Host Defenses Overview and Nonspecific Defenses I-C

MIcro451 Immunology

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- Inflammation
- Phagocytosis
- Interferon
- Complement

14.2 The Second Line of Defense

- Reaction to any traumatic event in the tissues
- Classic signs and symptoms
  - Rubor (redness)
  - Calor (warmth)
  - Tumor (swelling)
  - Dolor (pain)
- Fifth symptom has been added: loss of function

The Inflammatory Response: A Complex Concert of Reactions to Injury

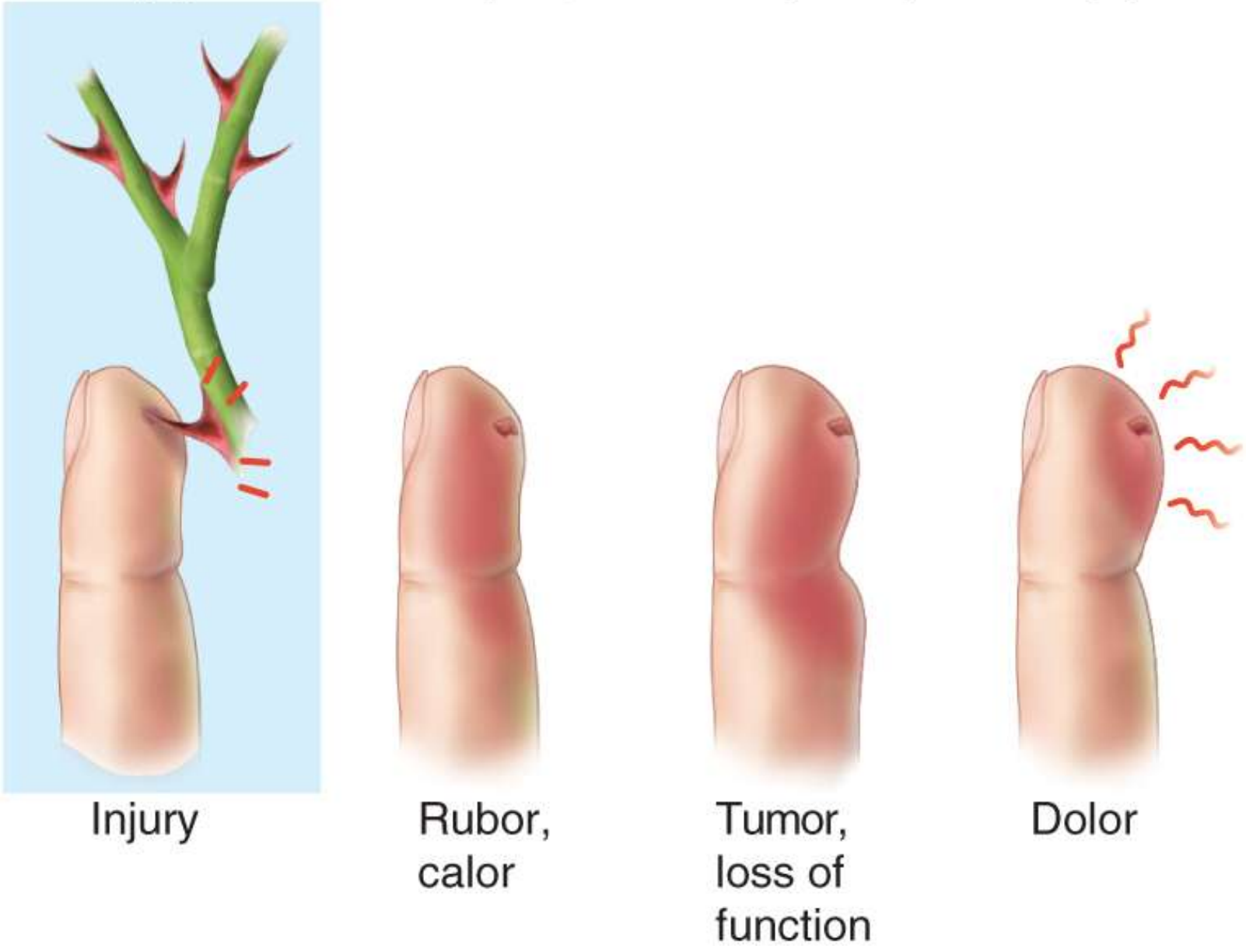
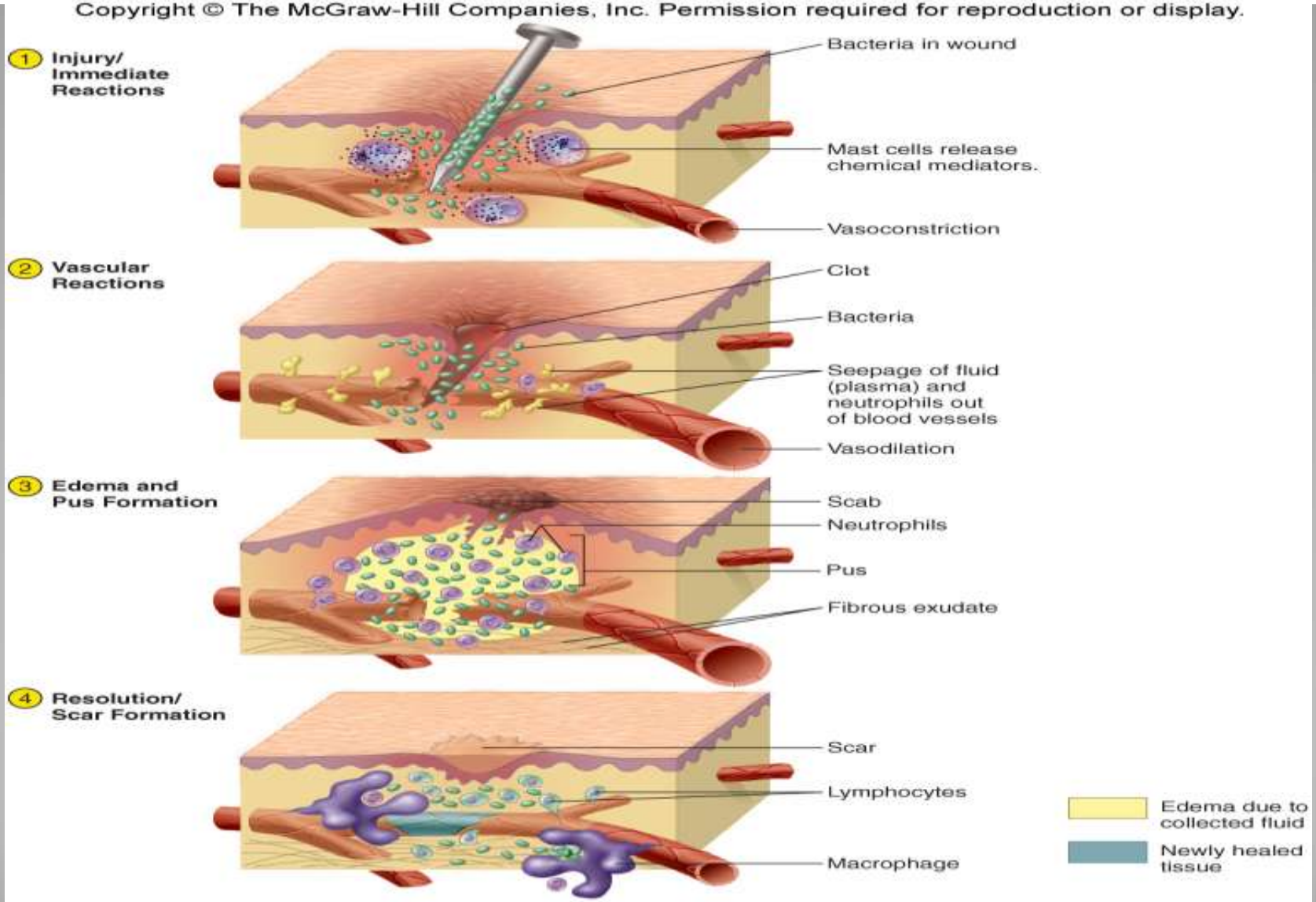


Figure 14.12

Chief Functions of Inflammation

- Chief functions of inflammation
  - Mobilize and attract immune components to the site of the injury
  - Set in motion mechanisms to repair tissue damage and localize and clear away harmful substances
  - Destroy microbes and block their further invasion



