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# Phagocytic Cells: Mechanisms of Bacterial Killing and Tissue Injury



**BY: Arria Belli**

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**J. Fantone, M.D.**

**2/12/08**

**9:00-10:00am**

# 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**  $\longrightarrow$  **Macrophages** (tissues)
- Kupffer cells (lining liver sinusoids)



# Peripheral Blood Smear

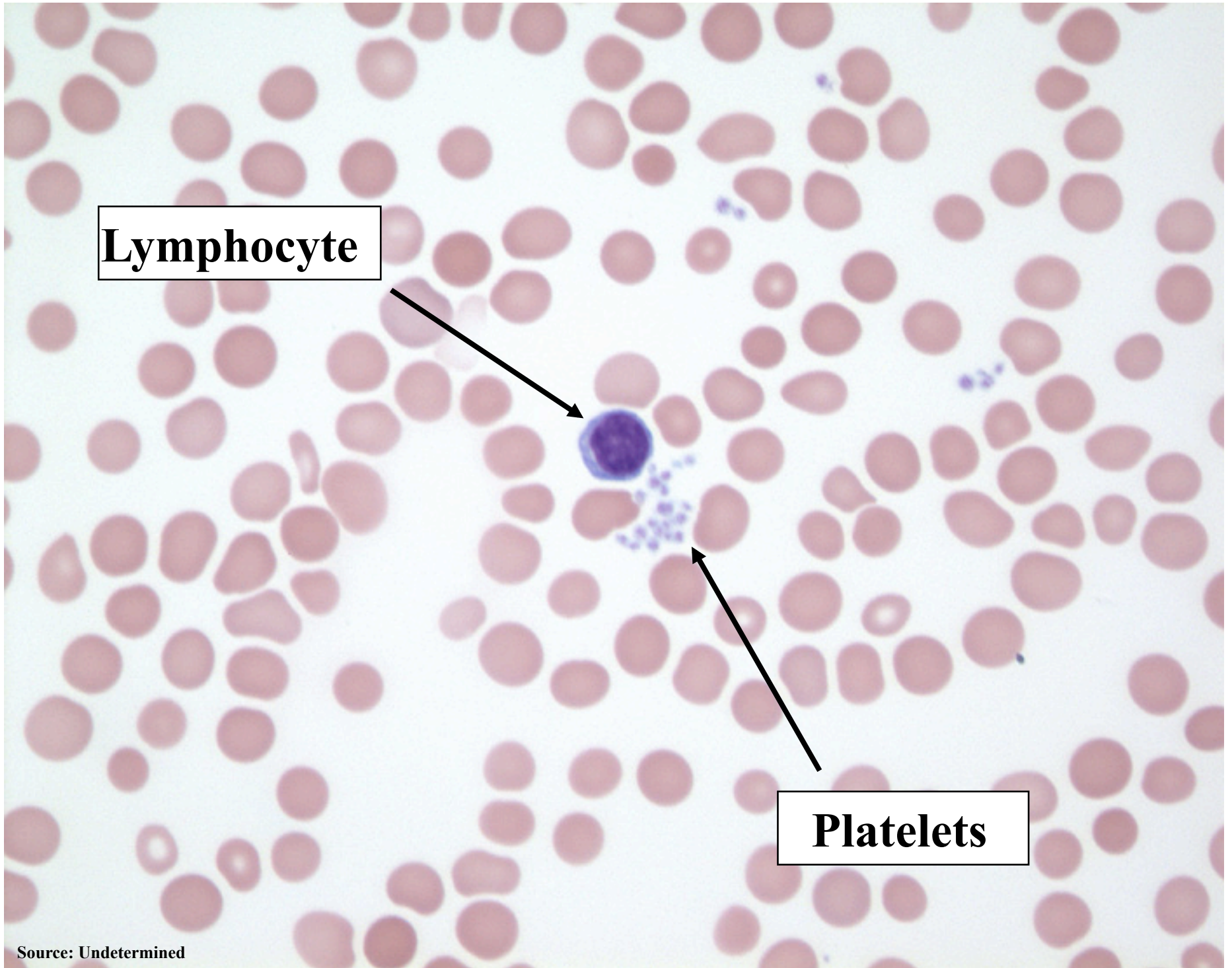
Neutrophil

Lymphocyte



**Lymphocyte**

**Platelets**

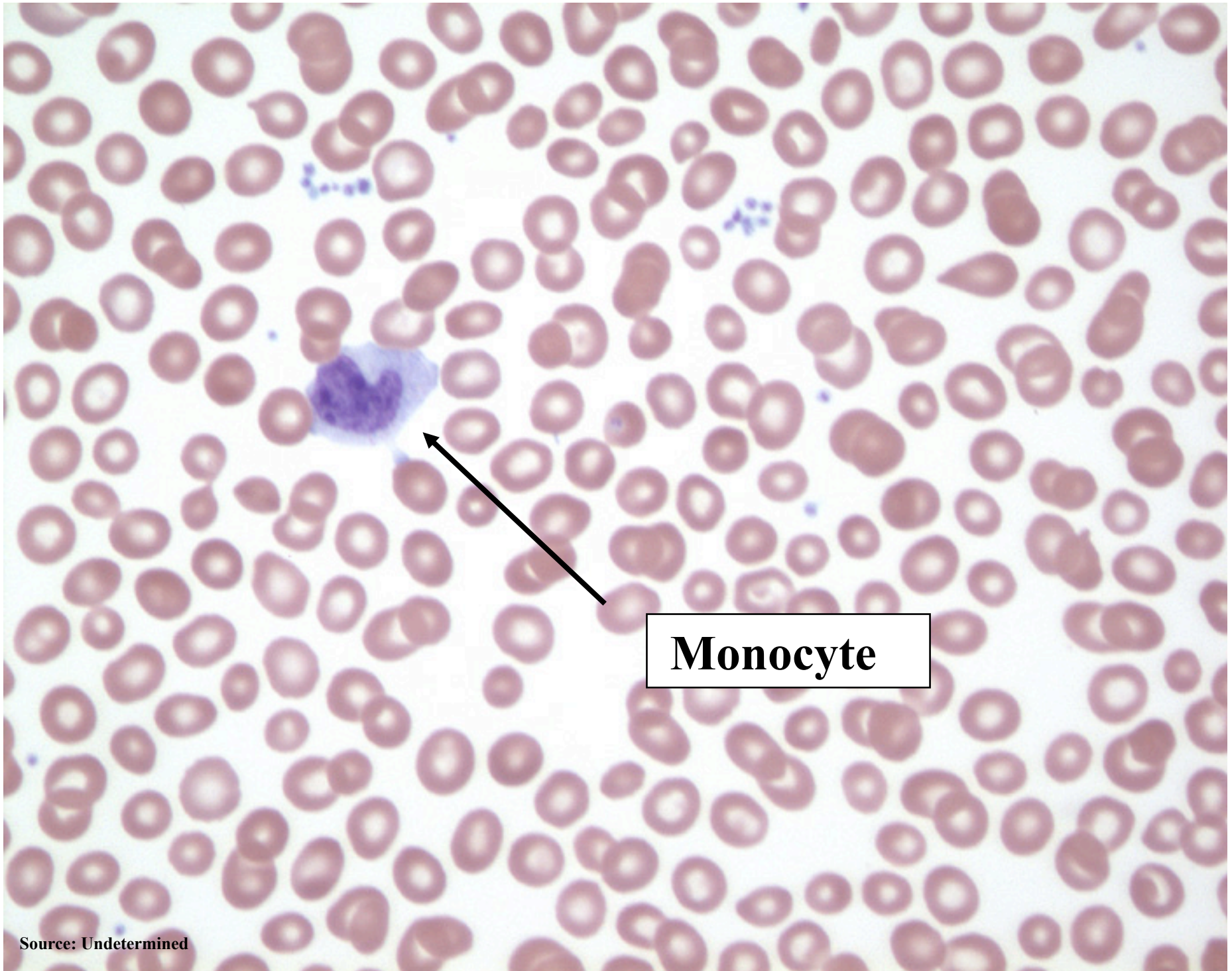




**Neutrophil**







**Monocyte**



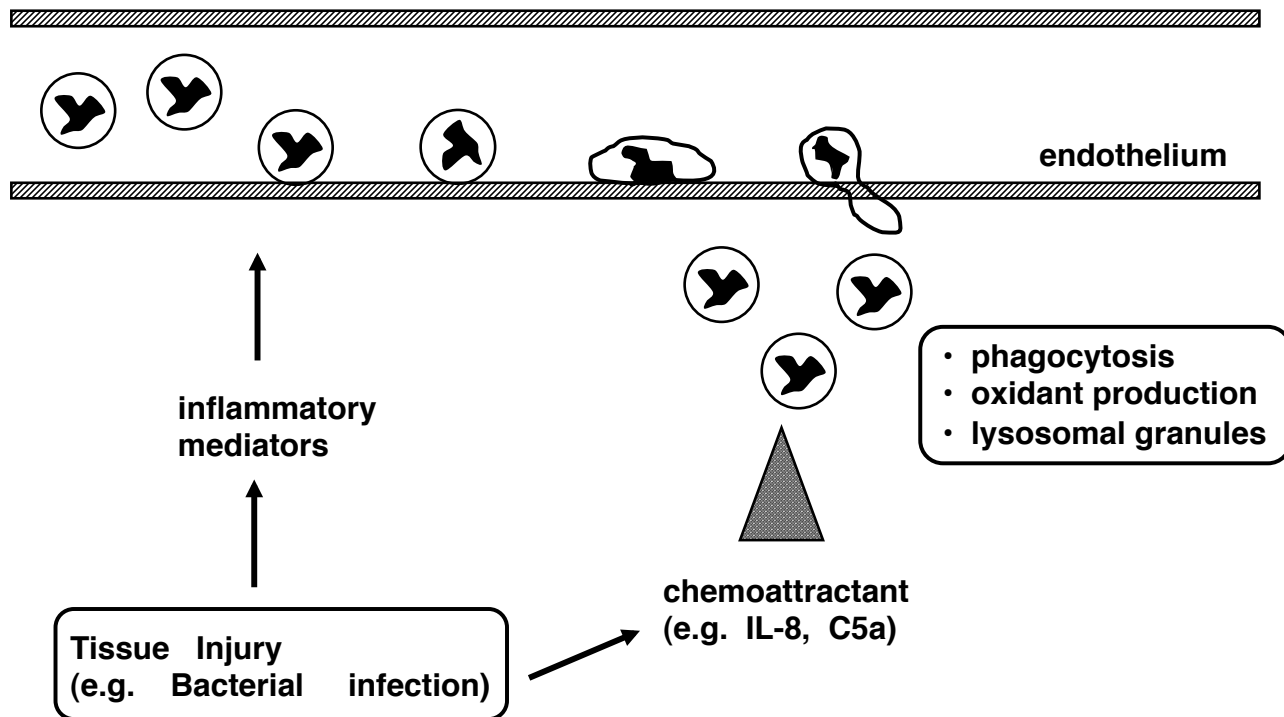
# Neutrophils and Macrophages

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

# Neutrophil Recruitment

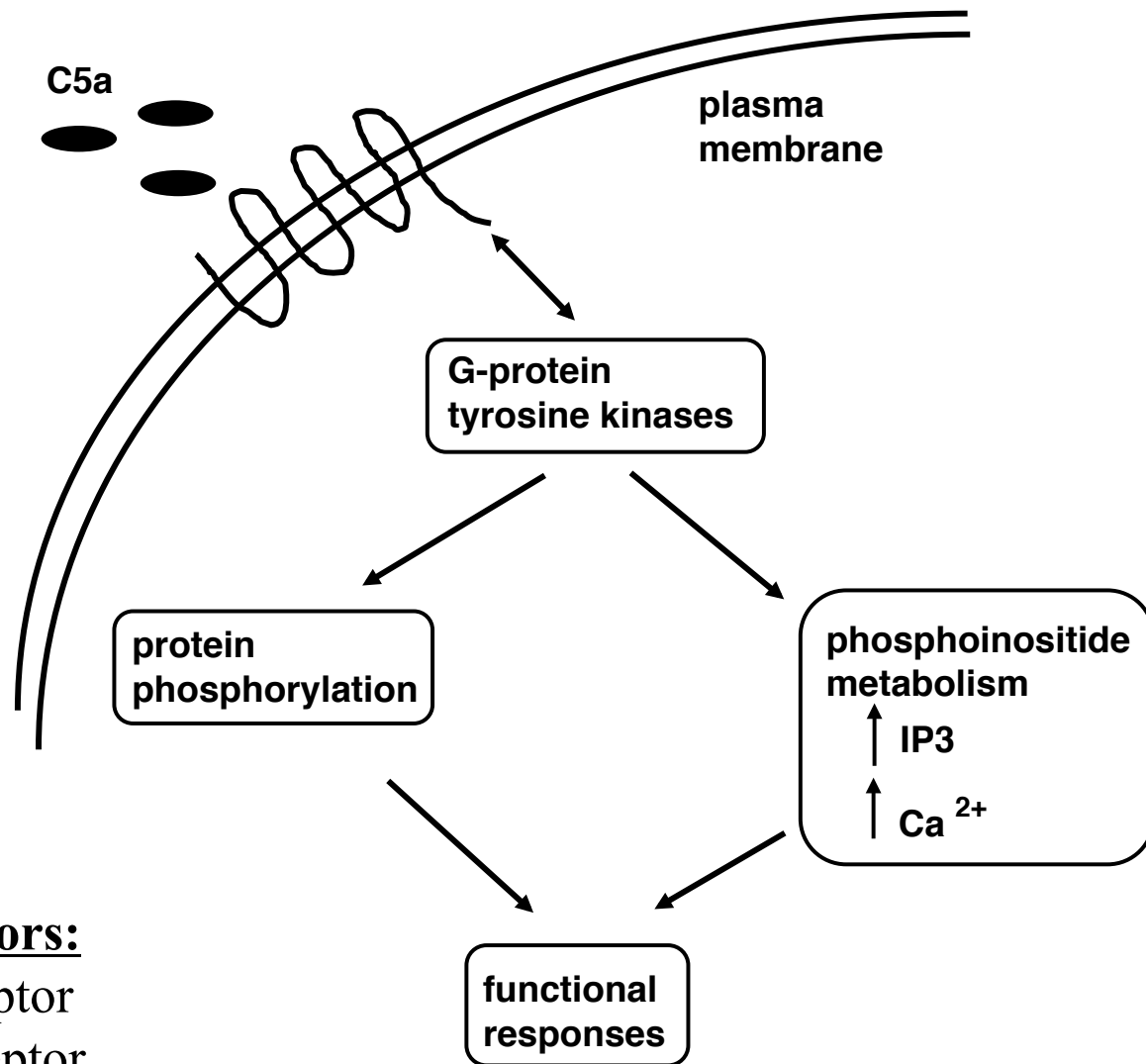
