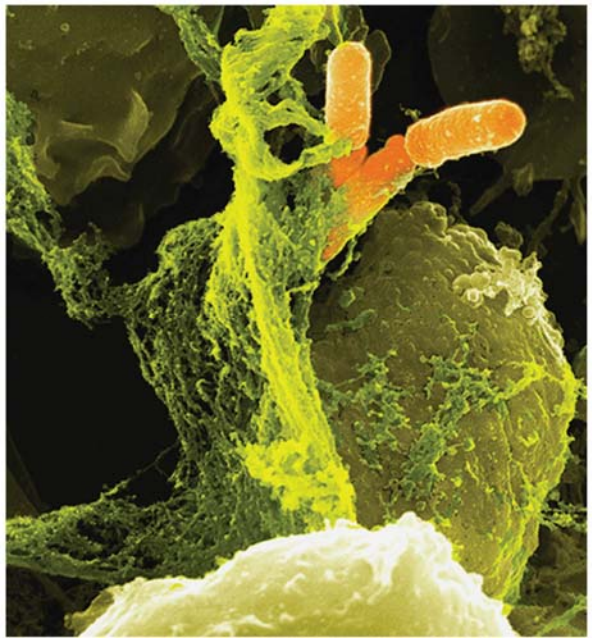
Chapter 16

Innate Immunity:

The Host's Nonspecific Resistance Against Microbes



The Concept of Immunity

- **Immunity**: ability to ward off disease
- **Susceptibility**: host's lack of resistance to a disease
- **Innate immunity**: defenses against any pathogen // present at birth
- **Adaptive immunity**: is not present at birth /// must have "first contact" with pathogen to stimulate resistance /// results in resistance to a specific pathogen plus formation of memory cells activated upon second exposure

Defenses Against Pathogens

- *The human host has three lines of defense against pathogens*
  - first line of defense // external barriers = Skin + mucous membranes /// this is called innate or non specific defenses
  - second line of defense – several nonspecific defense mechanisms // also called innate // 1st and 2nd are both non specific forms of resistance
    - leukocytes and macrophages, antimicrobial proteins, immune surveillance, inflammation, and fever
    - effective against a broad range of pathogens / but not any one specific type of pathogen!
  - third line of defense (the immune system) // defeats specific pathogens // after first exposure special 'memory cells' created which can be used to kill pathogen rapidly if a second exposure occurs in the future

Overview of the body's defenses.

Innate Immunity		Adaptive Immunity (Chapter 17)
First line of defense	**Second line of defense**	**Third line of defense**
• Intact skin • Mucous membranes and their secretions • Normal microbiota	• Phagocytes, such as neutrophils, eosinophils, dendritic cells, and macrophages • Inflammation • Fever • Antimicrobial substances	• Specialized lymphocytes: T cells and B cells • Cellular response & Antibodies

What is the difference between nonspecific resistance and immunity?

- Non-specific resistance (innate defenses) / First Two Lines of Defenses – physical barriers and innate defenses)
  - guards against a broad range of pathogens
  - their effectiveness does not depend on prior exposure
  - skin and mucous membranes
  - leukocytes and macrophages, antimicrobial proteins, immune surveillance, inflammation, and fever
- Immunity (acquired defenses) / Third Line of Defense
  - Specificity - recognition of pathogen
  - Memory – rapid response after first exposure
  - Humoral and cellular response / tagged vs killed!
  - Able to learns from prior exposure so faster response for a second exposure to same pathogen (ie. memory)
  - The three “R”s of immunity: recognize / react / remember

Factors used by Innate Immunity

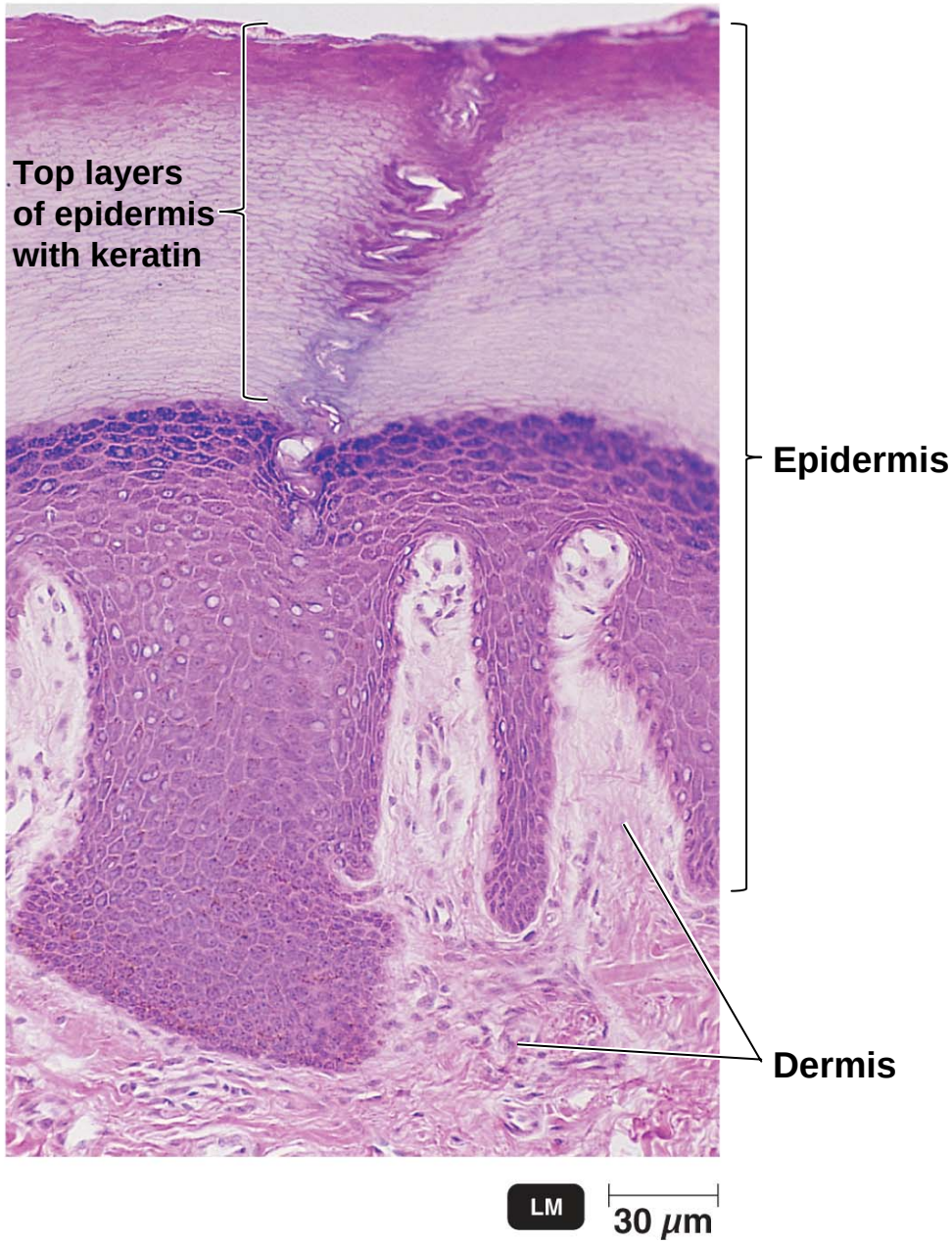
- **Transferrins** // Designed to keep iron away from bacteria – iron essential growth factor for bacteria // Bind serum iron when in blood // ferritin – binds and stores iron in liver
  - Note: Siderophores produced by bacteria to "capture" iron from host // considered a community good for bacteria!
- **Antimicrobial peptides** // secreted onto surface of skin // Lyses bacterial cells – e.g. defensins

Physical Factors Used in Innate Immunity

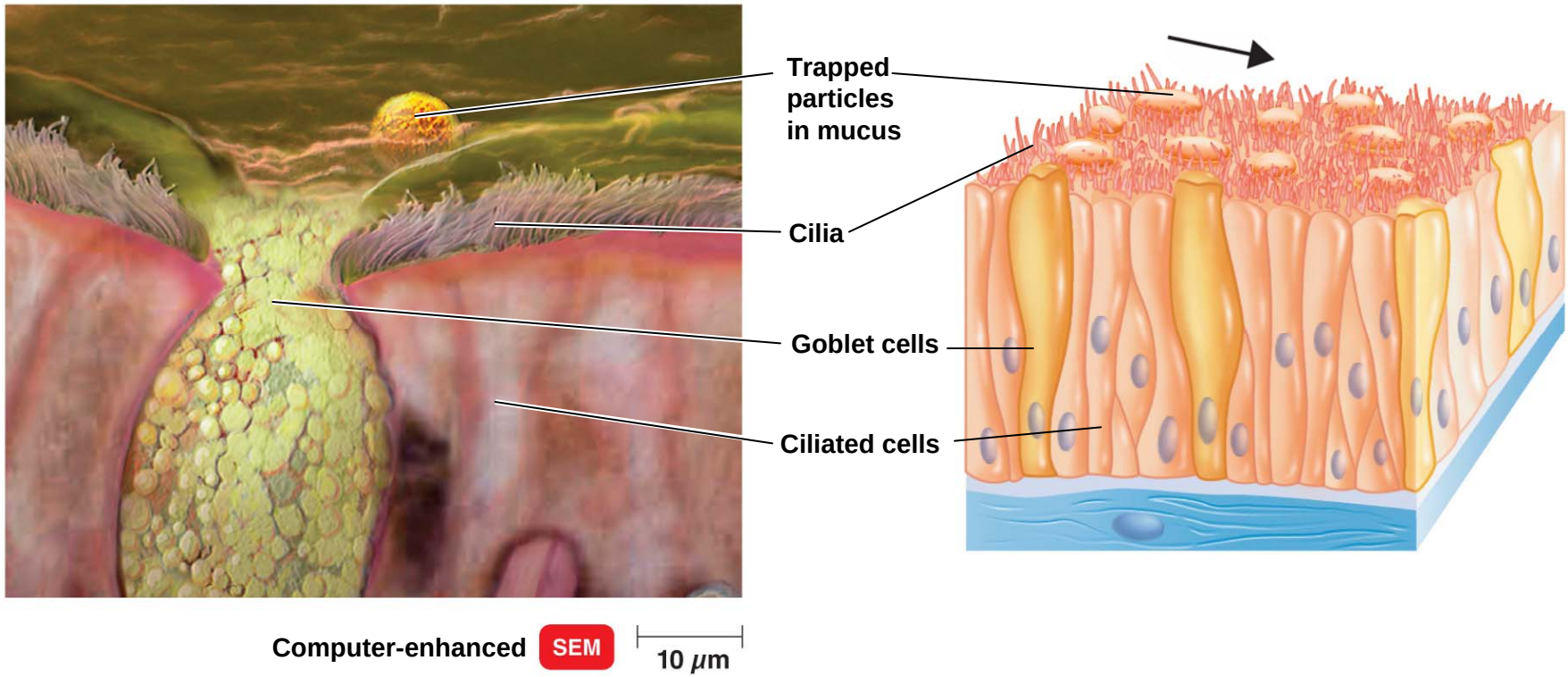
- **Skin** – dry and acidic / antimicrobial proteins like defensins

- **Epidermis** - consists of tightly packed cells with // **Keratin**, a protective protein

A section through human skin.



The ciliary escalator.