The Stages of Inflammation

Figure 14.13

- Controlled by nervous stimulation, **chemical mediators**, and **cytokines** released by blood cells, tissue cells, and platelets in the injured area
- Vasoactive mediators affect the endothelial cells and smooth muscle cells of blood vessels
- **Chemotactic factors** (**chemokines**) affect white blood cells
- Cause fever, stimulate lymphocytes, prevent virus spread, and cause allergic symptoms
- Arterioles constricted at first but quickly vasodilation takes place

Vascular Changes: Early Inflammatory Events

- Exudates: the fluid that escapes through gaps in the walls of postcapillary venules
- Accumulation of exudates causes edema
- Contains plasma proteins, blood cells, and cellular debris
- May be clear (serous) or may contain red blood cells or **pus**
- **Diapedesis**: how WBCs leave the blood vessels and into tissue spaces
- **Chemotaxis**: the tendency of WBCs to migrate in response to a specific chemical stimulus

Edema: Leakage of Vascular Fluid into Tissues

- Dilutes toxic substances
- Fibrin clot can trap microbes and prevent further spreading
- Phagocytosis occurs immediately

Benefits of Edema and Chemotaxis

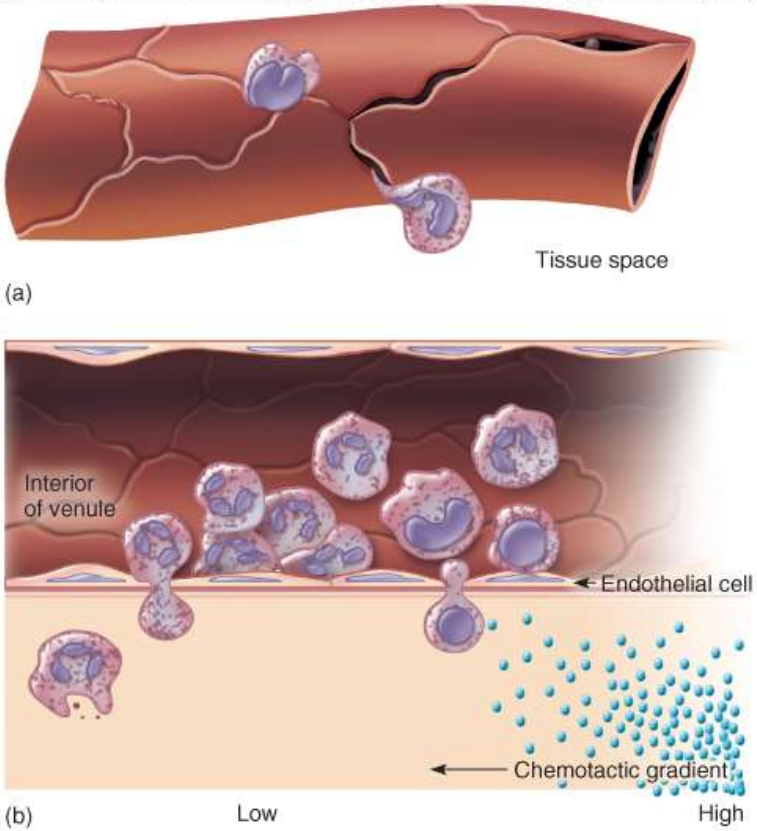


Figure 14.14

- Long-lived inflammation attracts a collection of monocytes, lymphocytes, and macrophages to the reaction site
- Macrophages clear pus, cellular debris, dead neutrophils, and damaged tissue
- B lymphocytes produce antibodies
- T lymphocytes kill intruders directly
- Late in the process the tissue is repaired or replaced by connective tissue (scar)

Late Reactions of Inflammation

Fever: An Adjunct to Inflammation

- An abnormally elevated body temperature
- FUO: fevers of unknown origin
- Initiation of fever
  - Pyrogen sets the hypothalamic "thermostat" to a higher setting
    - Muscles increase heat production
    - Peripheral arterioles decrease heat loss through vasoconstriction
  - Pyrogens can be exogenous or endogenous

Benefits of Fever

- Inhibits multiplication of temperature-sensitive microorganisms
- Impedes the nutrition of bacteria by reducing the availability of iron
- Increases metabolism and stimulates immune reactions and naturally protective physiological processes