Selectins/Addressins  $\longrightarrow$   $\beta_2$ -Integrin/ICAM-1

flow  $\longrightarrow$  rolling  $\longrightarrow$  adhesion  $\longrightarrow$  transmigration





## Phagocytic Cell Activation: Chemotactic Factors



# Phagocytic Cell Functional Responses

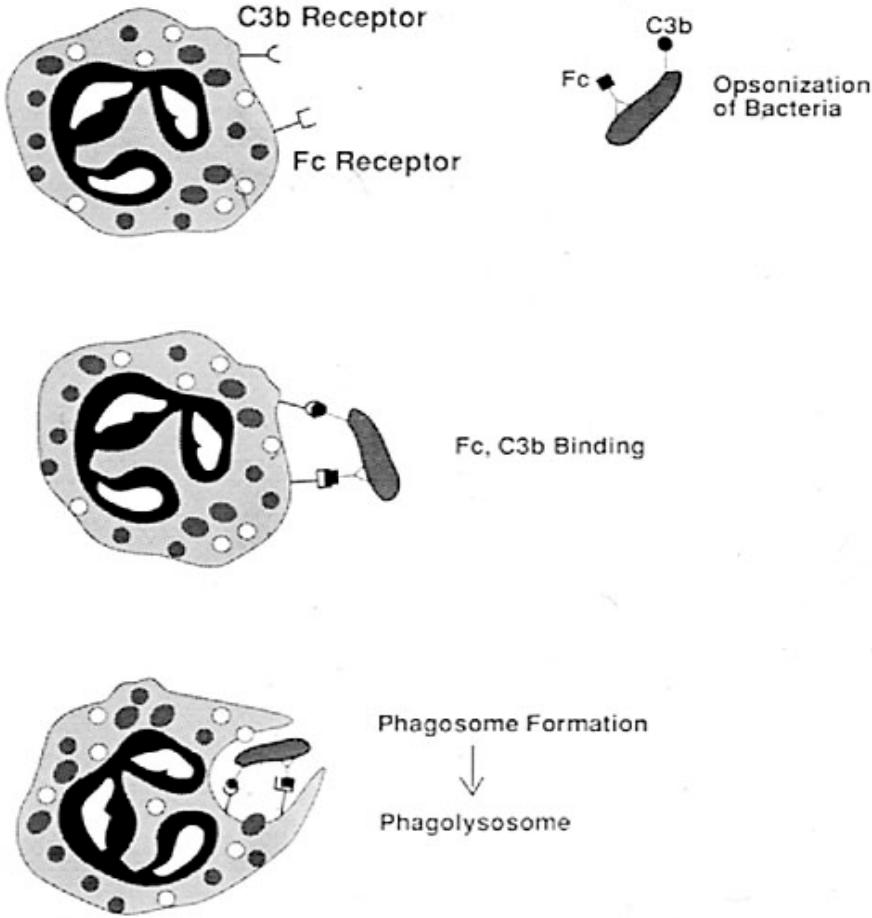
- Adhesion (localization)
- Chemotaxis (migration)
- Phagocytosis
- NADPH oxidase activation
- Lysosomal granule fusion: degranulation