Fever

- **Advantages**
  - Increases transferrins
  - Increases IL-1 activity
  - Produces interferon
  - Fever moves free iron into liver so bacteria denied iron
- **Disadvantages**
  - Tachycardia
  - Acidosis
  - Dehydration
  - 44–46°C fatal

How Fever Works

- Abnormally high body temperature
- Hypothalamus is normally set at 37°C
- Pyrogens // endogenous vs exogenous // released by neutrophils and bacteria
- Gram-negative endotoxins cause phagocytes to release interleukin-1 (IL-1)
- Hypothalamus releases prostaglandins that reset the hypothalamus to a high temperature
- Body increases rate of metabolism, and **shivering** occurs, which raise temperature
- Vasodilation and sweating: body temperature falls (**crisis**)

PAMPs & TLRs in Innate Immunity

- Host cells (e.g. macrophage) have **Toll-like receptors (TLRs) on their plasma membranes**

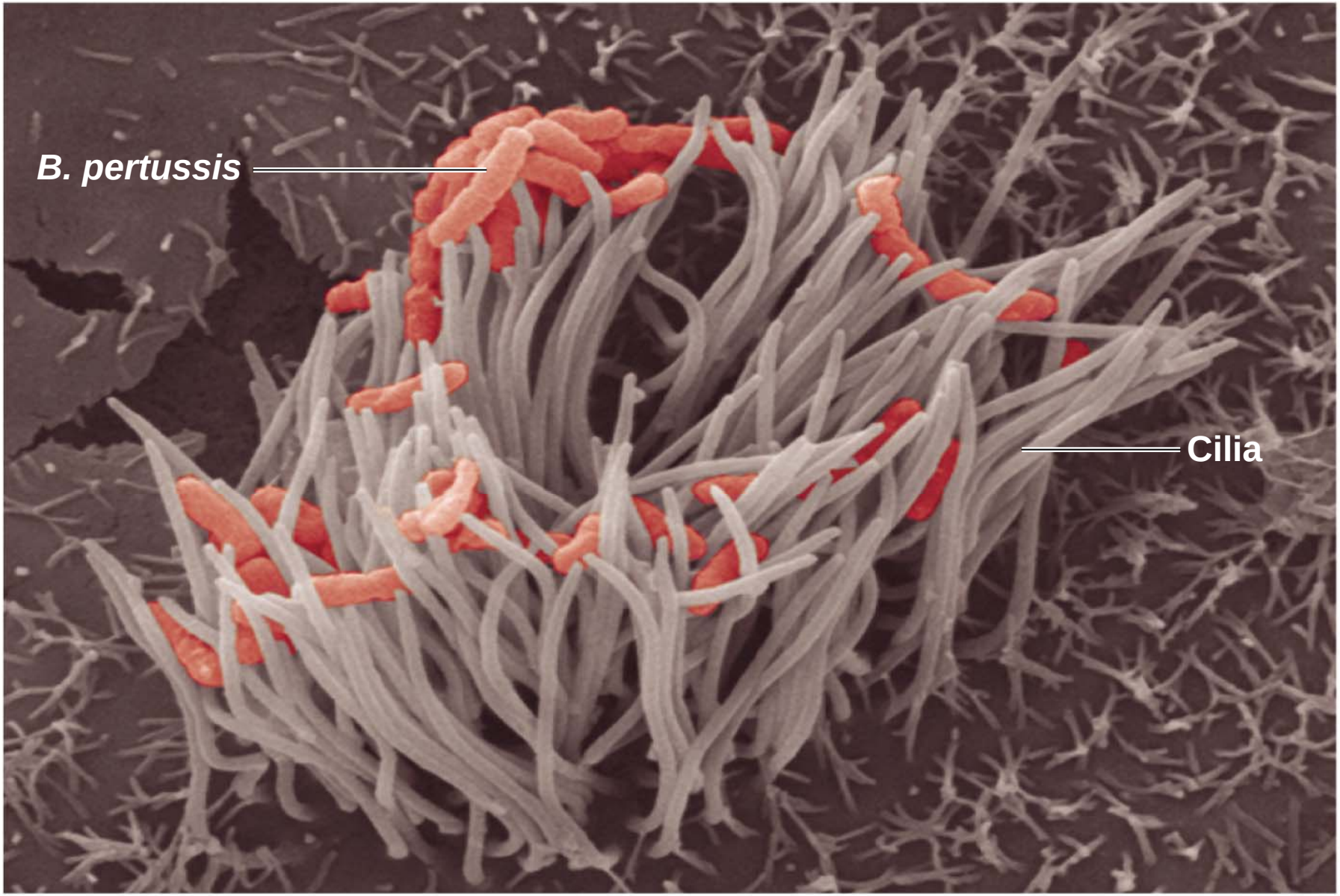
- **All microbes have some similar surface macromolecules = pathogen-associated molecular patterns (PAMPs) that can bind to TLRs**

- TLRs induce macrophage to release **cytokines** that regulate the intensity and duration of immune responses

Physical Factors

- **Mucous membranes**
- **Mucus**: traps microbes
- **Ciliary escalator**: transports microbes trapped in mucus away from the lungs

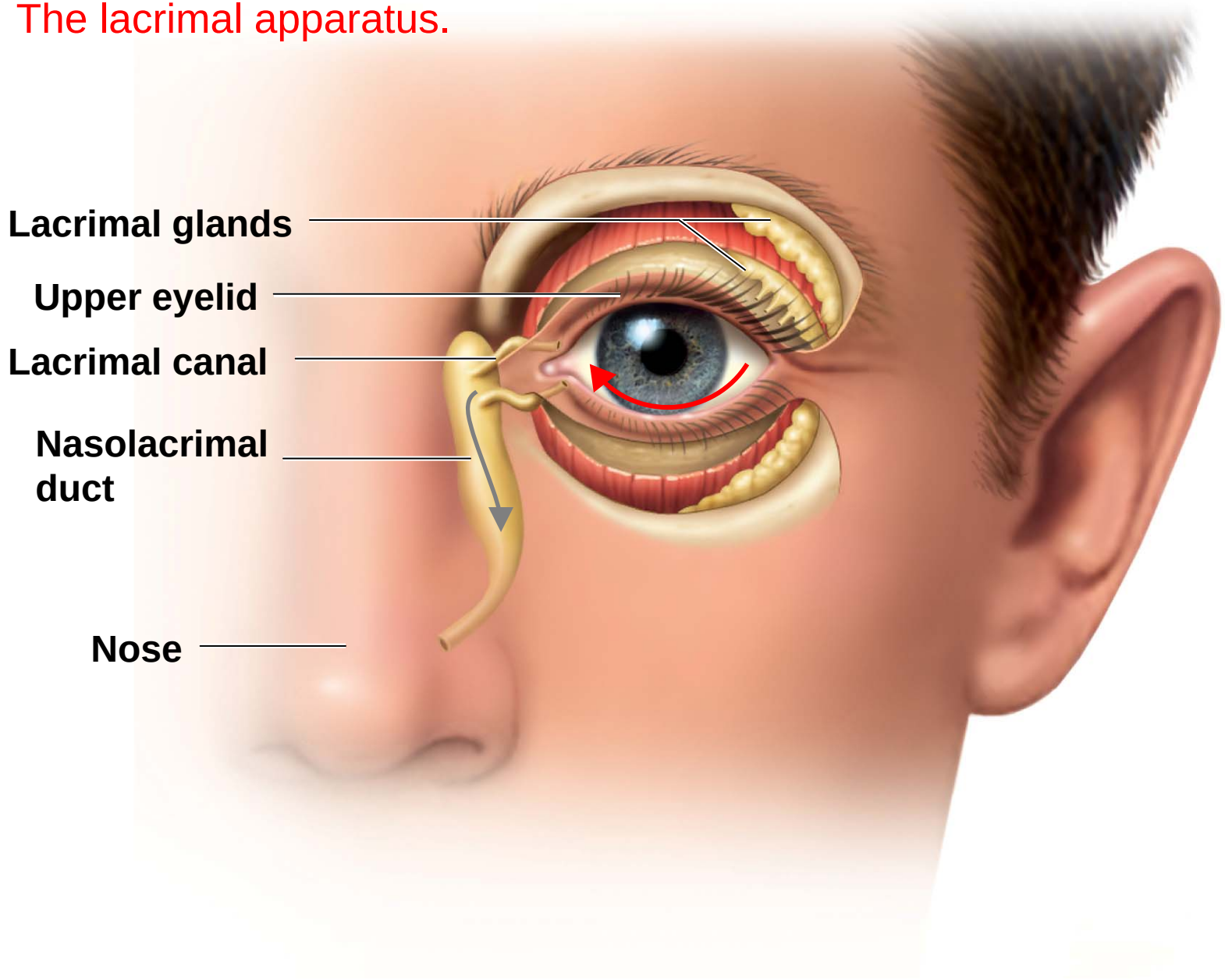
Ciliated cells of the respiratory system infected with *Bordetella pertussis*.



Physical Factors

- **Lacrimal apparatus**: washes eye
- **Saliva**: washes microbes off
- **Urine**: flows out
- **Vaginal secretions**: flow out

The lacrimal apparatus.



Chemical Factors by Host Cells

- Fungistatic fatty acids in sebum
- Low pH (3–5) of skin
- Lysozyme in perspiration, tears, saliva, and urine // breaks down peptidoglycan of cell wall // same action as penicillin
- Low pH (1.2–3.0) of gastric juice // kills bacteria
- Low pH (3–5) of vaginal secretions // epithelial cells secrete glycogen – Lactobacillus adidophilus metabolize sugar and secrete lactic acid – inhibits Candida albican (i.e. fungal infections)

Normal Microbiota and Innate Immunity

- **Microbial antagonism = competitive exclusion**

- **Normal microbiota** compete with pathogens for space and resources // or alter the environment to resist pathogens by secreting antimicrobial molecules (e.g. bacteriocidins)

  - Note: the normal microbiota may at a later time may become an opportunistic pathogens

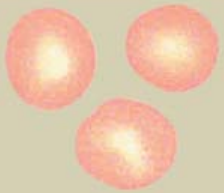
- **Commensal microbiota**: one organism (microbe) benefits, while the host is unharmed

Formed Elements in Blood (Part 1 of 2)

TABLE 16.1 Formed Elements in Blood

I. Erythrocytes (Red Blood Cells)

4.8–5.4 million per µl or mm^3
Function: Transport of O_2 and CO_2

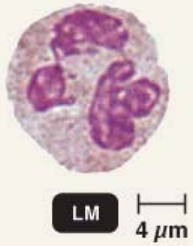


II. Leukocytes (White Blood Cells)

5000–10,000 per µl or mm^3

A. Granulocytes (stained)

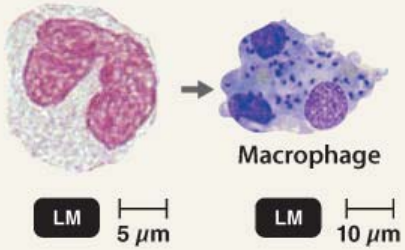
1. Neutrophils (PMNs)
(60–70% of leukocytes)
Function: Phagocytosis



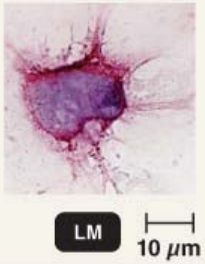
2. Basophils (0.5–1%)
Function: Production of histamine

B. Agranulocytes (stained)

1. Monocytes (3–8%)
Function: Phagocytosis (when they mature into macrophages)



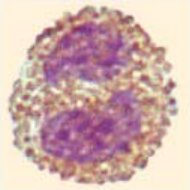
2. Dendritic cells
Functions: Derived from monocytes; phagocytosis and initiation of adaptive immune responses



Formed Elements in Blood (Part 2 of 2)

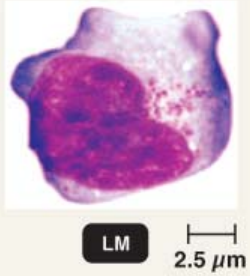
TABLE 16.1 Formed Elements in Blood

3. Eosinophils (2–4%)
Functions: Production of toxic proteins against certain parasites; some phagocytosis

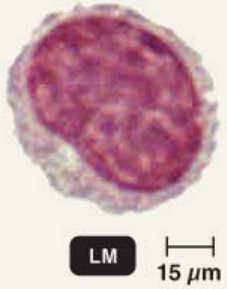


3. Lymphocytes (20–25%)

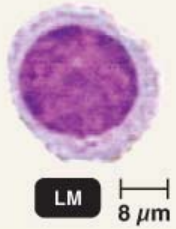
- Natural killer (NK) cells
Function: Destroy target cells by cytolysis and apoptosis



- T cells
Function: Cell-mediated immunity (discussed in Chapter 17)



