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Phagocytic Cells: Mechanisms of Bacterial Injury and Tissue Injury

M1 – Immunology Sequence

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Winter 2009

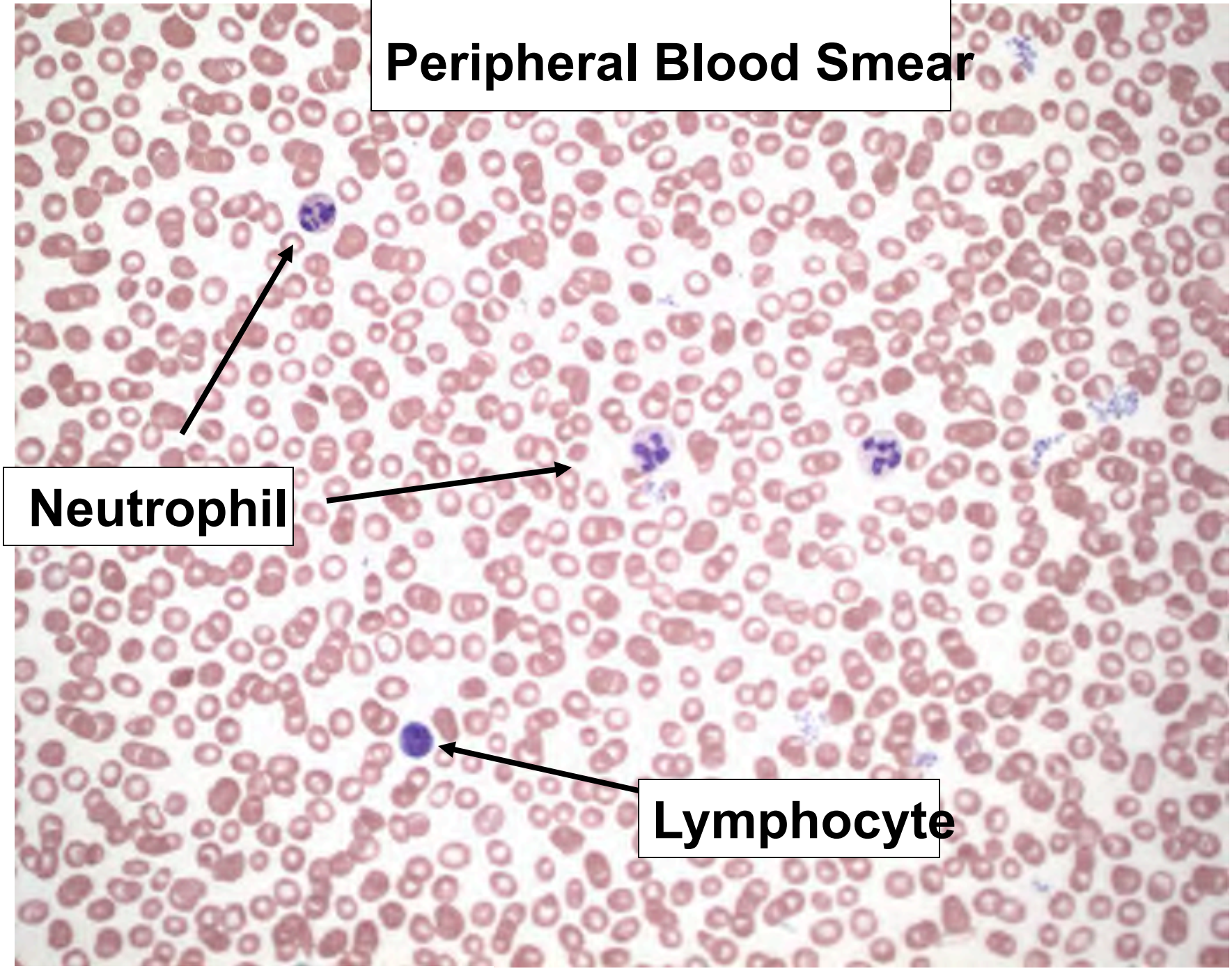
University of Michigan
Medical School

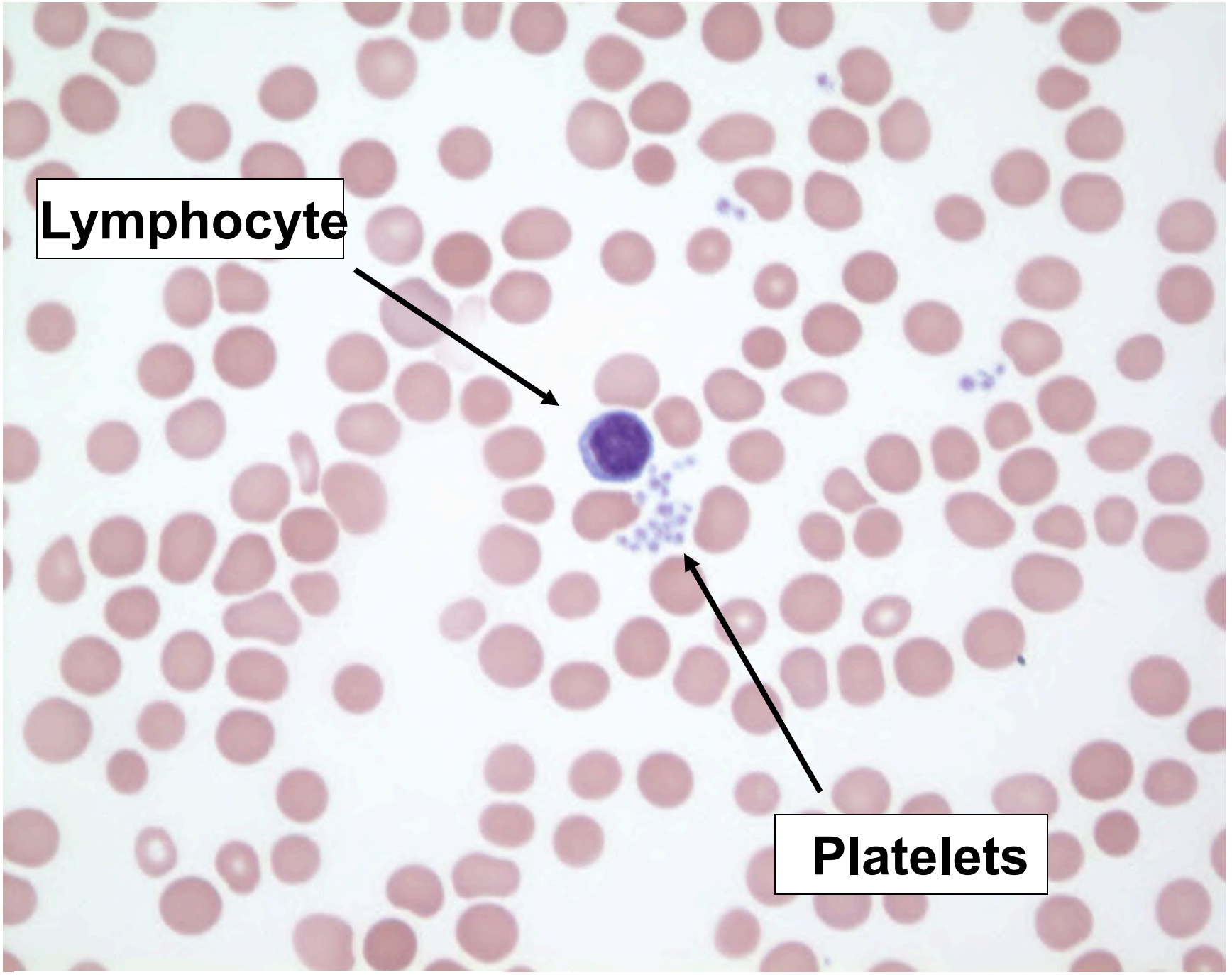
Phagocytic Cells: Mechanisms of Bacterial Killing and Tissue Injury