# Opsonization and Phagocytosis

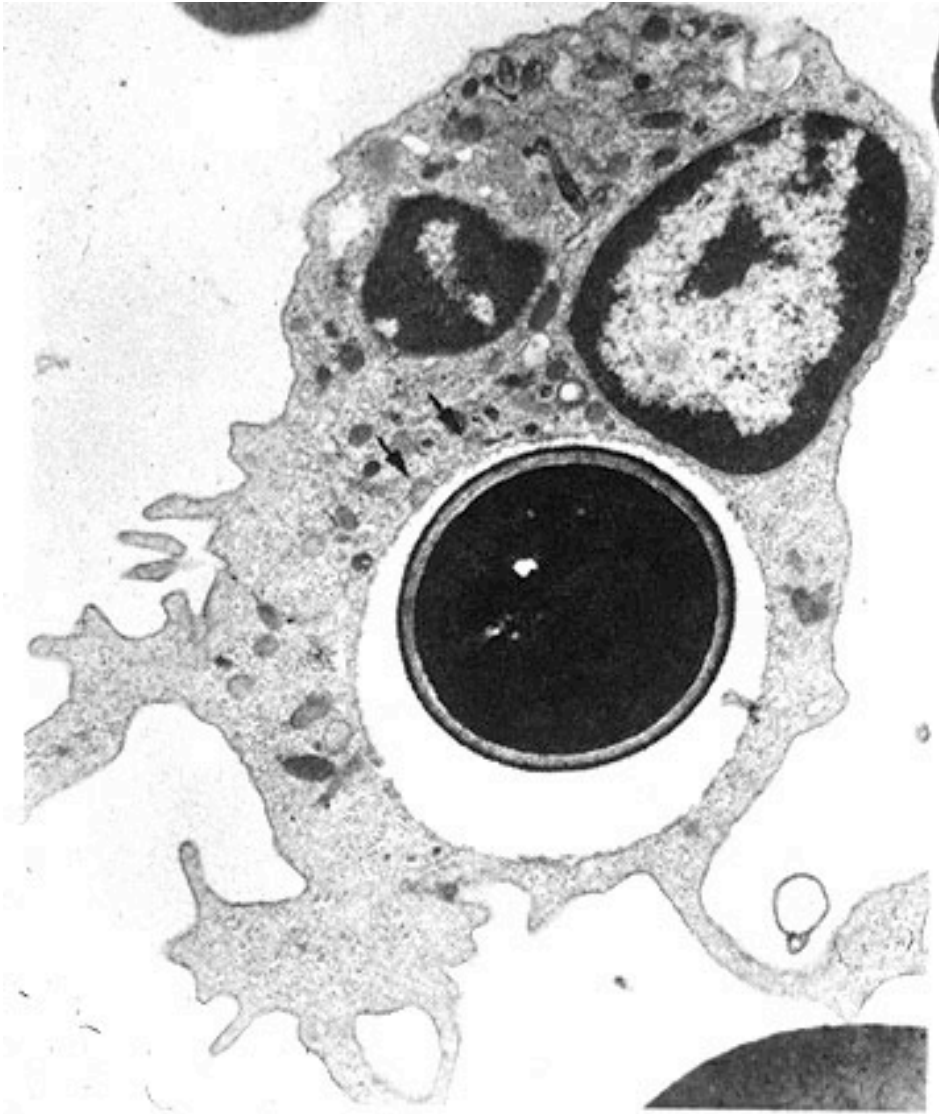
- Fc receptors for antibody
- Complement receptors: (e.g. C3b)
- Other
  - receptors for collectins (eg. mannose-binding protein)