- B cells
Function: Descendants of B cells (plasma cells) produce antibodies



III. Platelets

150,000–400,000 per μl or mm^3
Function: Blood clotting

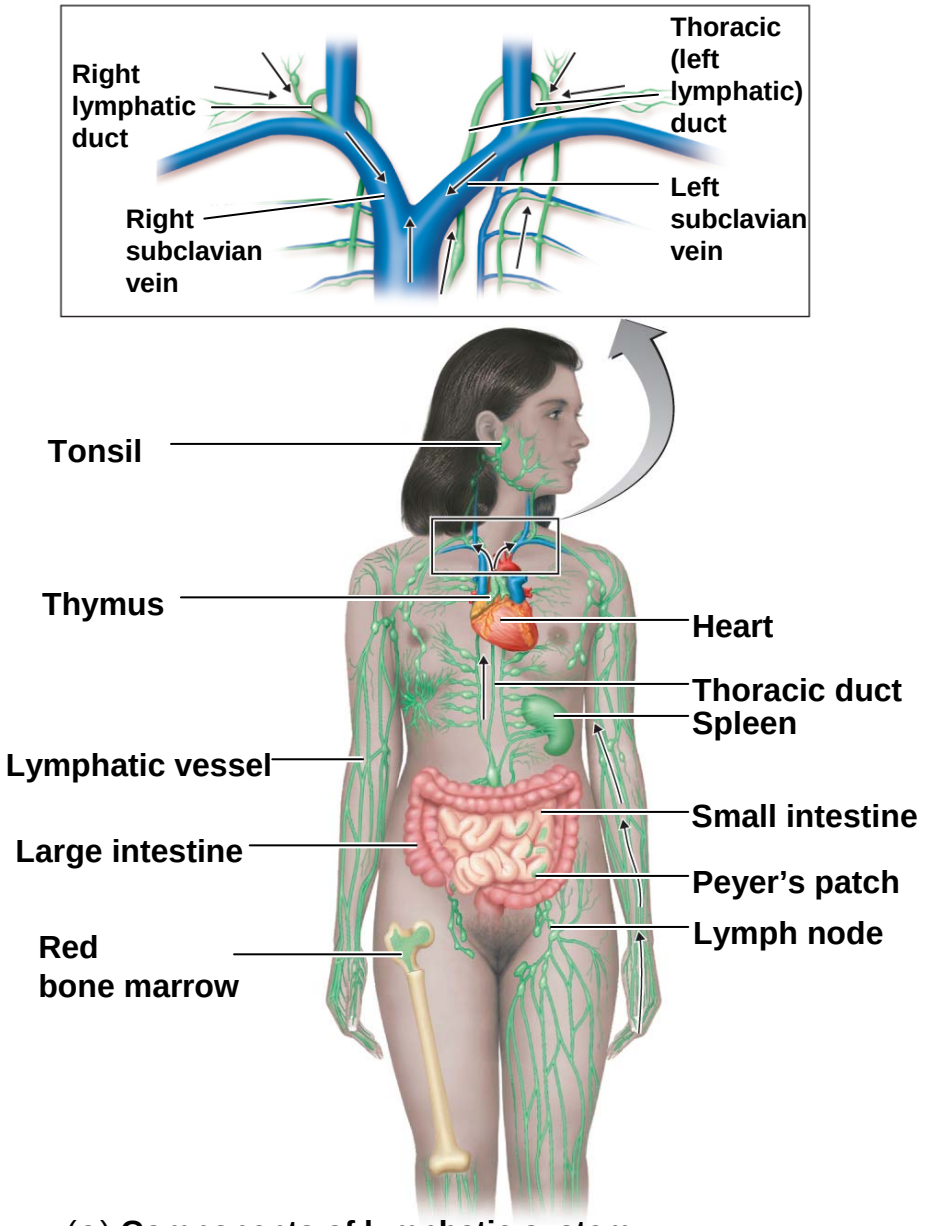
Differential White Cell Count

- Percentage of each type of white cell in a sample of 100 white blood cells

Neutrophils	60–70%
Basophils	0.5–1%
Eosinophils	2–4%
Monocytes	3–8%
Lymphocytes	20–25%

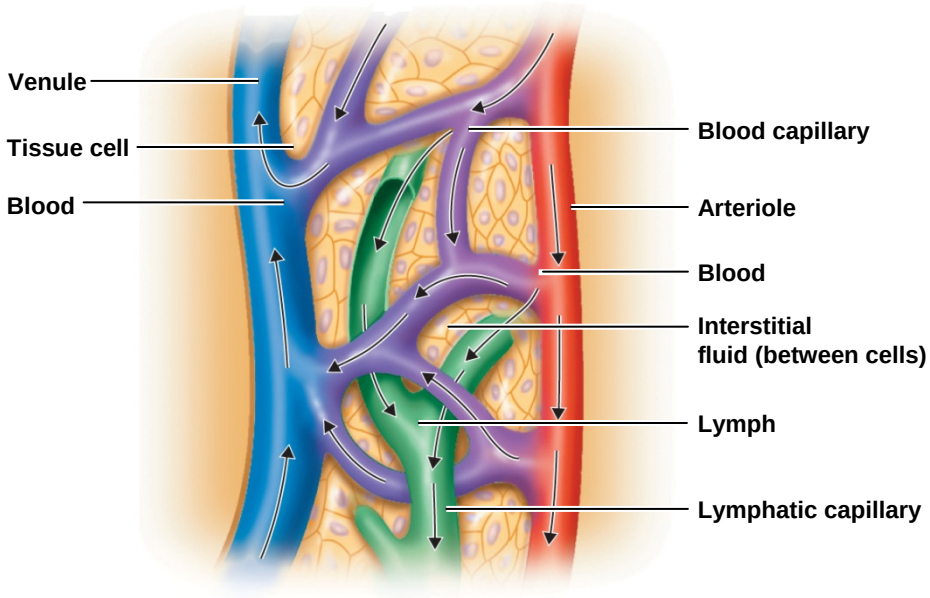
Never let monkeys eat bananas!

The lymphatic system.

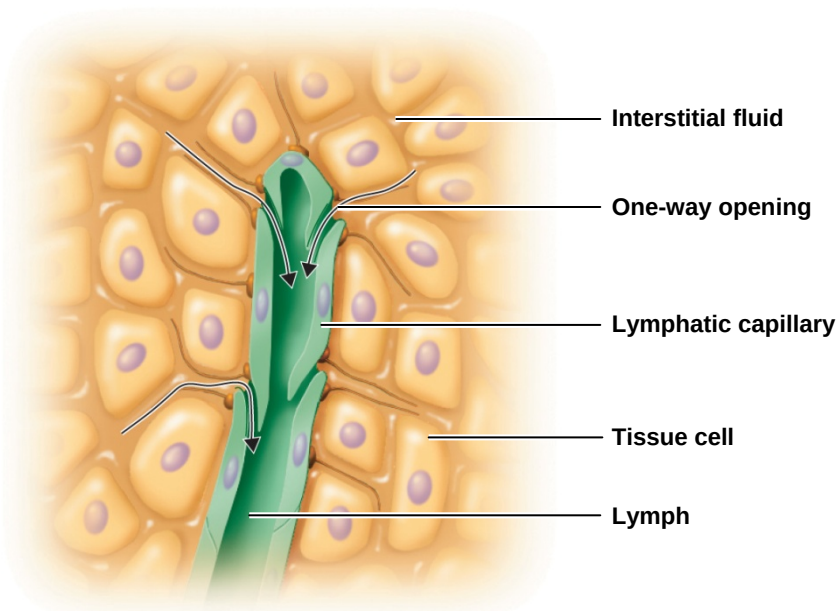


(a) **Components of lymphatic system**

The lymphatic system.



(b) Relationship of lymphatic capillaries to tissue cells and blood capillaries



(c) Details of a lymphatic capillary

Note: lymph nodes functions / filter & germination center for active immunity

Phagocytosis – Key Factor in Innate Immunity

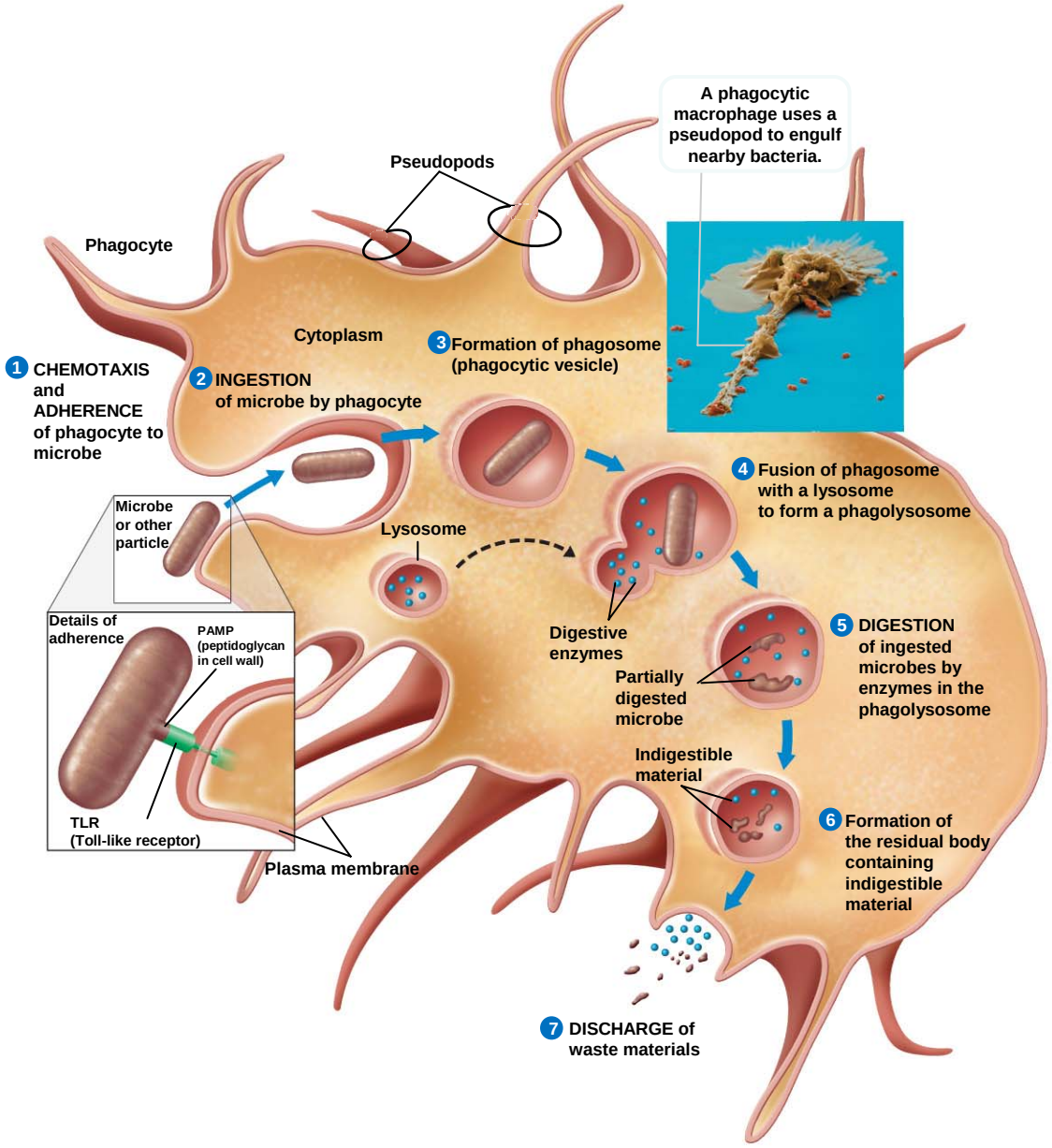
- *Phago*: from Greek, meaning eat
- *Cyte*: from Greek, meaning cell
- Ingestion of microbes or particles by a cell, performed by phagocytes
- Macrophage are the most active of all phagocytic cells

Cells Capable of Phagocytosis

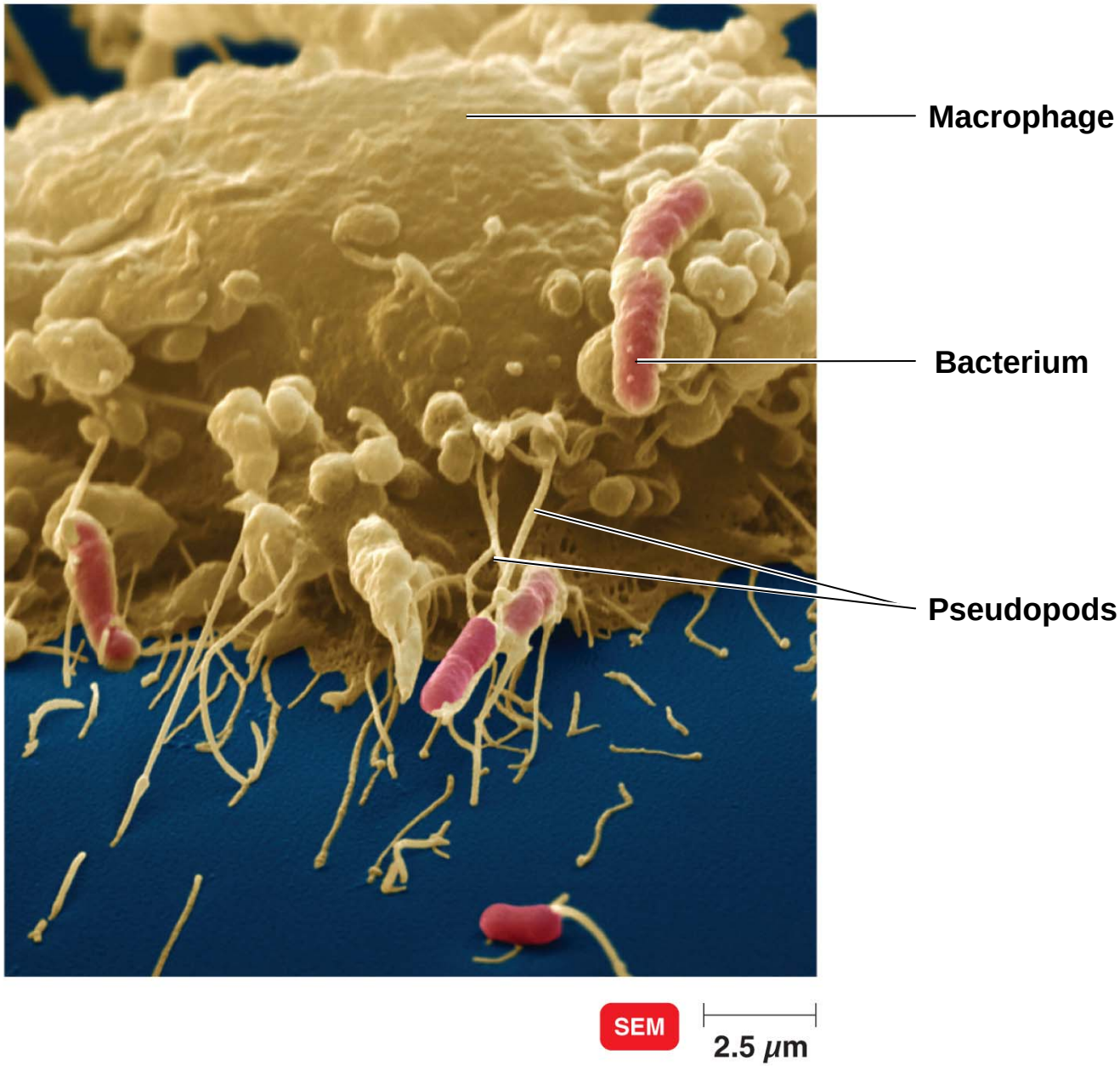
- **Neutrophils**
- **Fixed macrophages**
- **Wandering macrophages**

Note: other cells are also able to engulf particles // this is not a complete list.