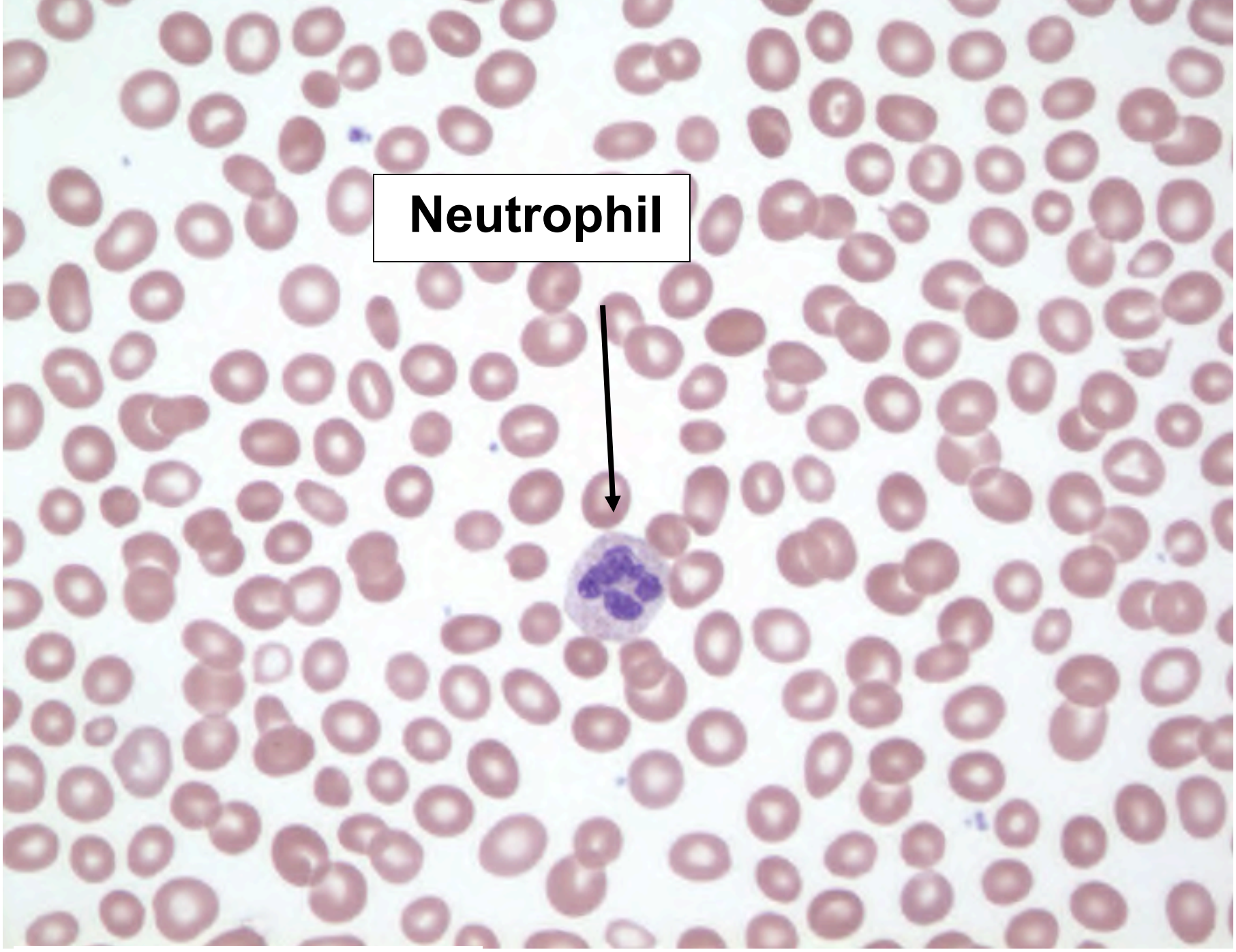
- Learning Outcomes:
  - To understand the pathophysiologic role of phagocytic cells in host defense.
  - To understand the role of reactive oxygen metabolites and lysosomal granules in phagocytic cell function