# NEUTROPHIL PHAGOCYTOSIS OF OPSONIZED BACTERIA

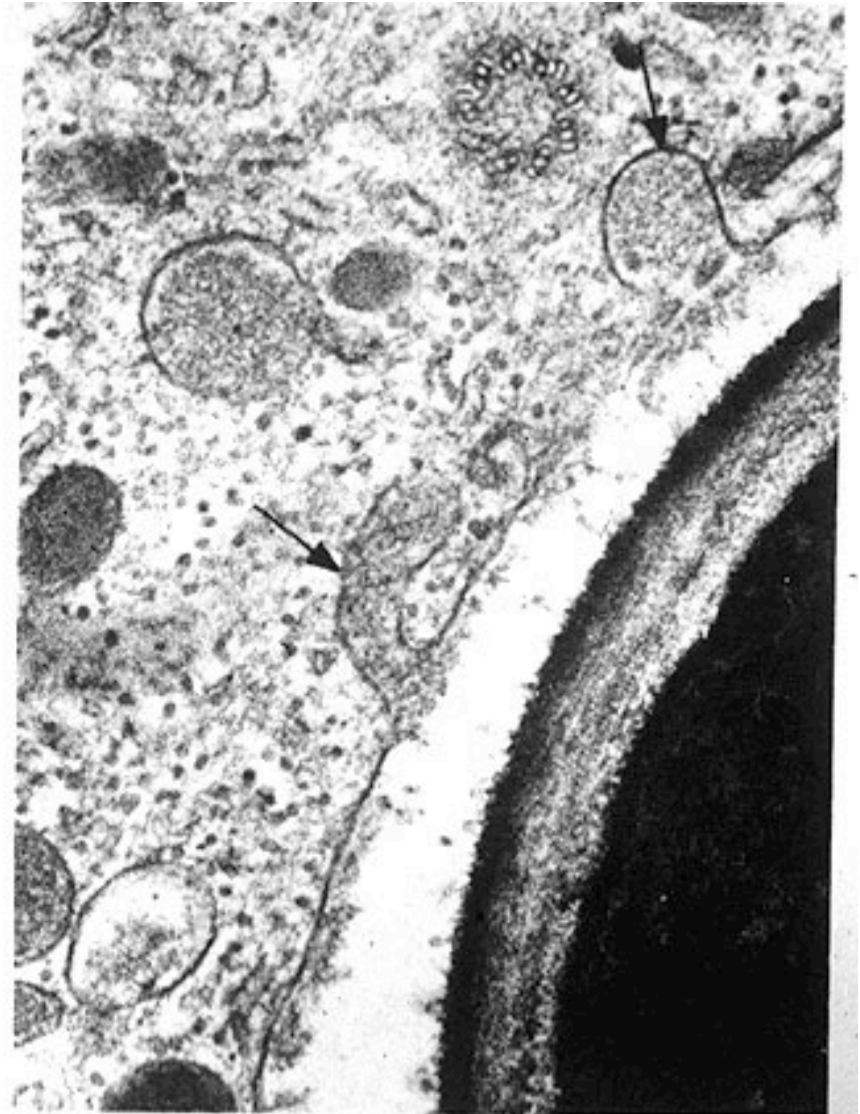


Source: Undetermined



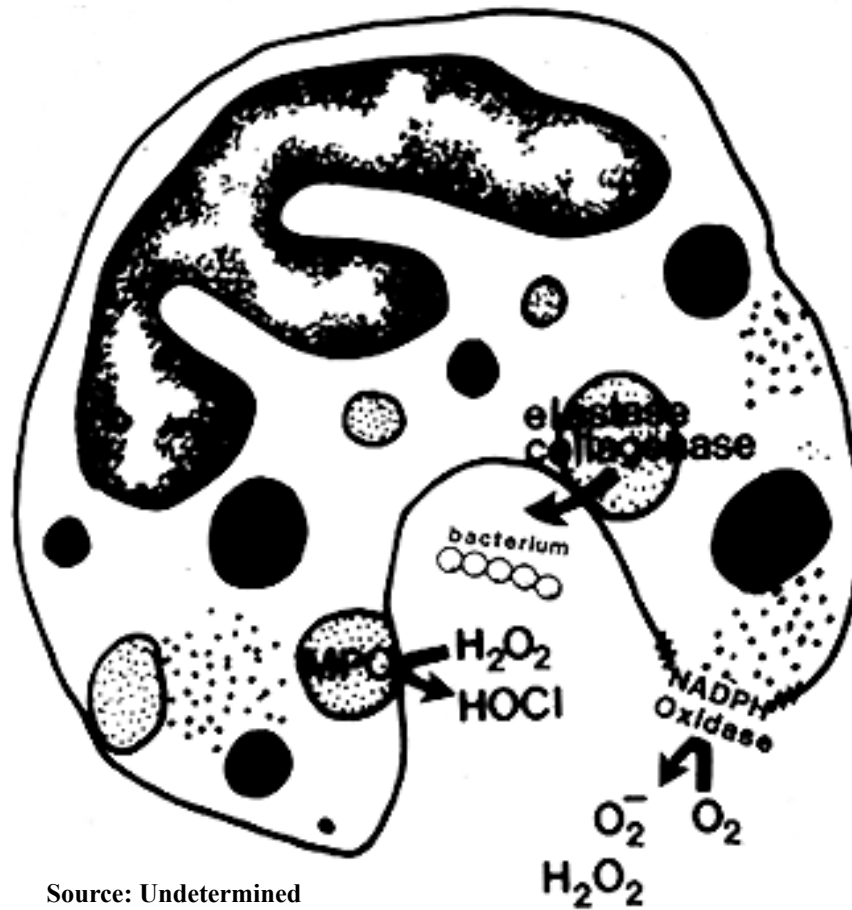


(a) Source: Undetermined



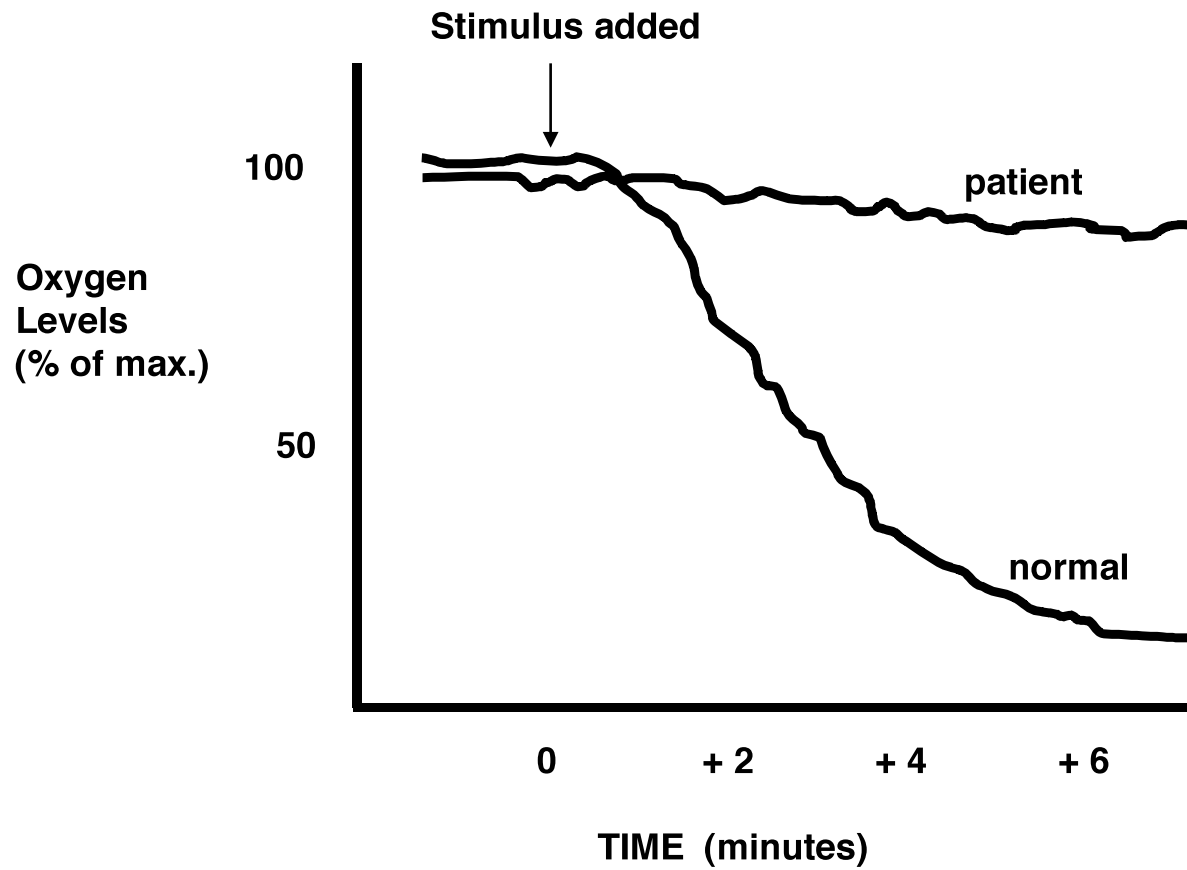
(b) Source: Undetermined

cell phagocytosis → Oxygen radicals  
→ Elastase  
Collagenase  
Acid hydrolases



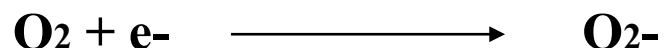
Source: Undetermined

# Respiratory Burst: NADPH Oxidase

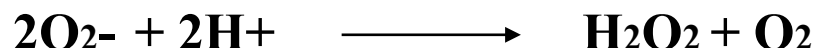


## Reactive Oxygen Metabolites

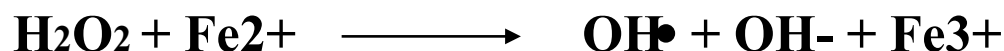