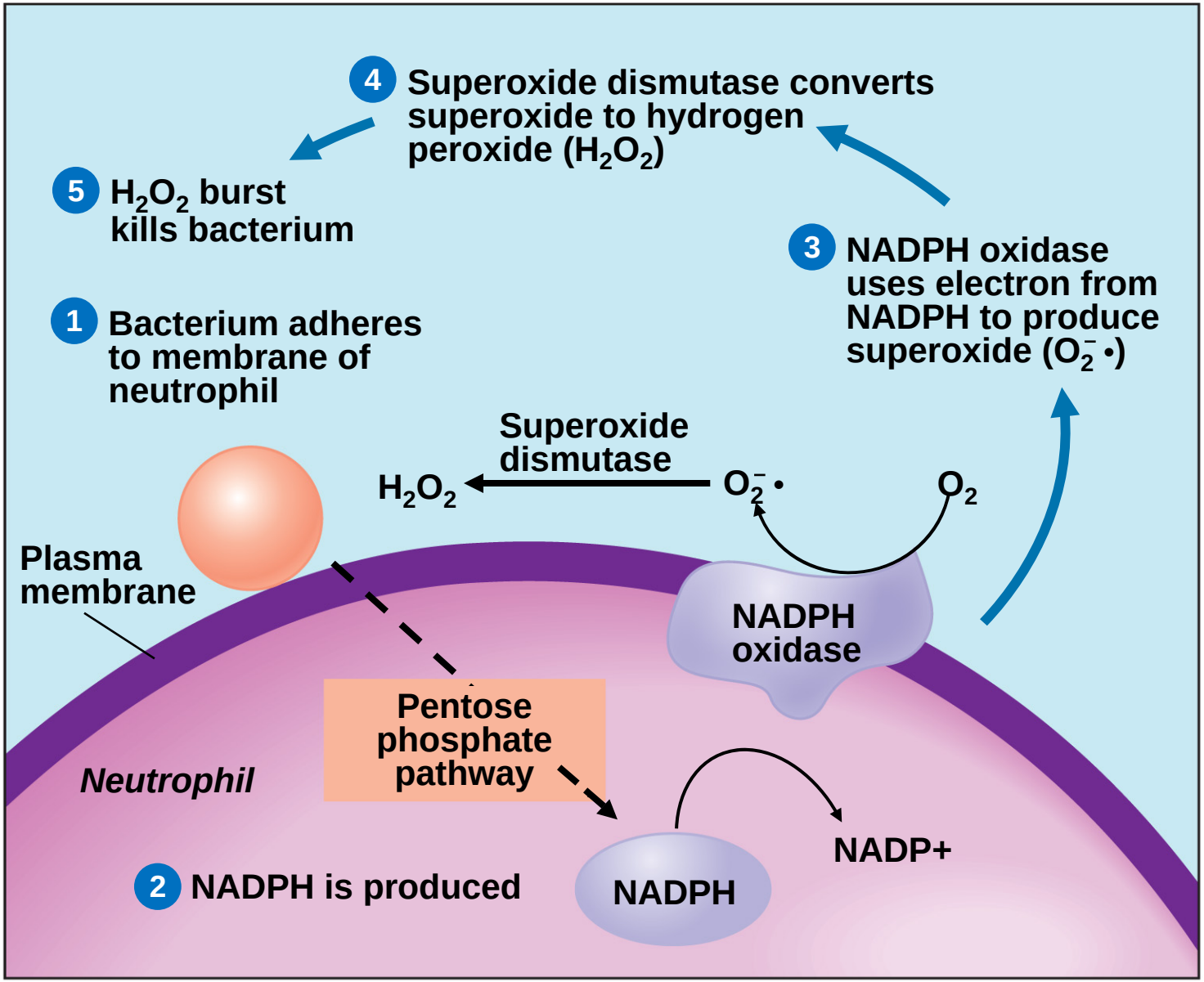
The Phases of Phagocytosis.



A macrophage engulfing rod-shaped bacteria.



Oxidative Burst (Neutrophils & Esinophils)



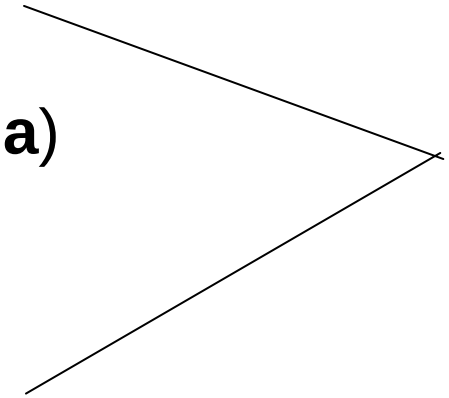
How Microbes Evade Destruction by Phagocytosis

Inhibit adherence: M protein, capsules	*Streptococcus pyogenes, S. pneumoniae*
Kill phagocytes: Leukocidins	*Staphylococcus aureus*
Lyse phagocytes: Membrane attack complex	*Listeria monocytogenes*
Escape phagosome	*Shigella*, *Rickettsia*
Prevent phagosome–lysosome fusion	HIV, *Mycobacterium tuberculosis*
Survive in phagolysosome	*Coxiella burnettii*

Inflammation

- Response to tissue injury // regardless of cause
- Activation of **acute-phase proteins** (complement, cytokine, and kinins)
- **First step is vasodilation** (caused by histamine, kinins, prostaglandins, and leukotrienes) – results in …….

- Redness
- Swelling (**edema**)
- Pain
- Heat



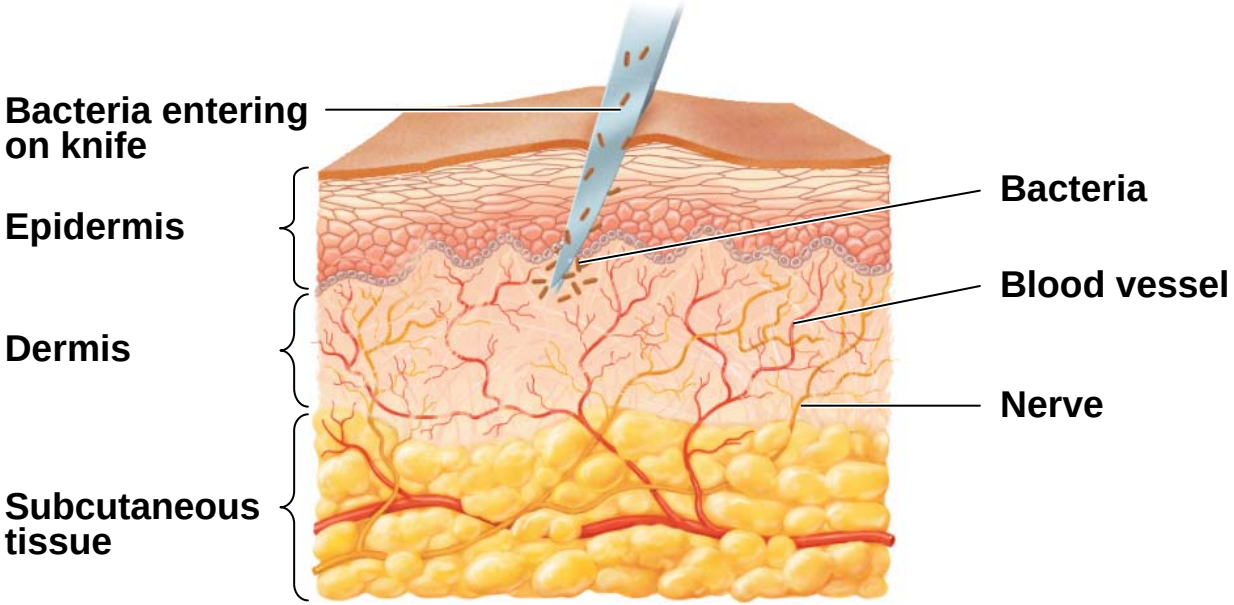
The Cardinal Signs of Inflammation

Chemicals Released by Damaged Cells

Histamine	Vasodilation, increased permeability of blood vessels
Kinins	Vasodilation, increased permeability of blood vessels
Prostaglandins	Intensify histamine and kinin effect
Leukotrienes	Increased permeability of blood vessels, phagocytic attachment

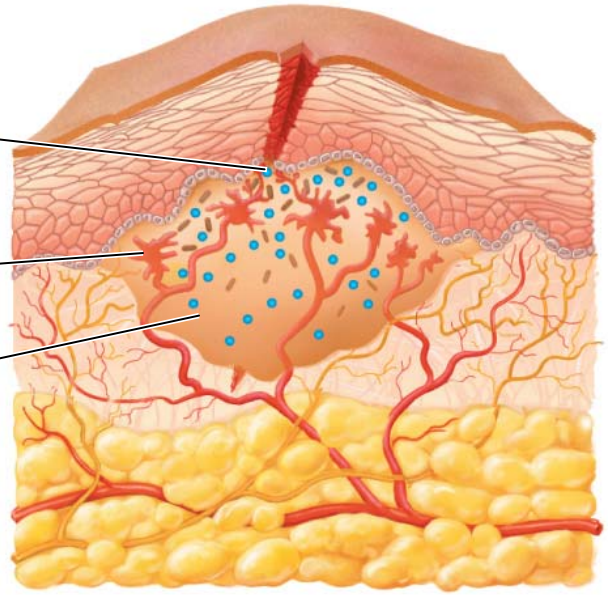
Note: aspirin reduces inflammation by lowering postaglandins production

The process of inflammation.



(a) **Tissue damage**

1. **Chemicals such as histamine, kinins, prostaglandins, leukotrienes, and cytokines (represented as blue dots) are released by damaged cells.**
2. **Blood clot forms.**
3. **Abscess starts to form (orange area).**



