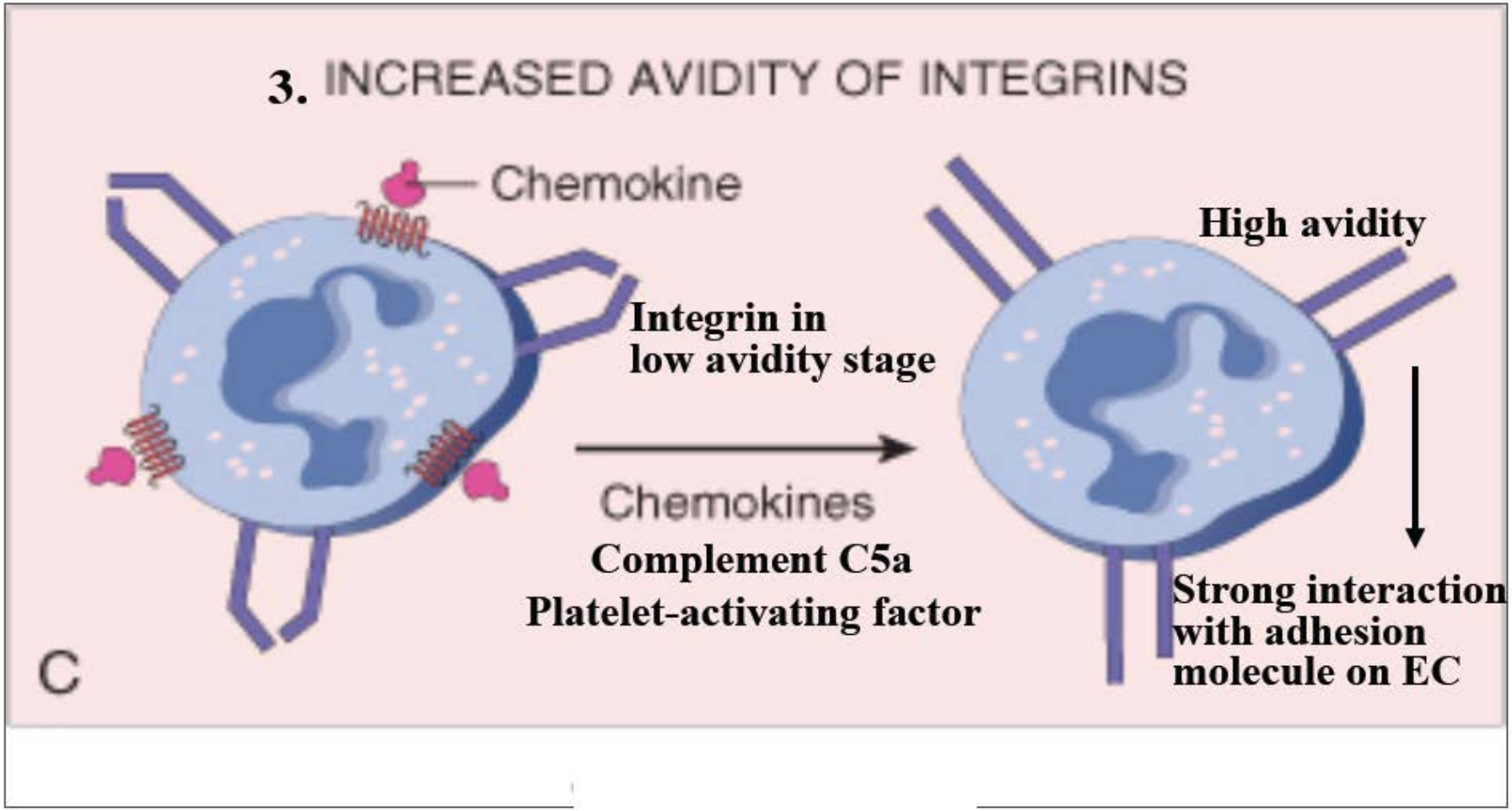
Mechanisms of increasing leukocyte-endothelial adhesion:
1. Redistribution of P-selectin and von Willebrand factor (vWf) stimulated by complement, histamine and thrombine