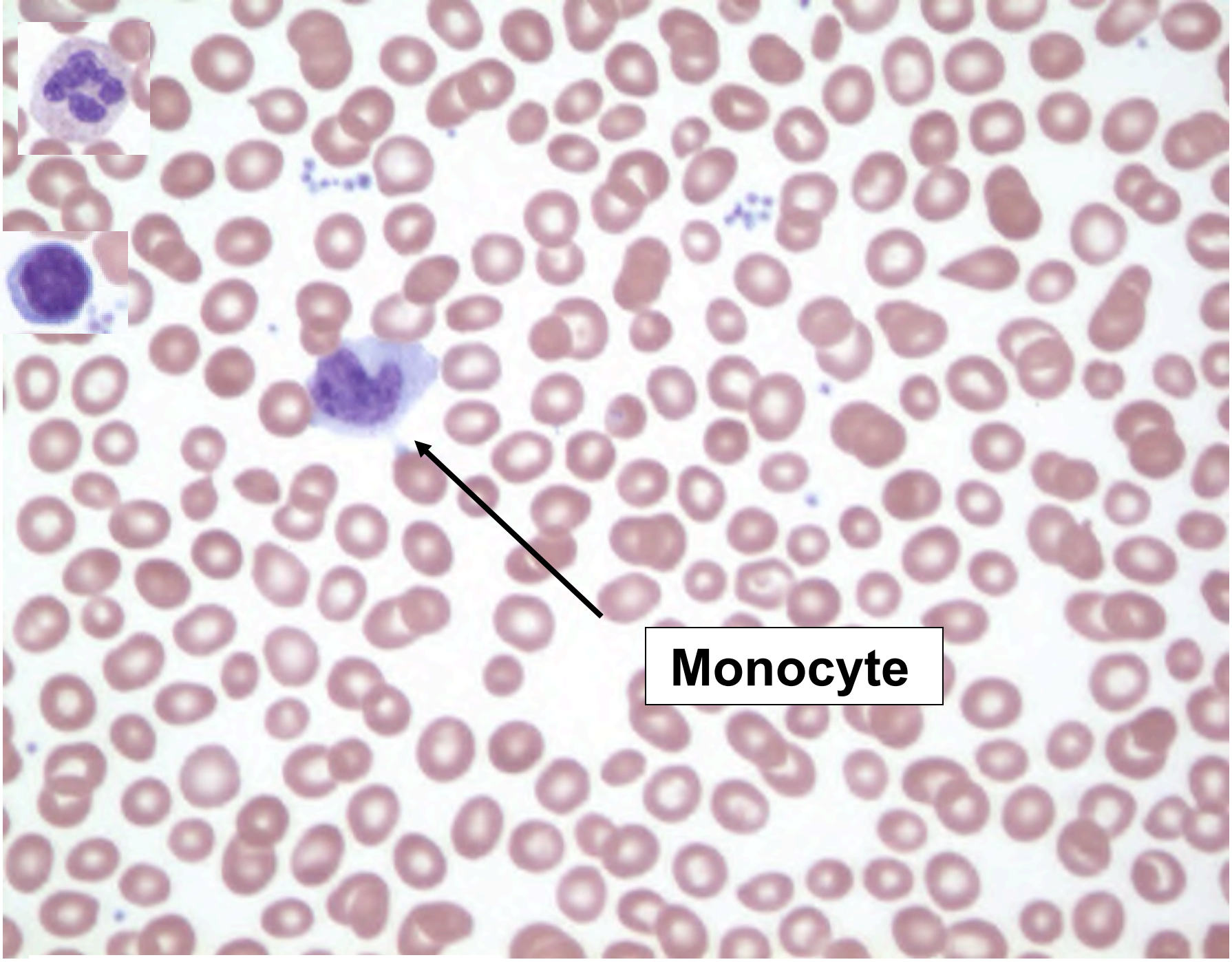
Phagocytic Cells

- Peripheral Blood Leukocytes (nrml. 4.5-11,000cells/ul)
  - Lymphocytes (~ 30%)
  - Granulocytes (~ 70%)
- Granulocytes:
  - **Neutrophils** (~ 60% of total leukocytes in blood)
  - Eosinophils (~ 3%)
  - Basophils (<1%, rare)
  - **Monocytes** (~ 6%)
  - **Monocytes** ⟶ **Macrophages** (tissues)
- Kupffer cells (lining liver sinusoids)