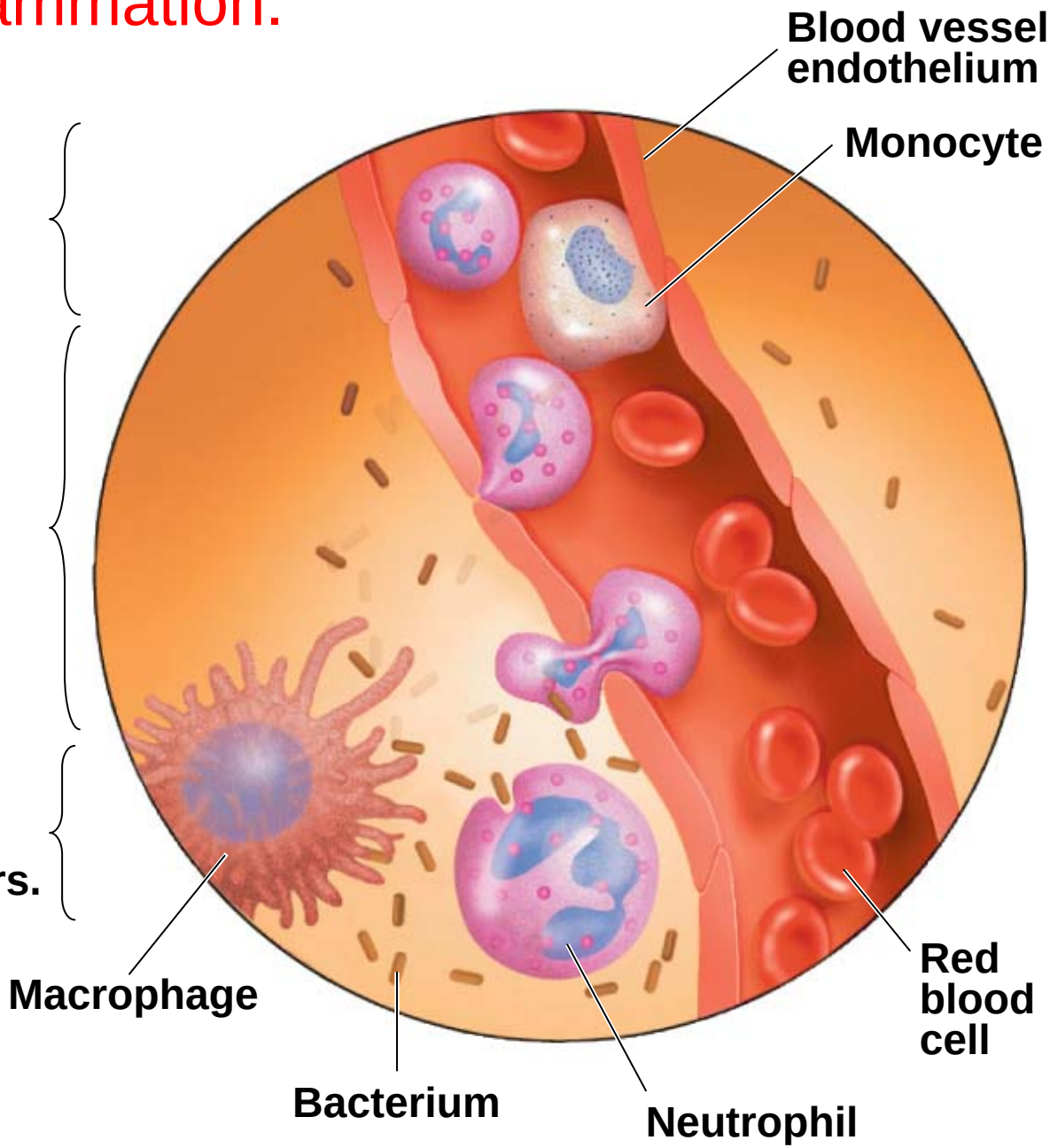
(b) **Vasodilation and increased permeability of blood vessels**

The process of inflammation.

4 **Margination—phagocytes stick to endothelium.**

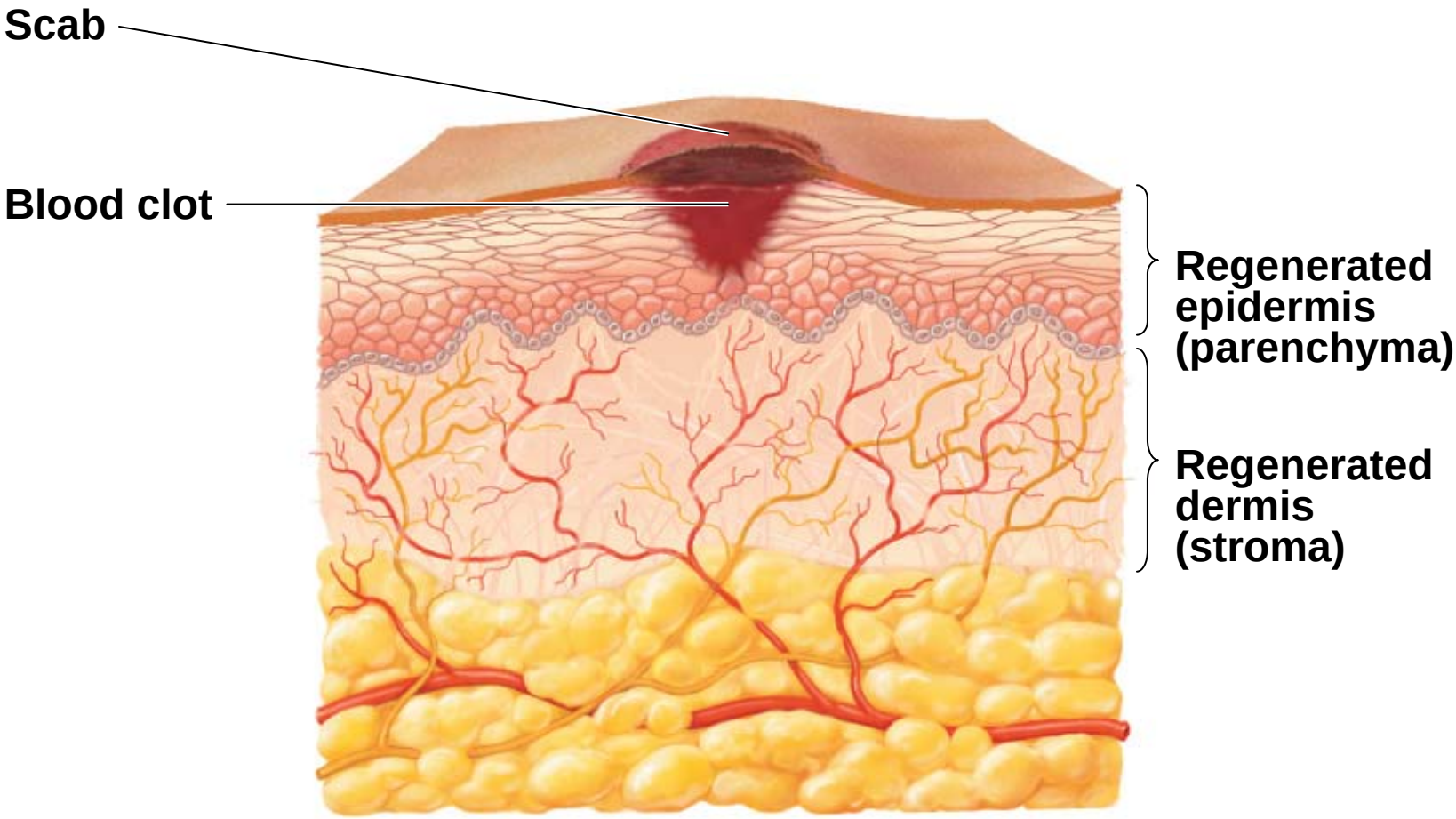
5 **Diapedesis—phagocytes squeeze between endothelial cells.**

6 **Phagocytosis of invading bacteria occurs.**



(c) **Phagocyte migration and phagocytosis**

The process of inflammation.



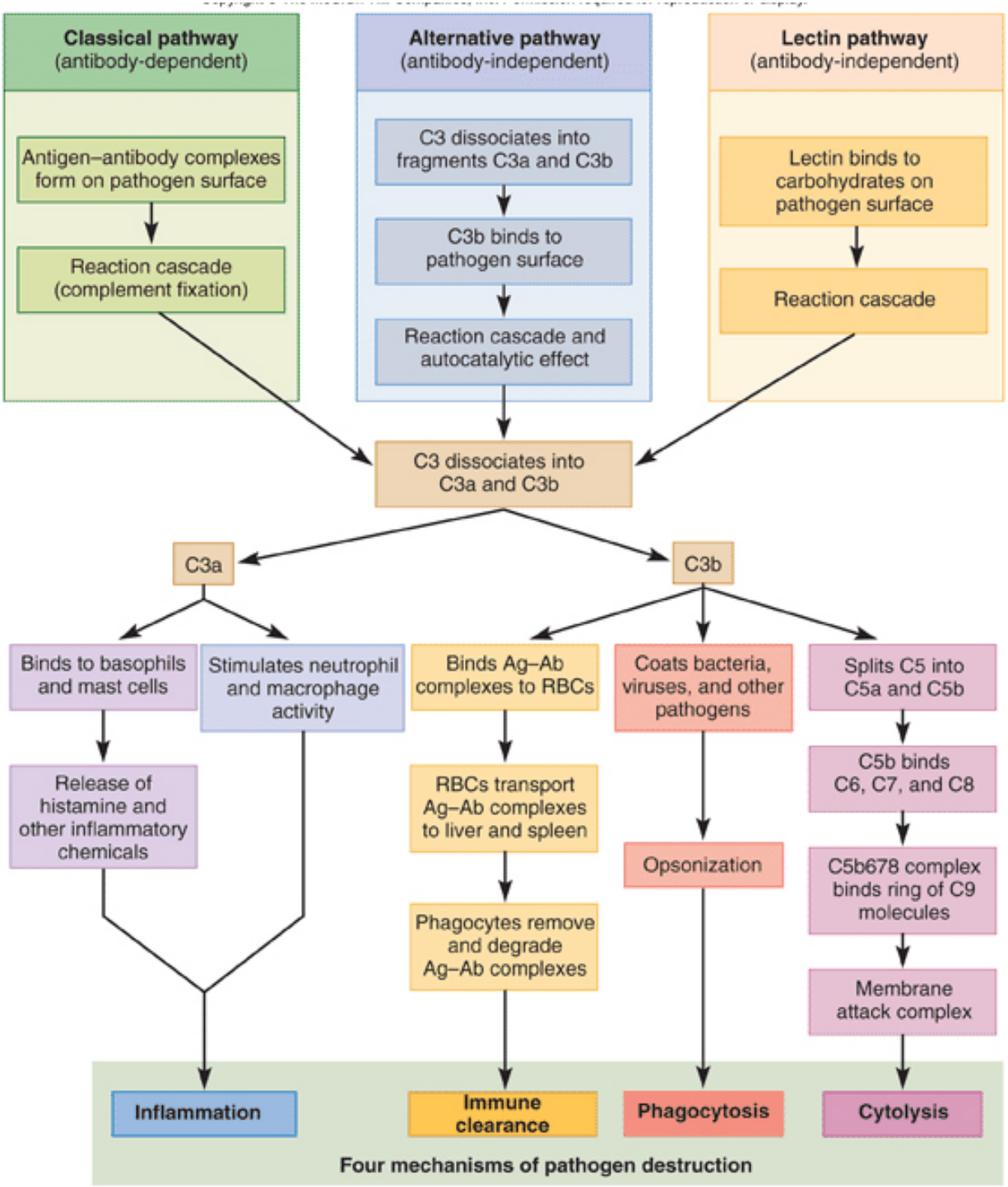
(d) **Tissue repair**

Note: Regeneration vs Fibrosis // tissue damage always results in certain amount of new additional extracellular fiber

The Complement System

- Serum proteins made by liver
- Circulates as “inactive” plasma proteins
- Activated in a cascade fashion / positive feedback
- Activation occurs by three different pathways