**Superoxide anion:  $O_2^-$**



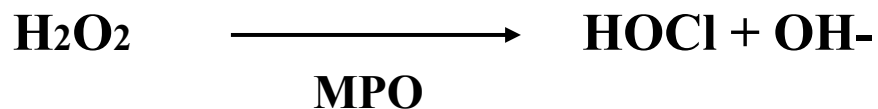
**Hydrogen peroxide:  $H_2O_2$**



**Hydroxyl radical:  $OH \cdot$**



**Hypochlorous acid:  $HOCl$**

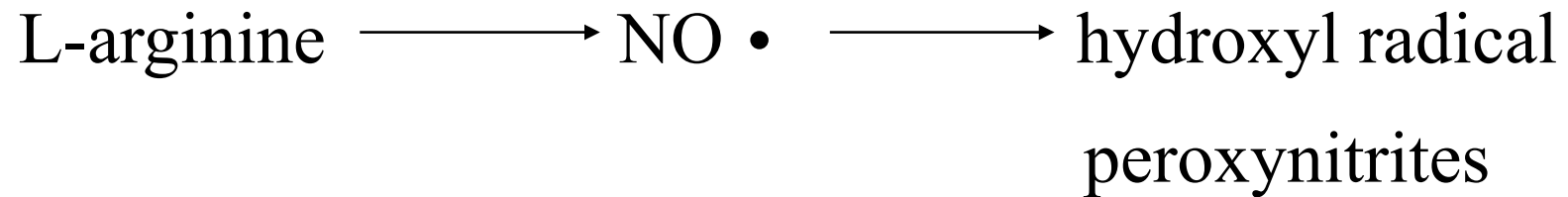


**myeloperoxidase = MPO**

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



# Nitric Oxide (NO •) Synthase



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

# Oxidant Targets

**a) unsaturated lipids: lipid peroxidation**

LOOH = lipid hydroperoxides