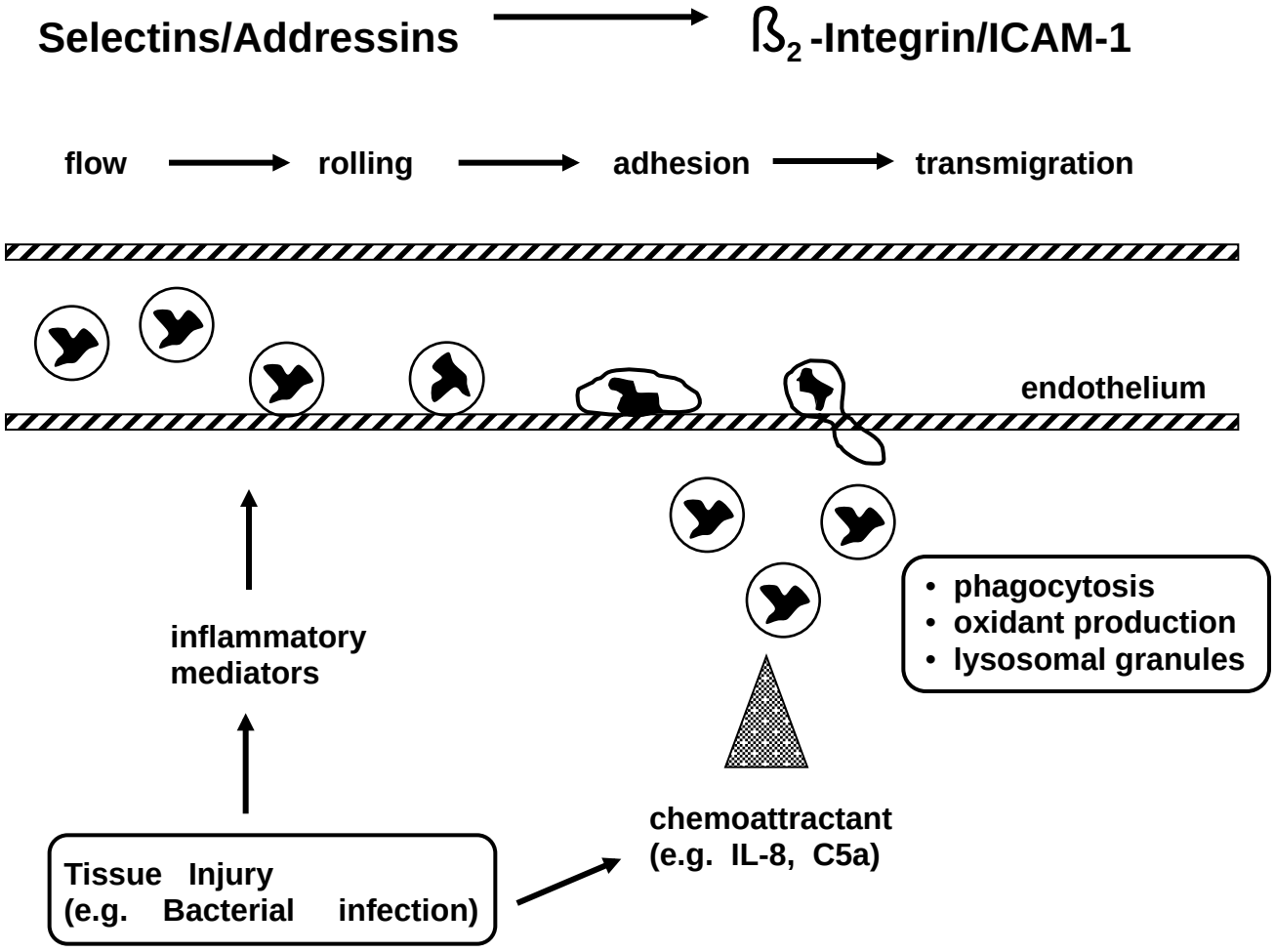




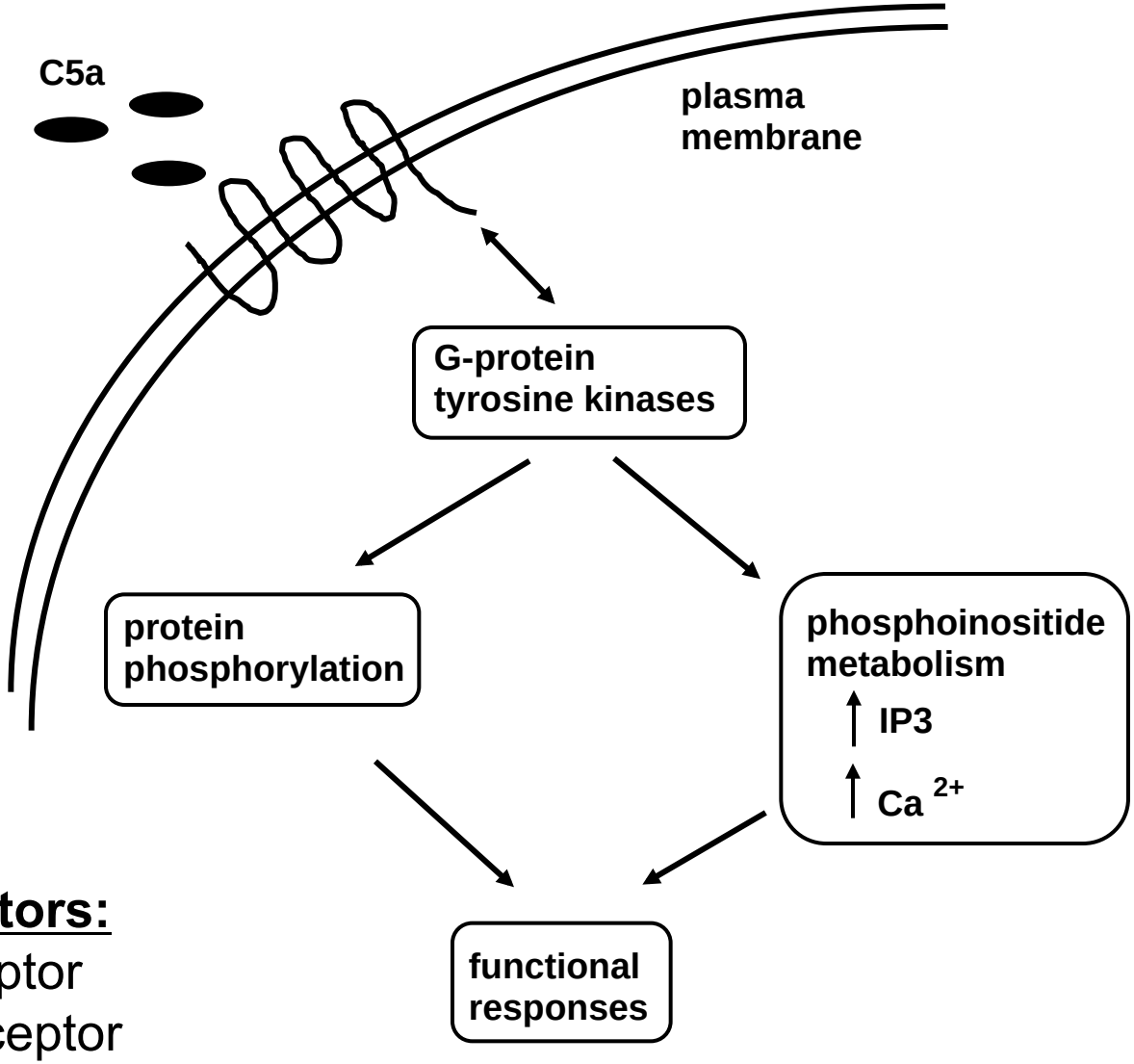
Neutrophils and Macrophages

- Function:
  - Injest foreign material
  - Kill bacteria and other microbes
  - Degrade necrotic tissue and foreign antigens
- Tissue damage during prolonged inflammation

Neutrophil Recruitment



Phagocytic Cell Activation: Chemotactic Factors



Other receptors:

Toll-like receptor

Mannose receptor

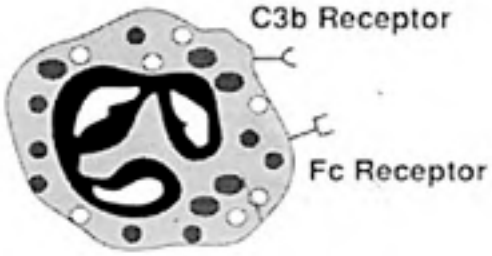
Phagocytic Cell Functional Responses

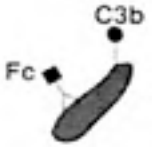
- Adhesion (localization)
- Chemotaxis (migration)
- Phagocytosis
- NADPH oxidase activation
- Lysosomal granule fusion: degranulation

Opsonization and Phagocytosis

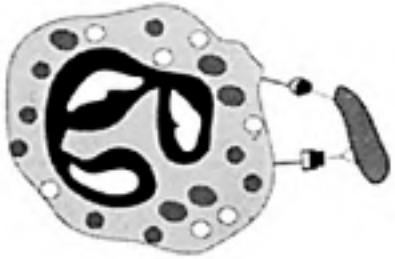
- Protein recognized by phagocytic cell binds to bacteria surface
- Enhances phagocytosis
  - Antibody IgM ⟷ Fc receptors: IgG, IgM
  - Complement ⟷ C3b receptors
  - Mannose binding protein ⟷ MBP receptors