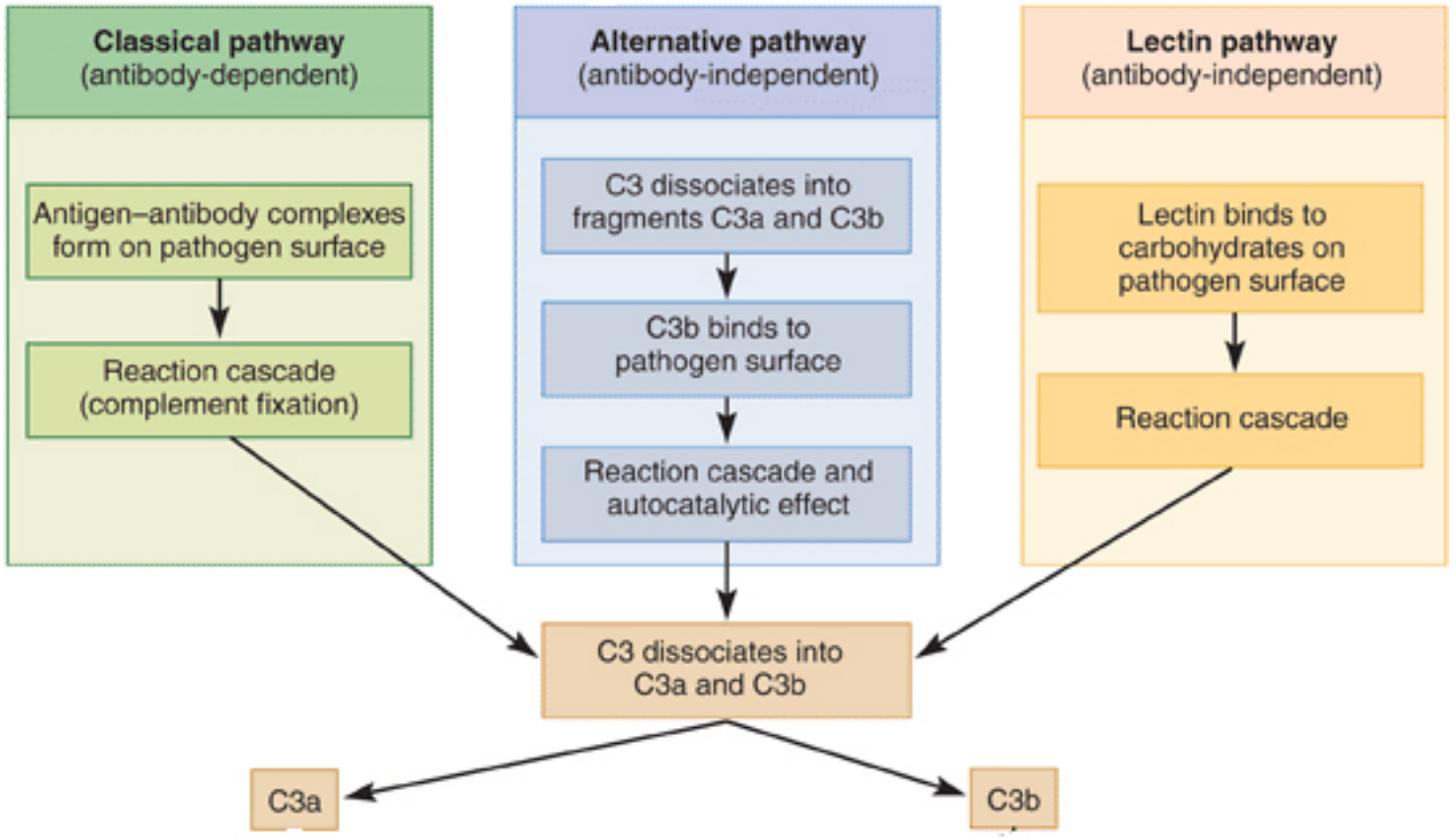
Complement Activation



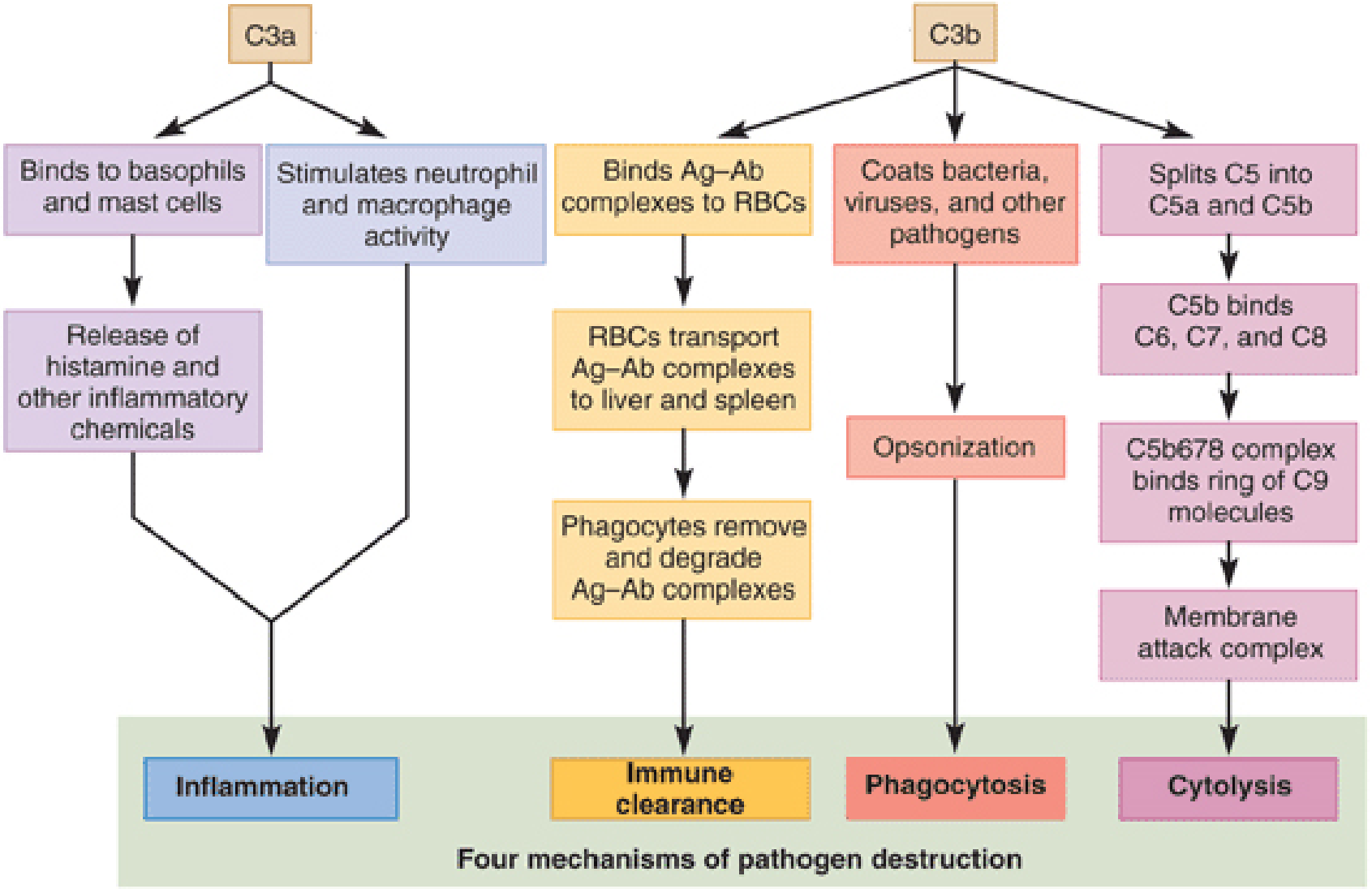
This is how complement is activated. (Three Options)

This pathway is part of specific immunity because it depends on the B Cells / plasma cells antibodies.

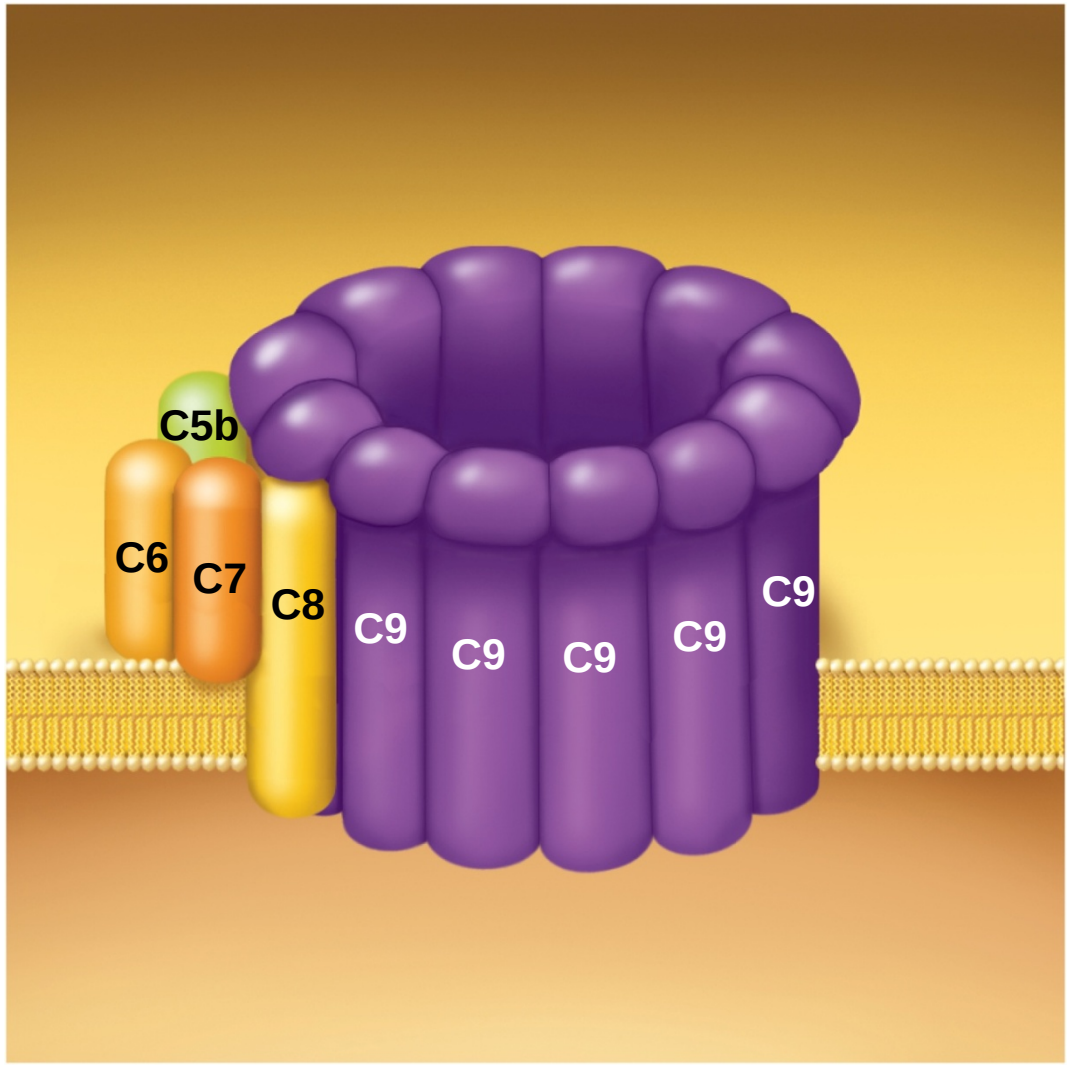
These pathways are part of the non specific resistance because they function independent of the B and T cells.



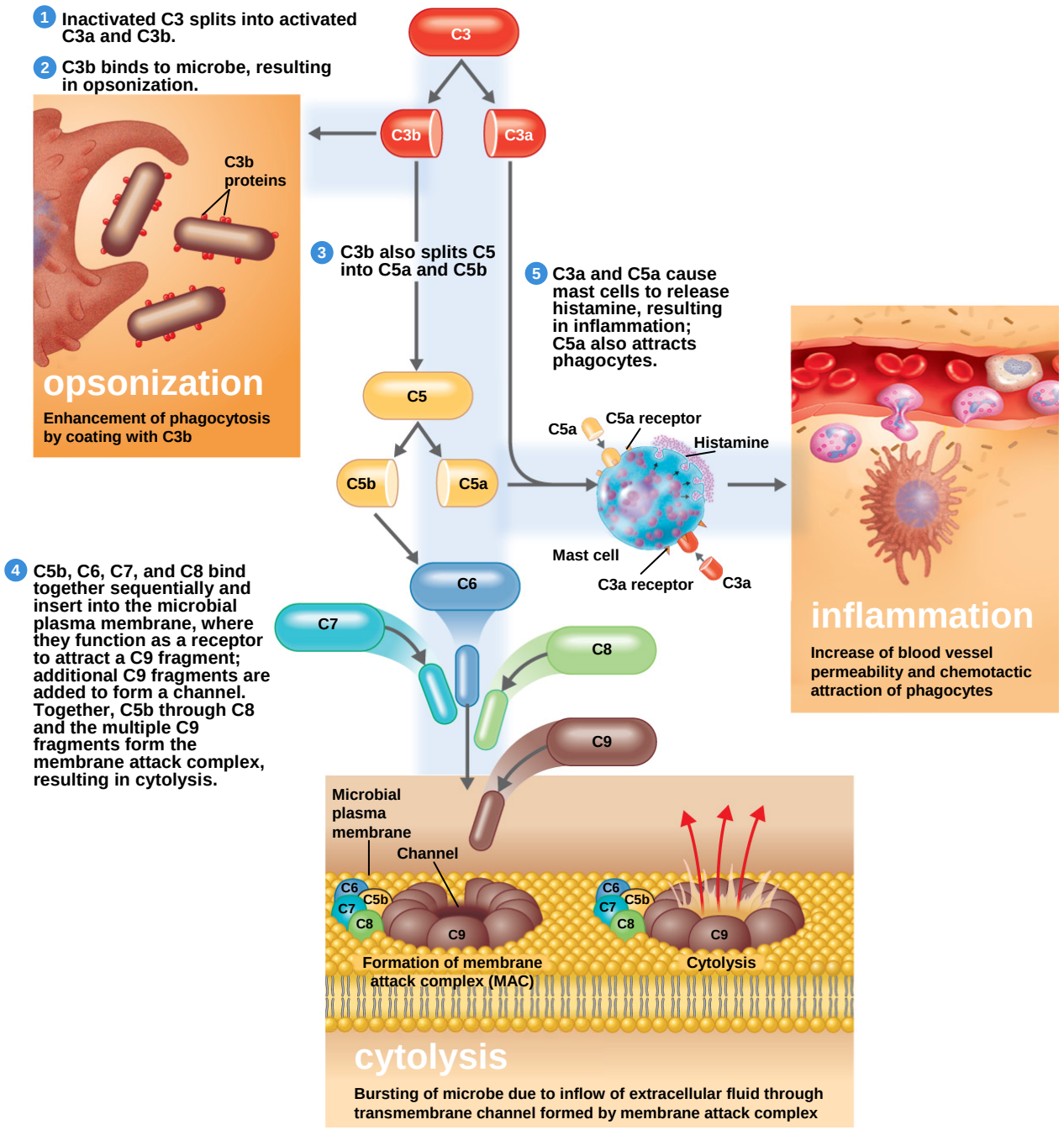
Complement's outcomes are a mixture of non-specific resistance and immunity:



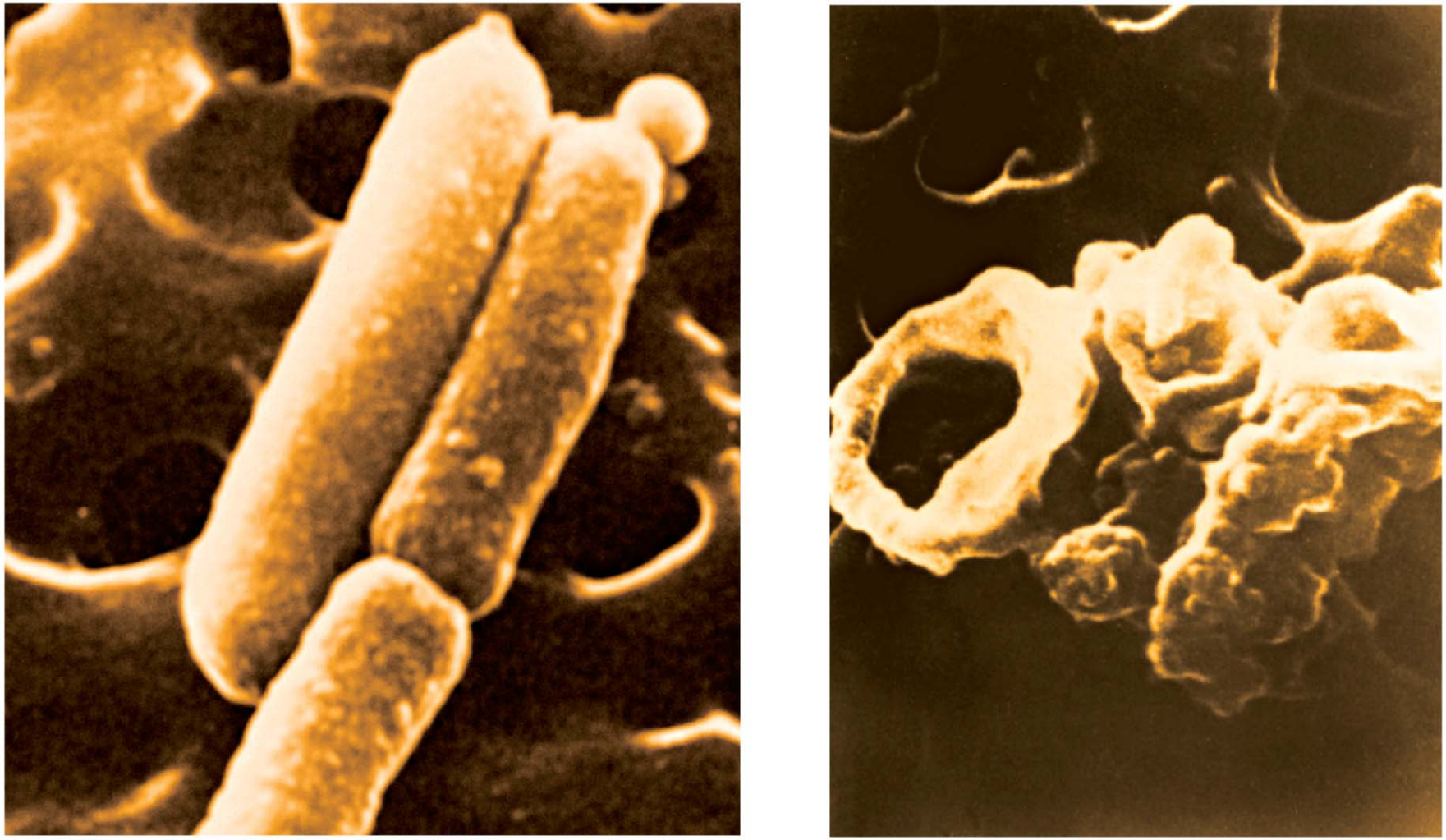
Membrane Attack Complex



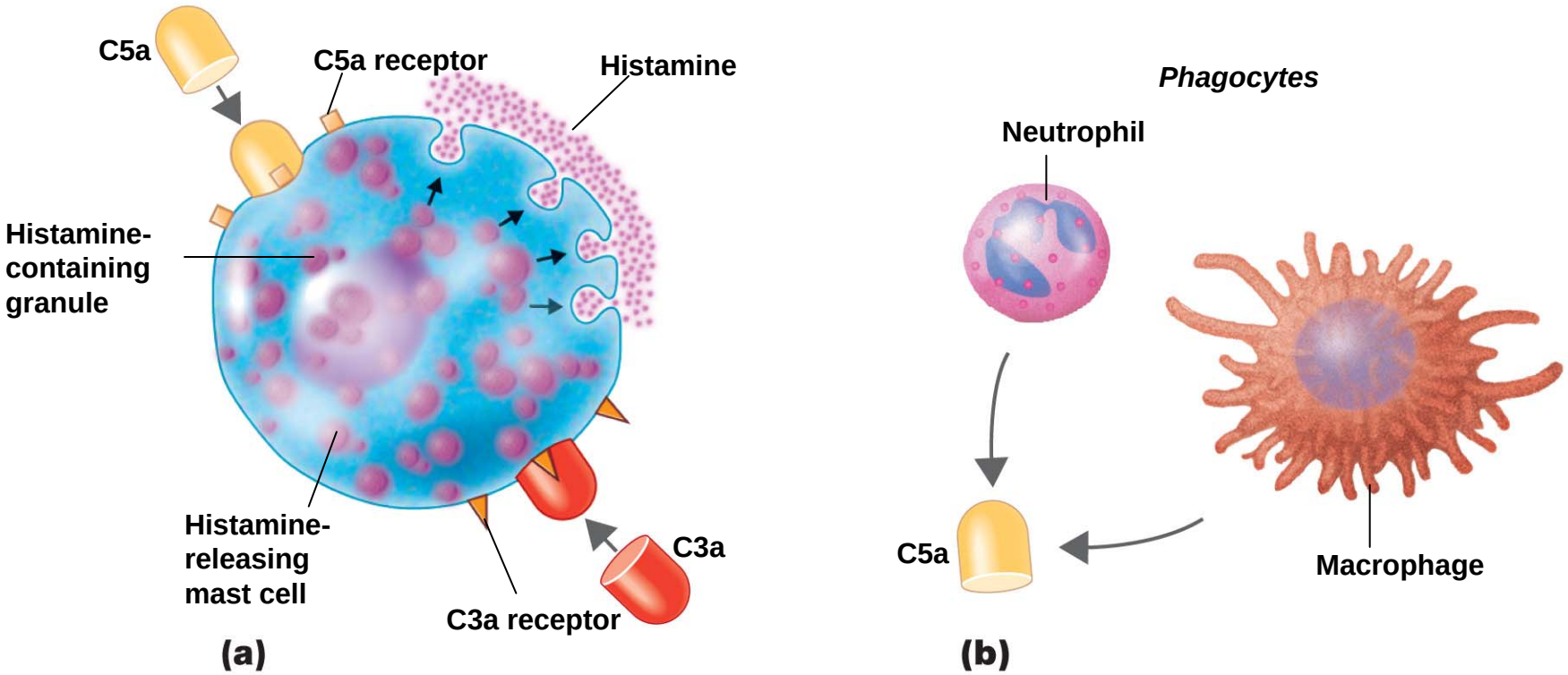
Outcomes of Complement Activation.



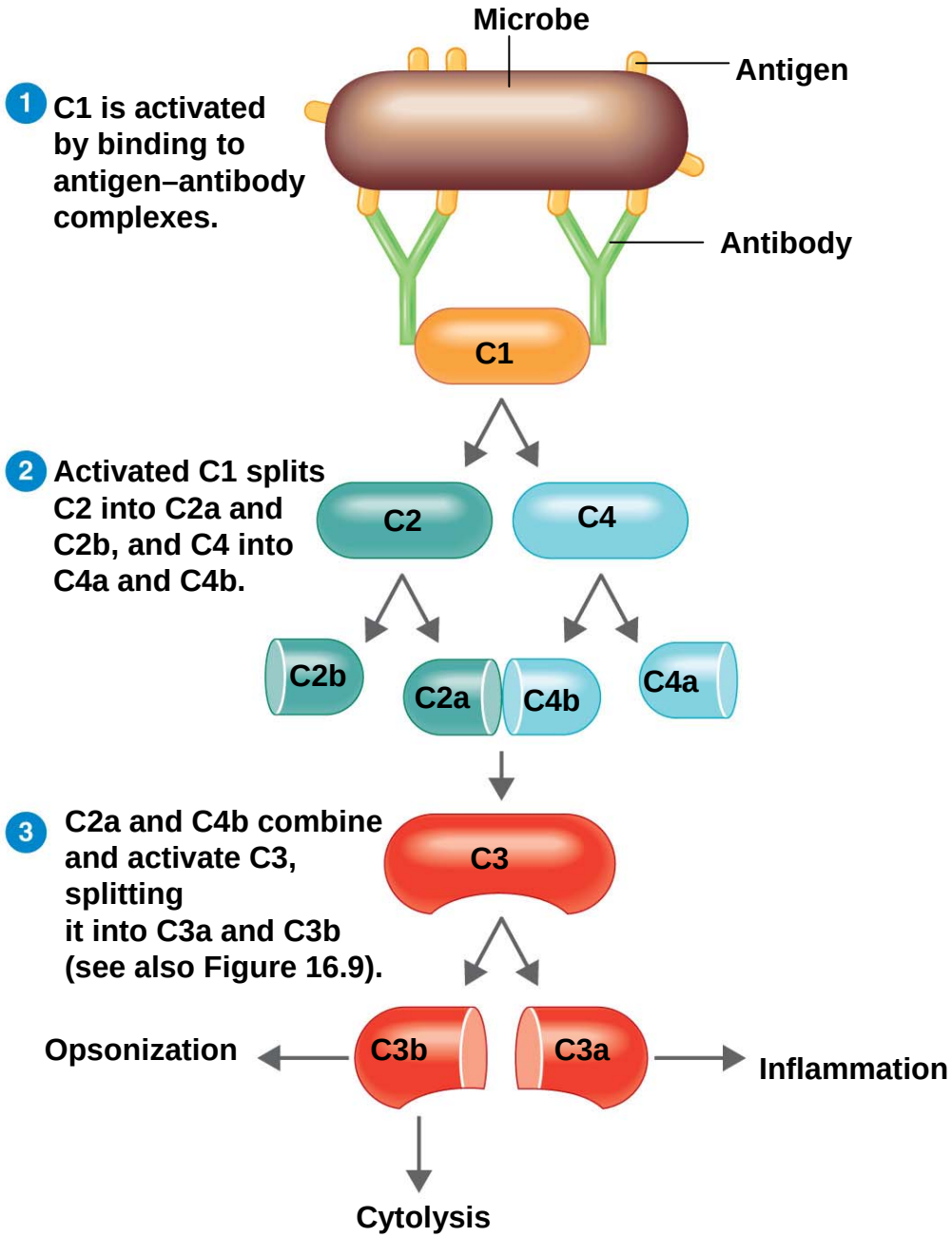
Cytolysis caused by complement.