**c) proteins**

- sulfhydryl groups

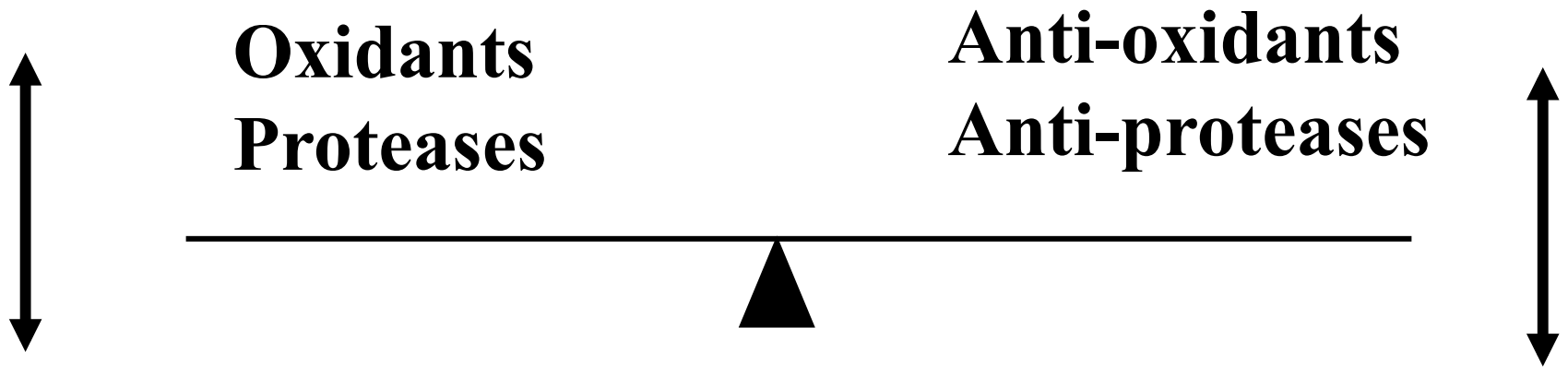
- methionine

- tyrosine

**d) nucleic acids**

# Degranulation

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



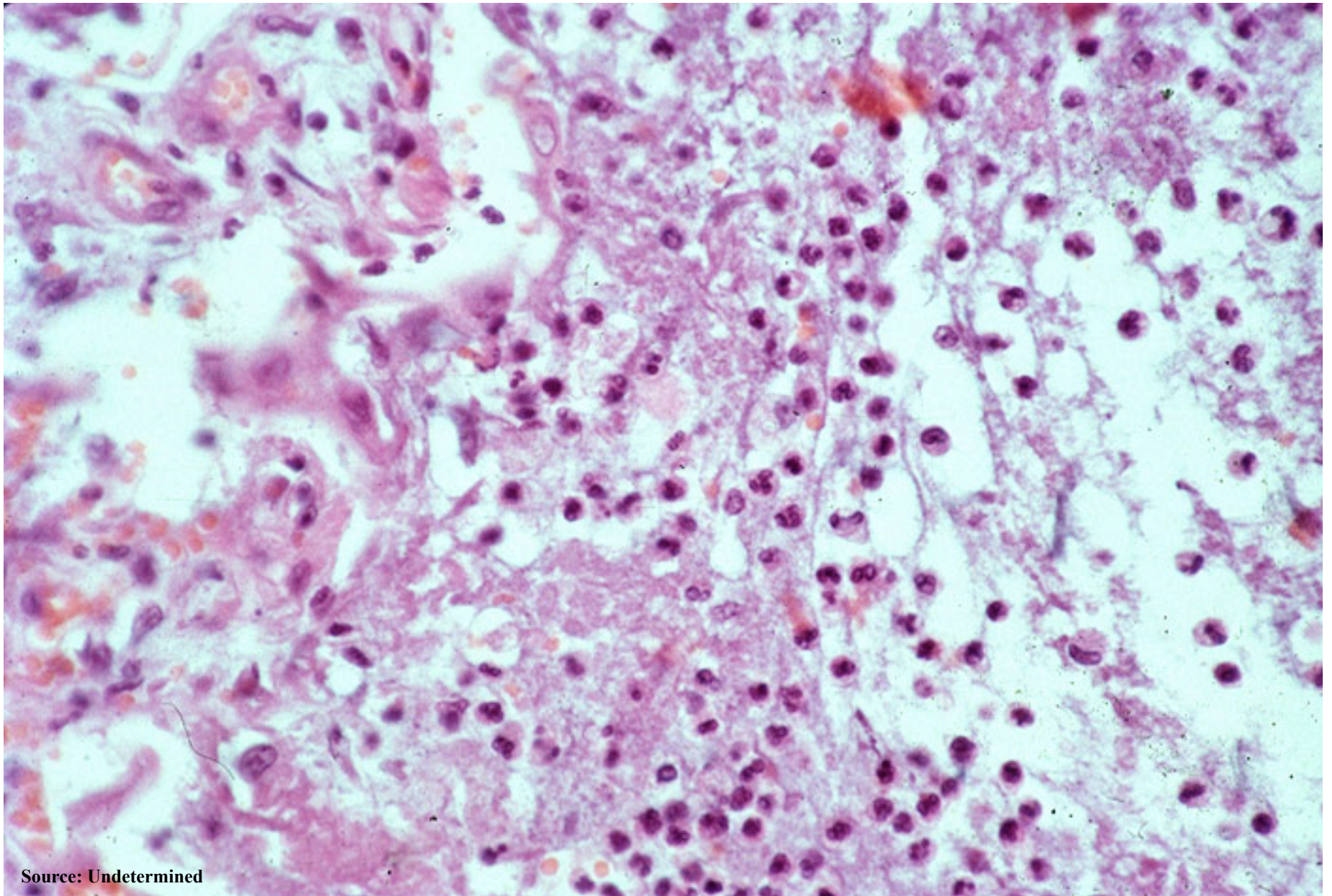




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A-38-BV





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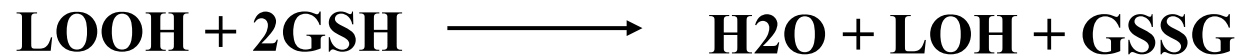
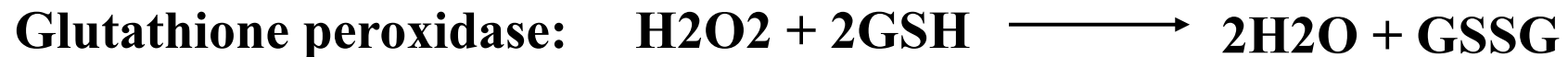
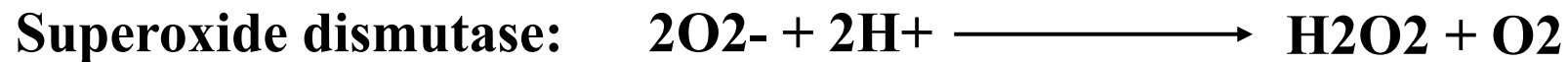
Source: Undetermined