Neutrophil Phagocytosis of Bacteria





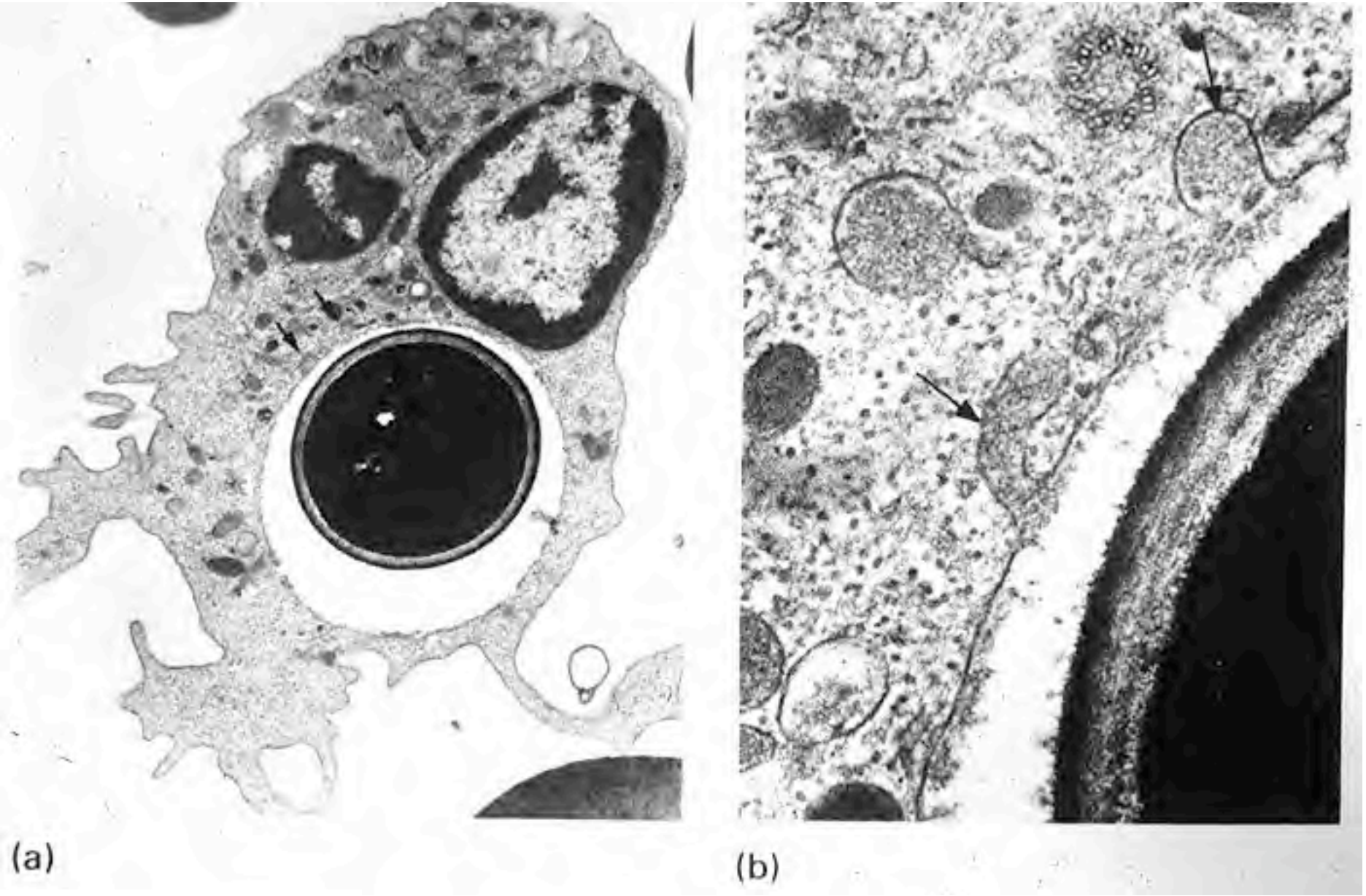
Opsonization of Bacteria



Fc, C3b binding

Phagosome formation

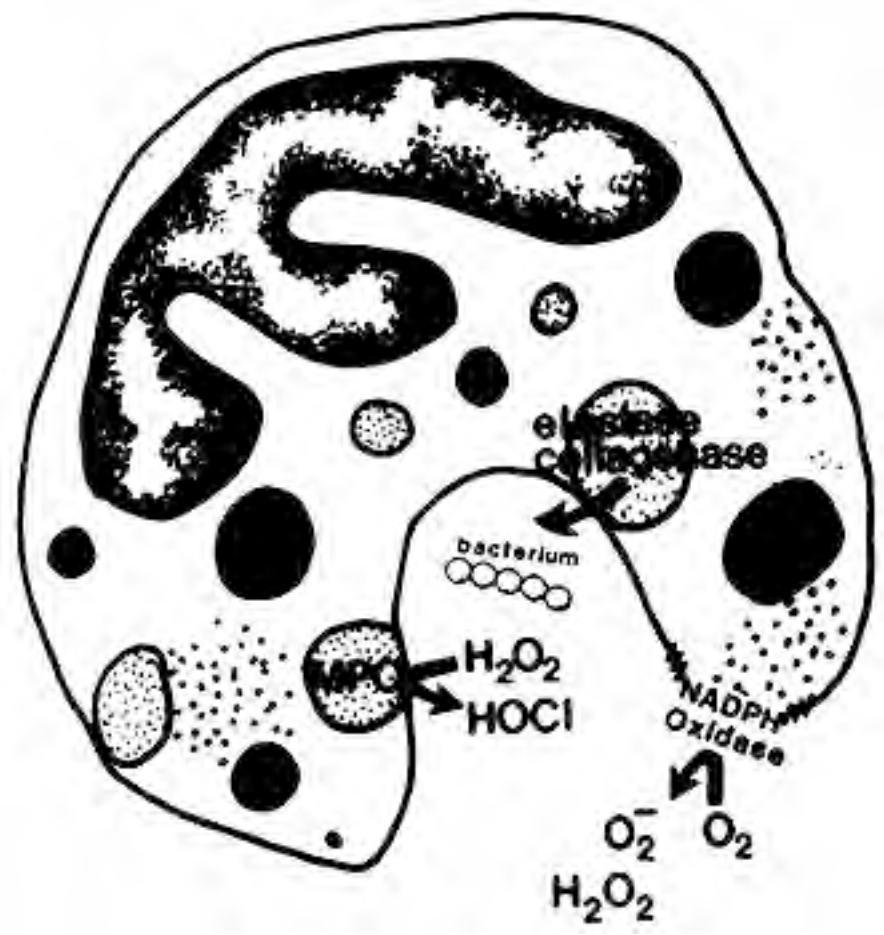
Phagolysosome



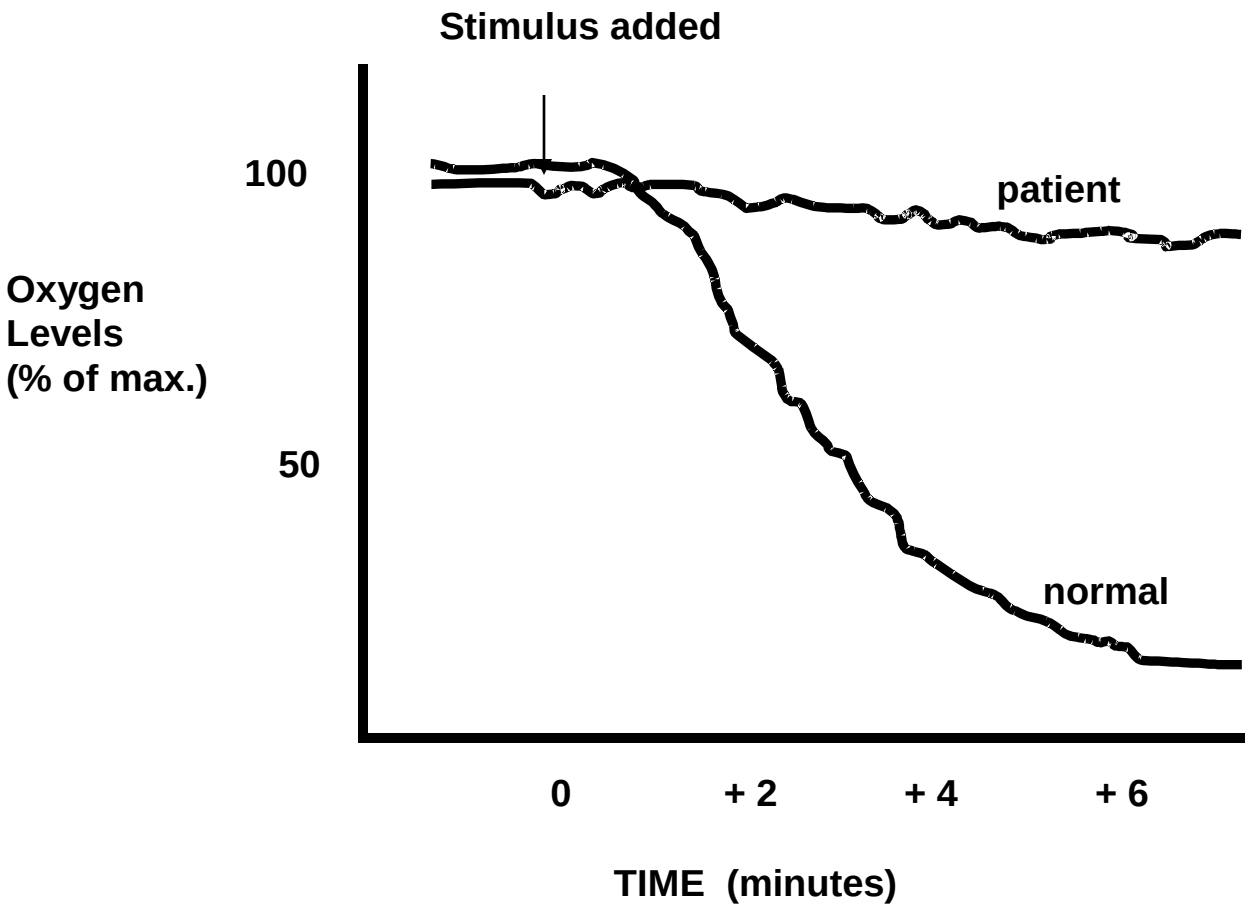
Cell phagocytosis

Oxygen radicals

Elastase
Collagenase
Acid
hydrolases



Respiratory Burst: NADPH Oxidase



Reactive Oxygen Metabolites

Superoxide anion: O_2^-

Hydrogen peroxide: H_2O_2

Hydroxyl radical: OH .