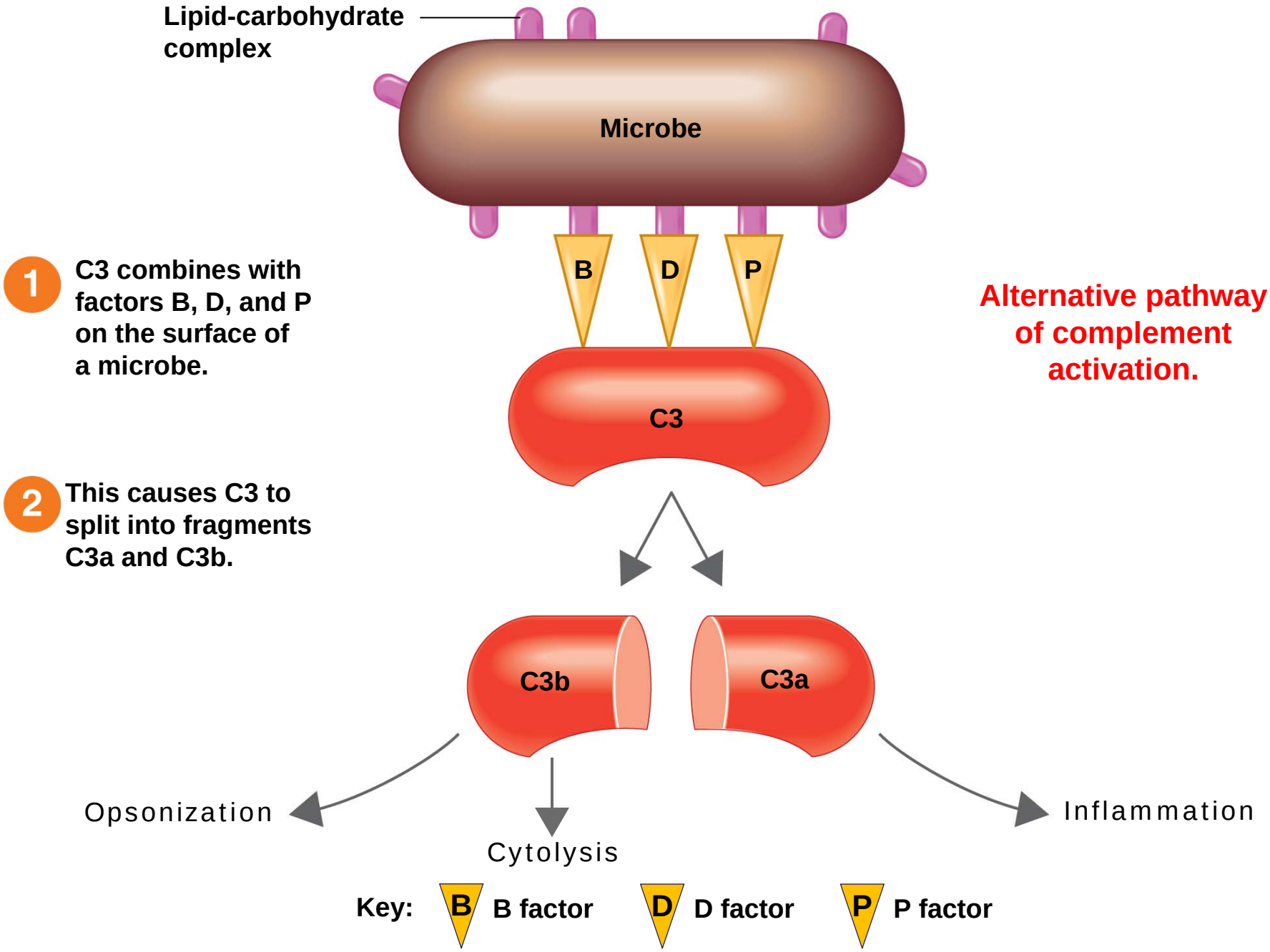


Inflammation stimulated by complement.

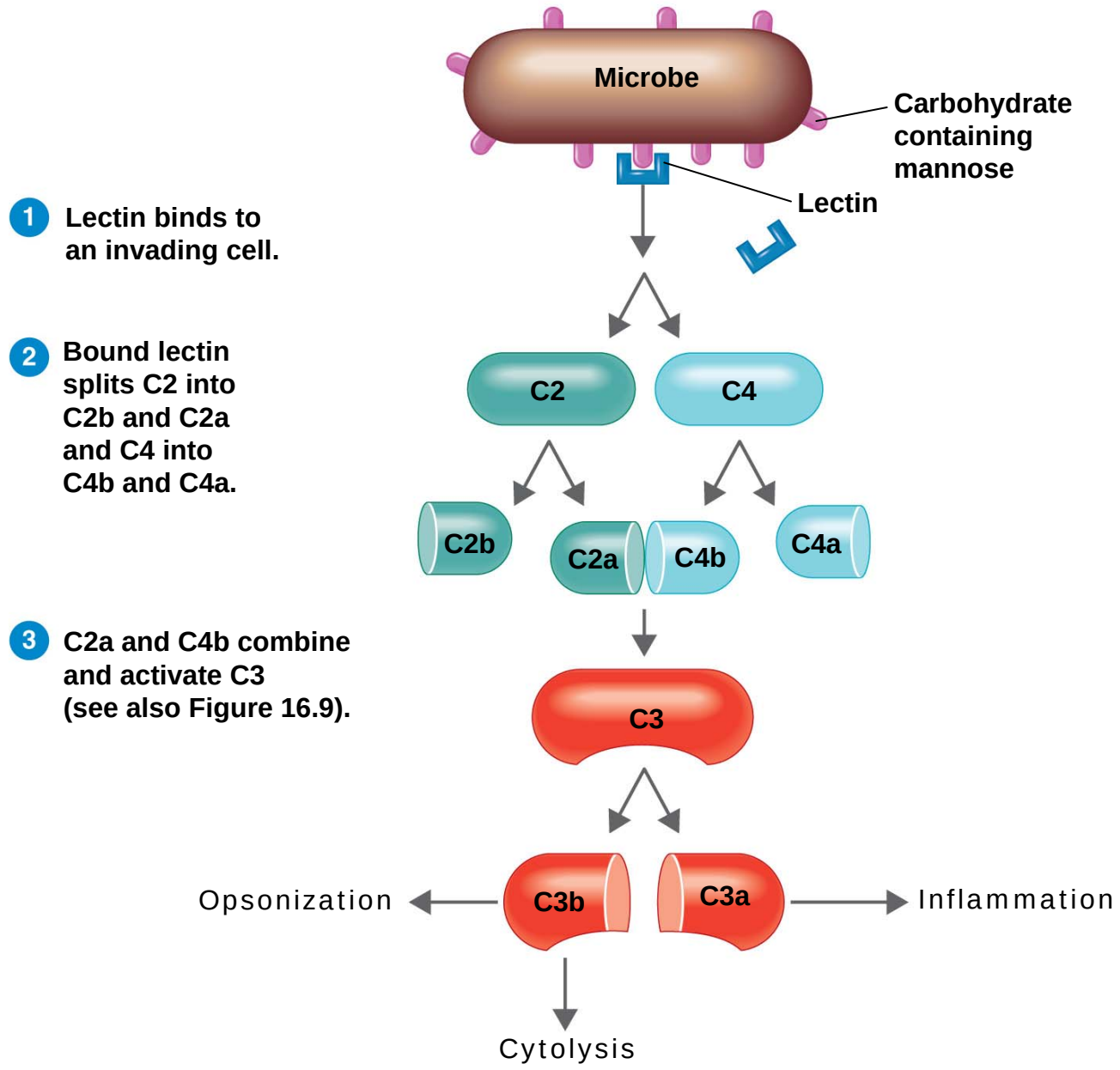


Classical pathway of complement activation.




Lipid-carbohydrate complex
Microbe
B
D
P
1
C3 combines with factors B, D, and P on the surface of a microbe.
C3
2
This causes C3 to split into fragments C3a and C3b.
Alternative pathway of complement activation.
C3b
C3a
Opsonization
Cytolysis
Inflammation
Key:
B B factor
D D factor
P P factor

The lectin pathway of complement activation.



How Some Bacteria Evade Complement

- Capsules prevent Complement activation
- Surface lipid–carbohydrate complexes prevent formation of membrane attack complex (MAC)
- Enzymatic digestion of C5a

Interferons (IFNs)

- IFN-α and IFN-β: cause cells to produce antiviral proteins that inhibit viral replication

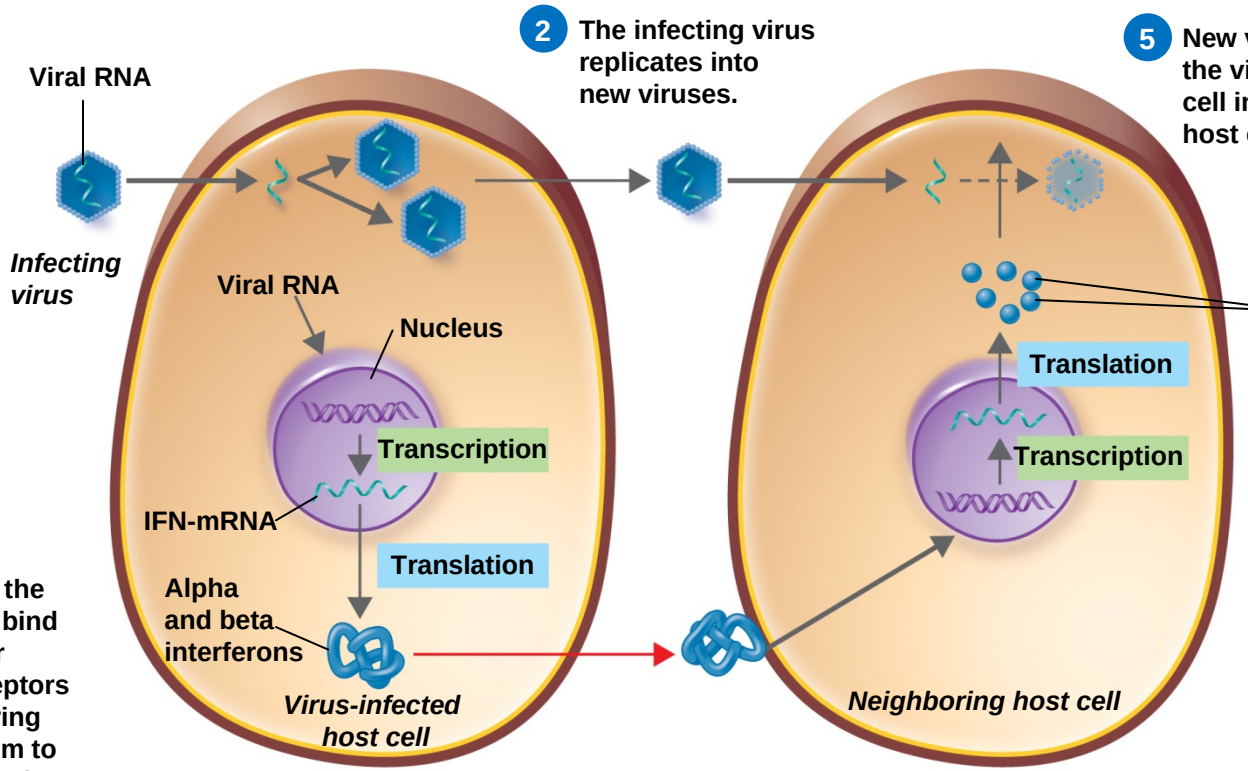
- IFN-γ: causes neutrophils and macrophages to phagocytize bacteria

Antiviral action of alpha and beta interferons (IFNs).

1 Viral RNA from an infecting virus enters the cell.

3 The infecting virus also induces the host cell to produce interferon mRNA (IFN-mRNA), which is translated into alpha and beta interferons.

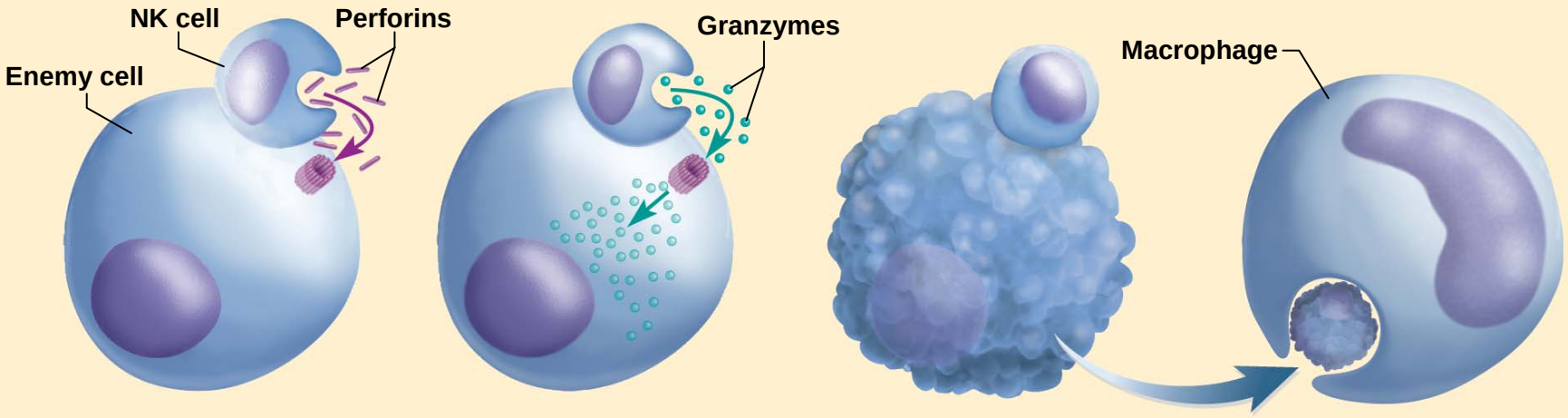
4 Interferons released by the virus-infected host cell bind to plasma membrane or nuclear membrane receptors on uninfected neighboring host cells, inducing them to synthesize antiviral proteins (AVPs). These include oligoadenylate synthetase and protein kinase.



Natural Killer Cells (NK Cells)

- Type of lymphocyte
- Circulate in blood, lymph, and body tissues
- Kill host cells infected with cancer or virus
- Non-specific reaction using granzymes and performin
- Call “immune surveillance

Action of NK cell



Note: same mechanism used by cytotoxic T cells in specific immunity!