Mechanisms of increasing leukocyte-endothelial adhesion



Mechanisms of increasing leukocyte-endothelial adhesion



Cytokines and inflammation

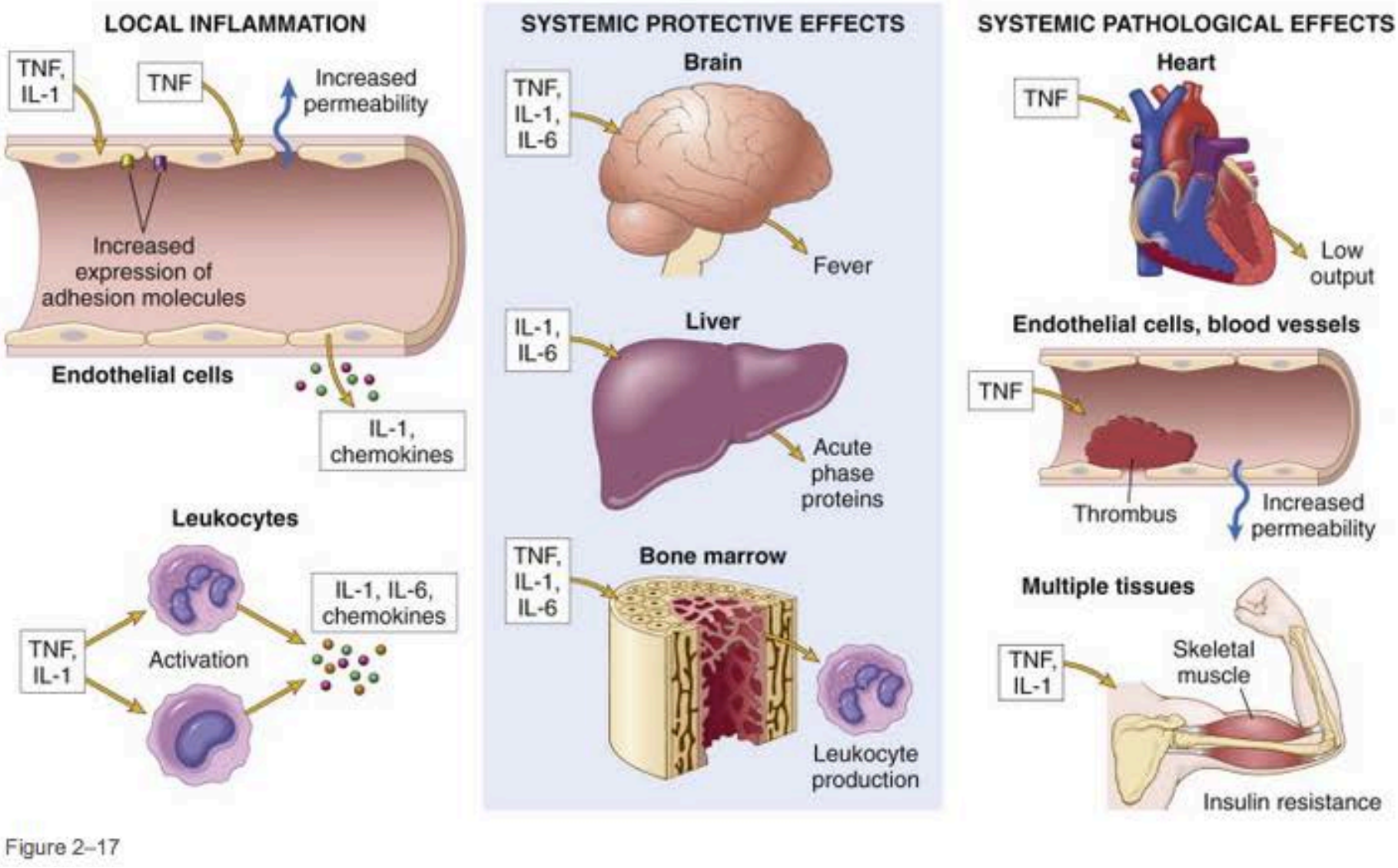


Figure 2–17

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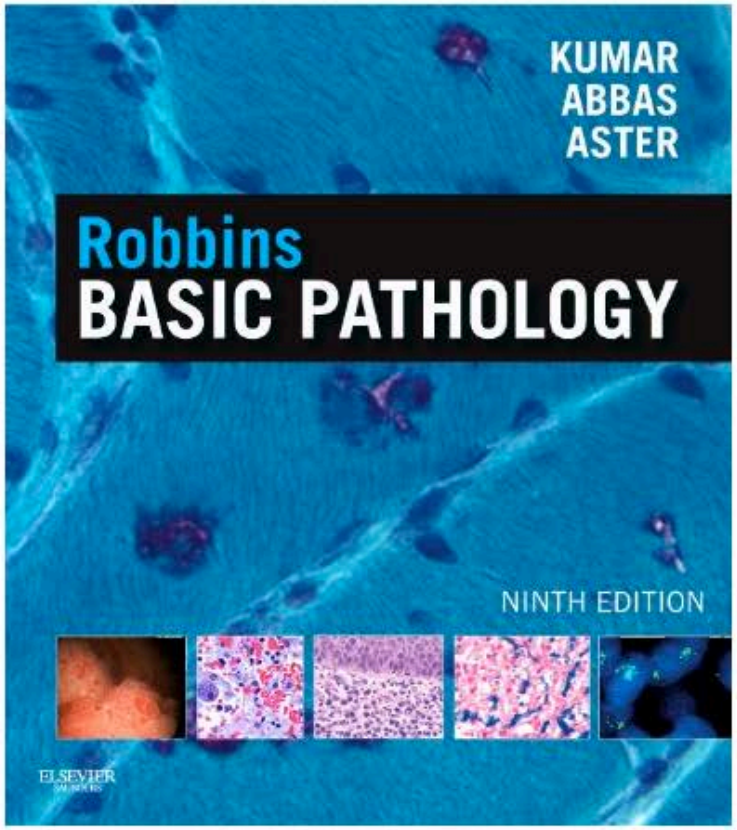
Important points

- Know the **5 cardinal signs** of inflammation
- Know the main features of **acute** vs **chronic** inflammation and the predominant **cell types** in each
- Know some clinical examples of acute and chronic inflammation
- Know the **stages of immune cell emigration** from the blood vessels
- Understand the basics of **immune cell activation** and **chemical mediators**

Recommended books

- Robbins Basic Pathology, Ninth Edition
  - Vinay Kumar, Abul K. Abbas, and Jon C. Aster



Questions??