Hypochlorous acid: HOCl

myeloperoxidase = MPO

$$O_2 + e^- \longrightarrow O_2^-$$

$$2O_2^- + 2H^+ \longrightarrow H_2O_2 + O_2$$

$$H_2O_2 + Fe2+ \longrightarrow OH^{\bullet} + OH^- + Fe3+$$

$$H_2O_2 \xrightarrow{MPO} HOCl + OH^-$$

Chronic Granulomatous Disease of Childhood (CGD): deficiency of NADPH Oxidase

Nitric Oxide ($NO^{\bullet}$) Synthase

L-arginine → $NO^{\bullet}$ → hydroxyl radical

peroxynitrites

-Endothelial cell
-Macrophages (inducible): intracellular cytotoxic agent
-Nervous system

Oxidant Targets

a) **unsaturated lipids:** lipid peroxidation

LOOH = lipid hydroperoxides

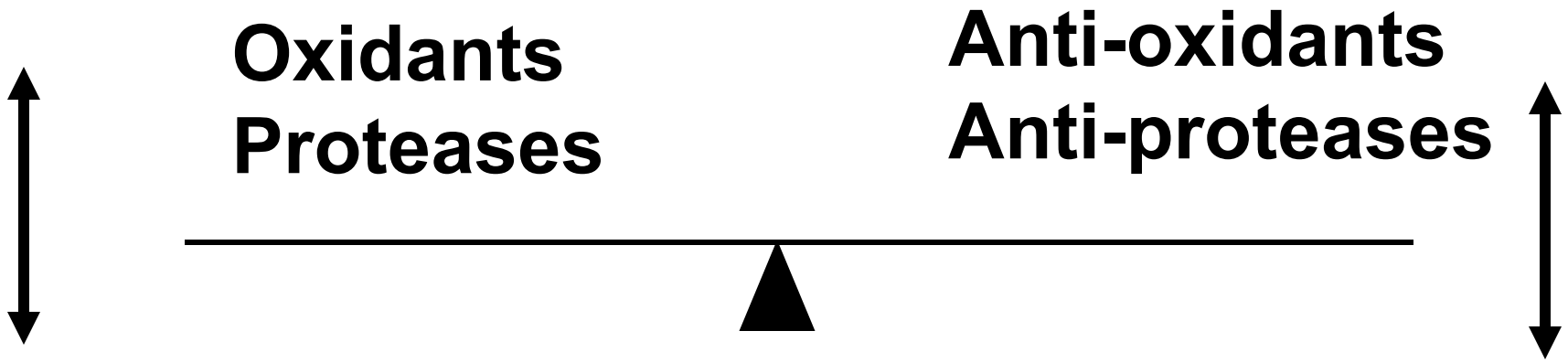
c) **proteins**

- sulfhydryl groups
- methionine
- tyrosine

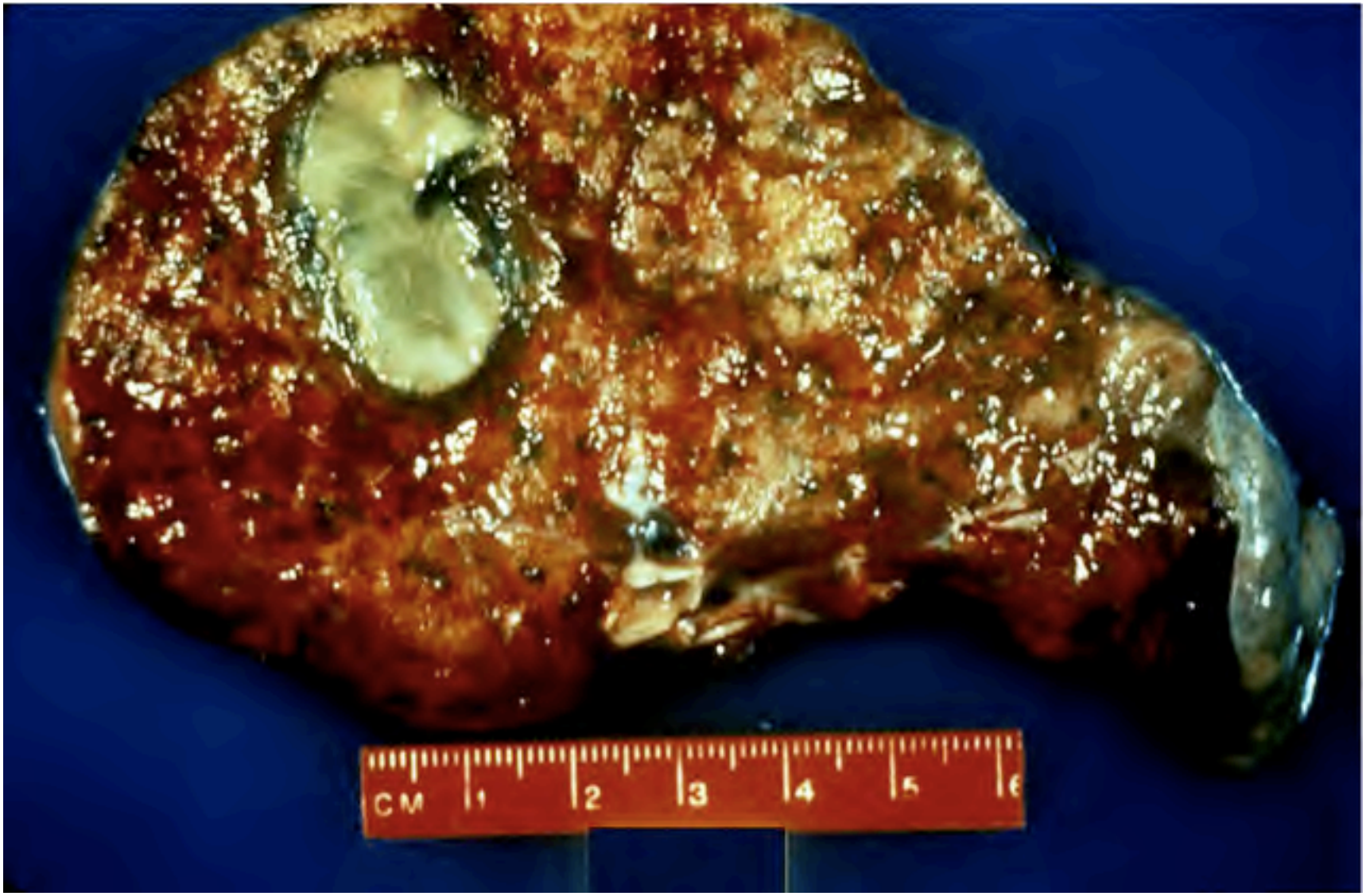
d) **nucleic acids**

Degranulation

- **Bactericidal proteins** (e.g. defensins)
- **Proteases**
  - serine proteases (e.g. elastase)
  - metalloproteinases (e.g. collagenase, gelatinase)
- **Acid hydrolases**