A-38-BV

# Protective Mechanisms

**Anti-oxidant: specific vs. non-specific**

**Specific enzymes:**



LOOH = lipid hydroperoxides

GSH = reduced glutathione

GSSG = oxidized glutathione



## Non-specific scavengers:

**-Vitamin E**

**-Vitamin C**

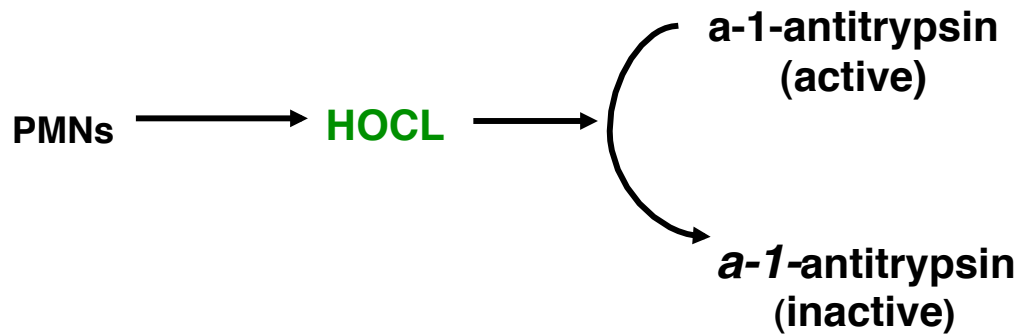
**-Beta-carotene**

## Anti-proteases

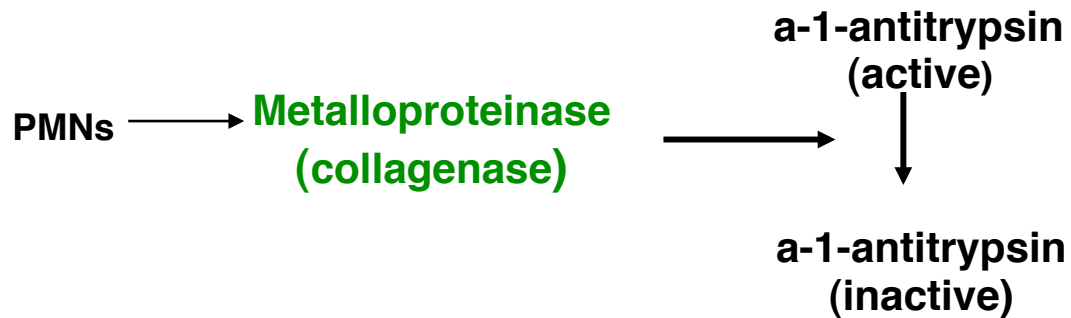
- $\alpha$ -1- anti-protease (anti-trypsin):
  - plasma protein
  - binds proteases including elastase
  - inactivated by oxidants
- $\alpha$ -2- macroglobulin
  - plasma protein
  - binds proteases
- TIMPs: tissue inhibitors of metalloproteinases
  - cell derived

# Synergism: Inactivation of alpha-1-Anti-trypsin

## 1. HOCl Dependent



## 2. Metalloproteinase Dependent



**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 patient's increased susceptibility to bacterial infection:**

1. \_\_\_\_\_

2. \_\_\_\_\_

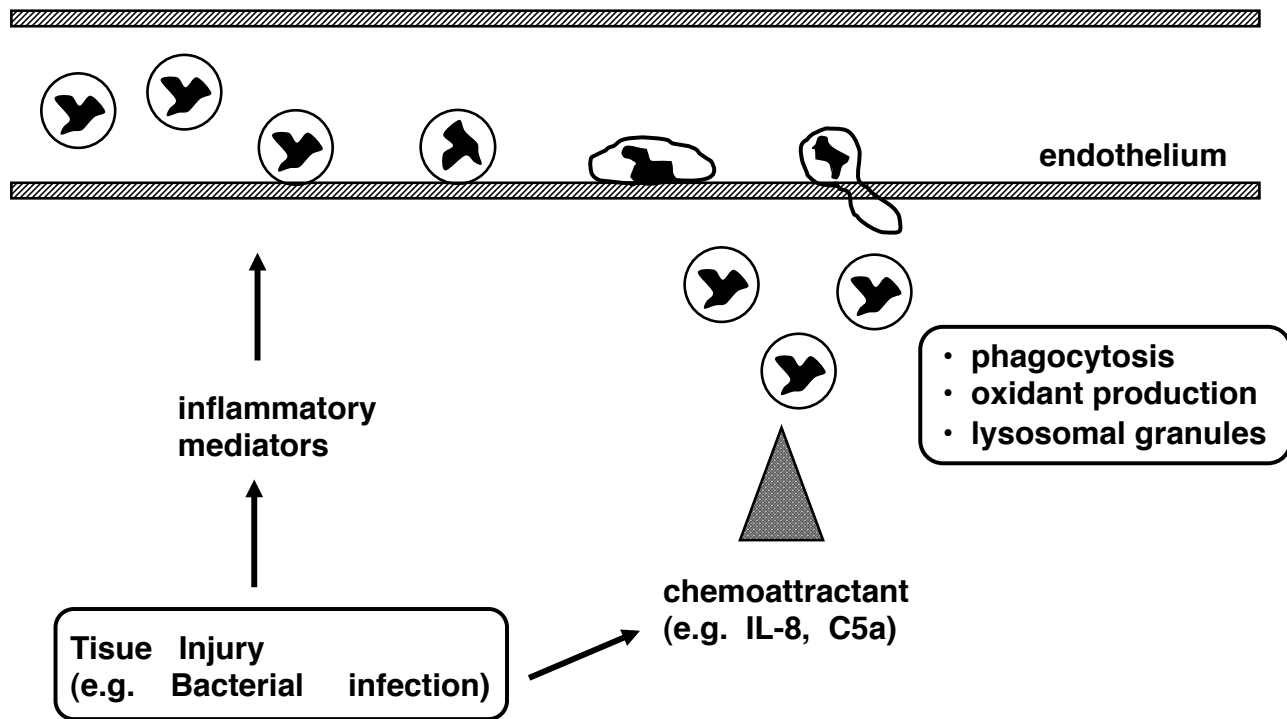
3. \_\_\_\_\_



# Neutrophil Recruitment

Selectins/Addressins  $\longrightarrow$   $\beta_2$ -Integrin/ICAM-1

flow  $\longrightarrow$  rolling  $\longrightarrow$  adhesion  $\longrightarrow$  transmigration



# **Different mechanisms that could account for this patients 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 (2<sup>nd</sup> ed.): pgs. 15-17, 202-209.