Oxidants
Proteases
Anti-oxidants
Anti-proteases

Pneumonia and Abscess



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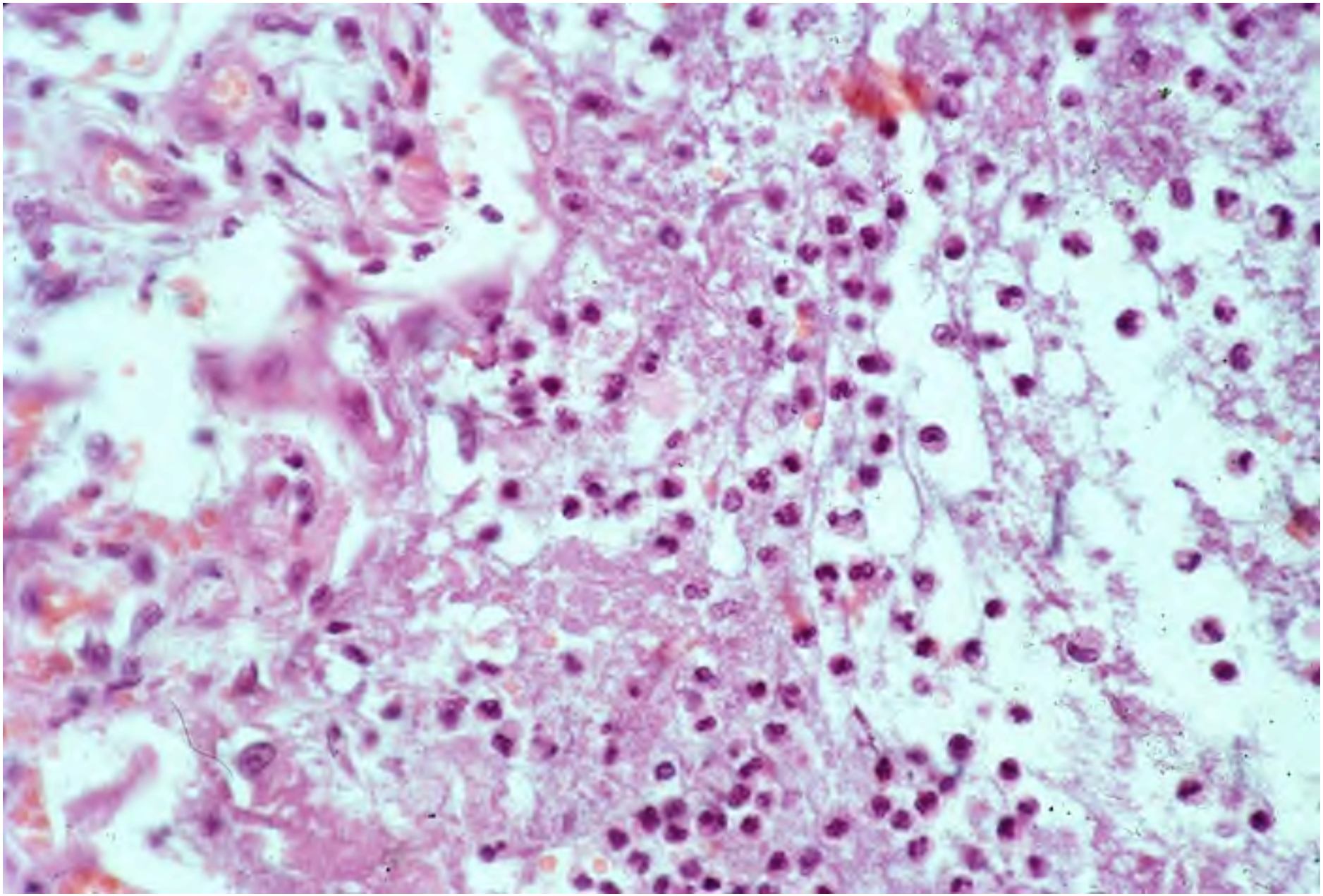


Protective Mechanisms

Anti-oxidant: specific vs. non-specific

Specific enzymes:

Superoxide dismutase: $2O_2^- + 2H^+ \longrightarrow H_2O_2 + O_2$

Catalase: $2H_2O_2 \longrightarrow 2H_2O + O_2$

Glutathione peroxidase: $H_2O_2 + 2GSH \longrightarrow 2H_2O + GSSG$

$LOOH + 2GSH \longrightarrow H_2O + LOH + GSSG$

LOOH = lipid hydroperoxides
GSH = reduced glutathione
GSSG = oxidized glutathione

Non- specific scavengers:

-Vitamin E

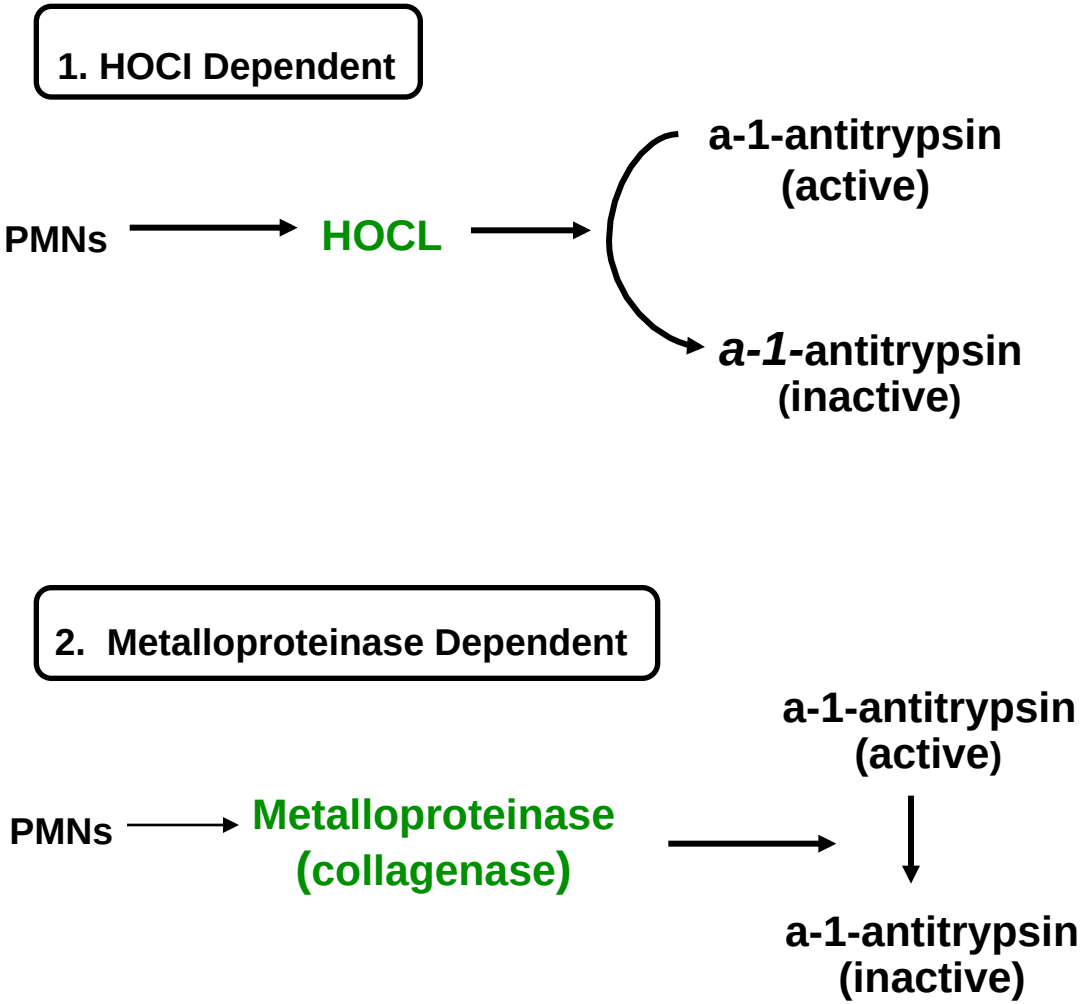
-Vitamin C

-Beta-carotene

Anti-proteases

- α-1- anti-protease (anti-trypsin):
  - plasma protein
  - binds proteases including elastase
  - inactivated by oxidants
- α-2- macroglobulin
  - plasma protein
  - binds proteases
- TIMPs: tissue inhibitors of metalloproteinases
  - cell derived

Synergism: Inactivation of alpha-1-anti-trypsin



Case: A 3 year old boy is brought to the emergency department

- **CC:** a productive cough, fever (temp 102.1 C), and headache.
- **PEx:** healthy boy with rales present on auscultation of the left lower chest.
- **CxR:**intra-alveolar infiltrate in the left lower lobe.
- **Hx:** mother reports multiple episodes (approx. 5 per year) of recurrent bacterial infections including otitis media, sinusitis, pneumonia, and purulent skin lesions. These infections usually responded to antibiotic treatment.

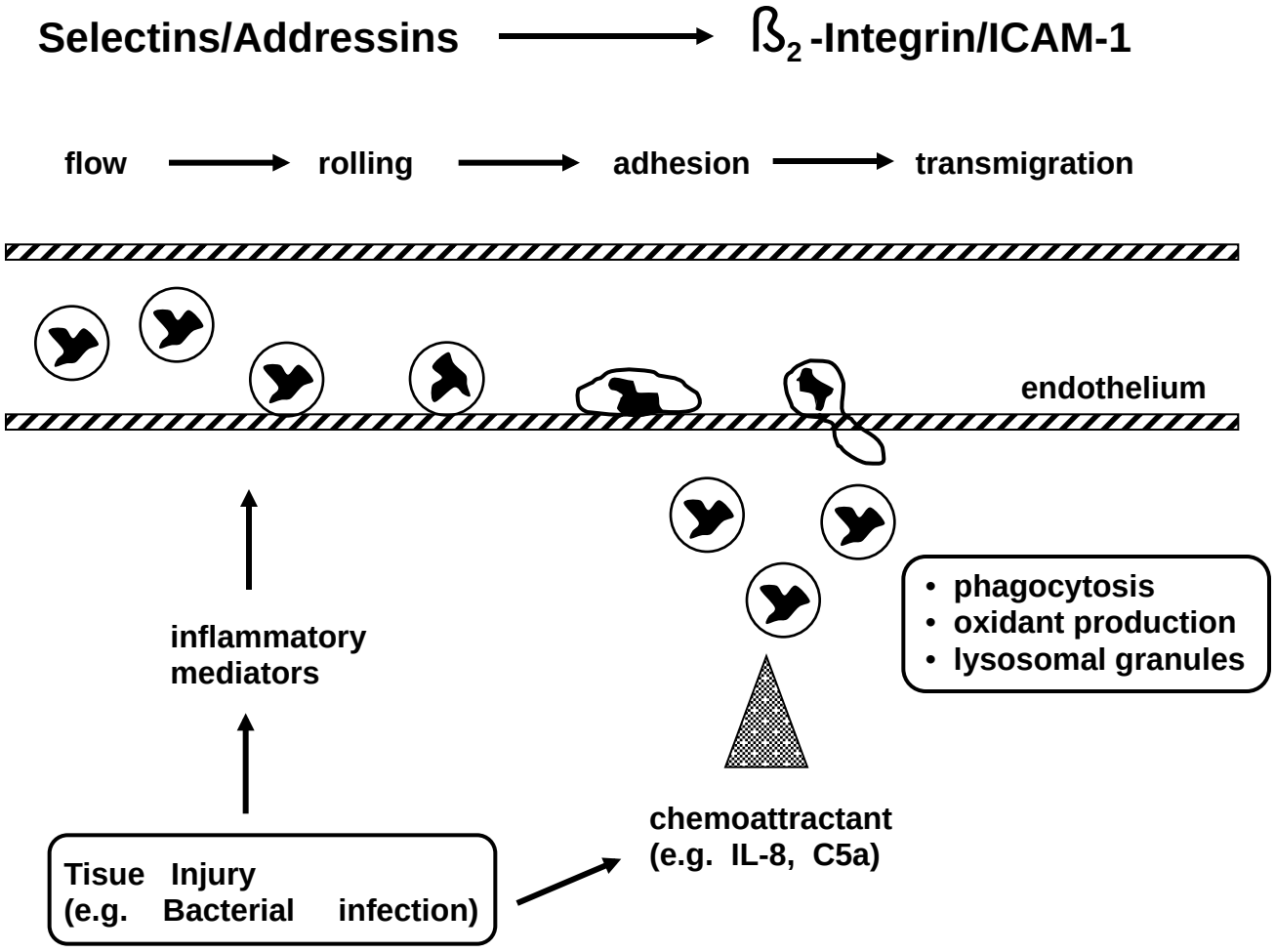
List three different mechanisms that could account for this patients increased susceptibility to bacterial infection:

1. _____

2. _____

3. _____

Neutrophil Recruitment



Mechanisms Associated with Increased Susceptibility to Bacterial Infection:

1. Lack of neutrophils: leukopenia
2. Defective neutrophil function
   - Adhesion / migration
   - Phagocytosis
   - Bacterial killing
3. Lack of chemoattractants: deficiency
4. Lack of opsoninization of bacteria

   - antibody deficiency / complement def.

Additional References:

Phagocytic Cells:

Kumar, Abas, and Fausto: Pathologic Basis of Disease (7th ed.) pages 16-18, 53-62,71-74.

Parham, The Immune System (2nd ed.): pgs. 15-17, 202-209.

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