Phagocytosis: Cornerstone of Inflammation and Specific Immunity

- General activities of phagocytes
  - Survey the tissue compartments and discover microbes, particulate matter, and injured or dead cells
  - Ingest and eliminate these materials
  - Extract immunogenic information (antigens) from foreign matter
- Three main types
  - Neutrophils
  - Monocytes
  - Macrophages

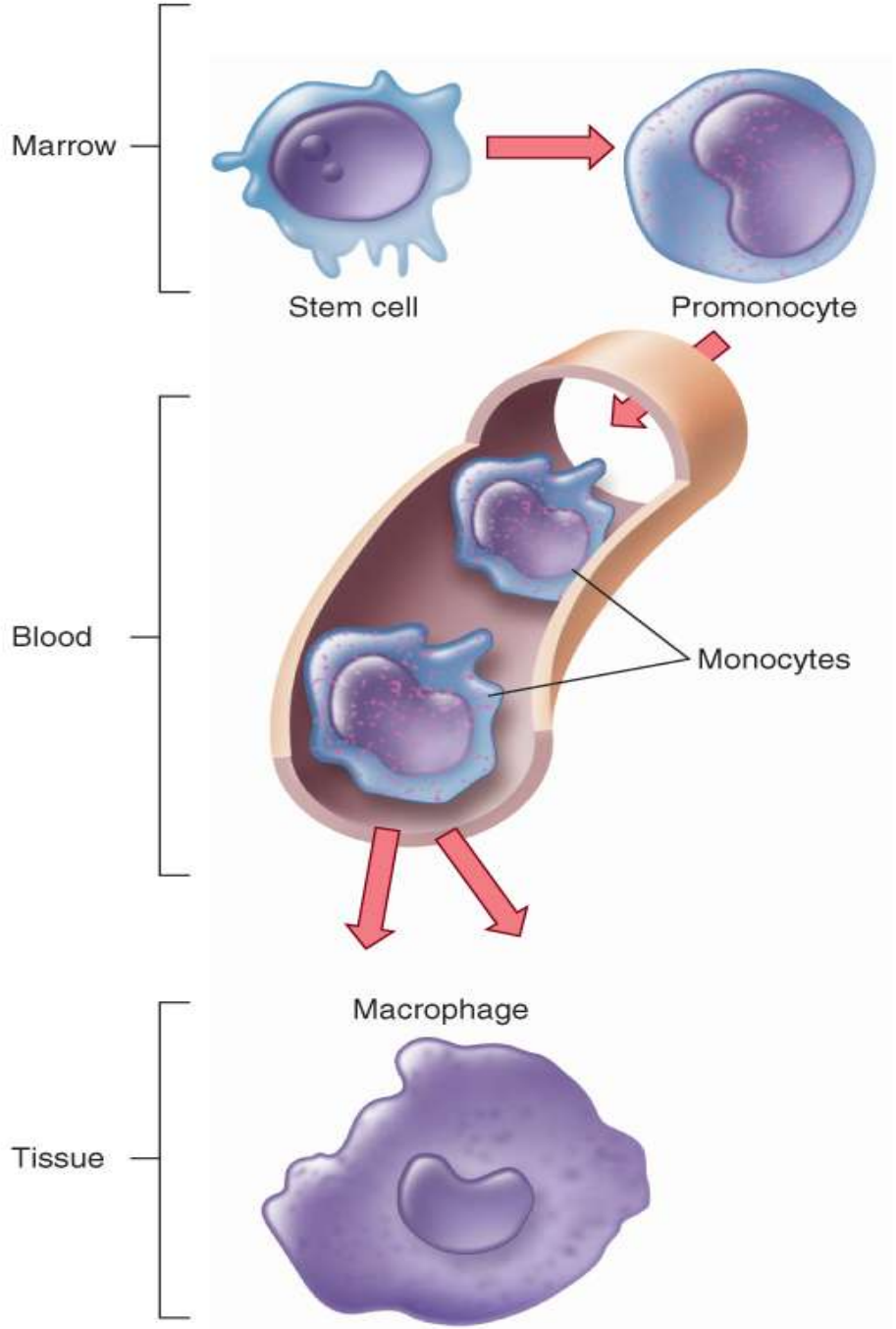


Figure 14.15

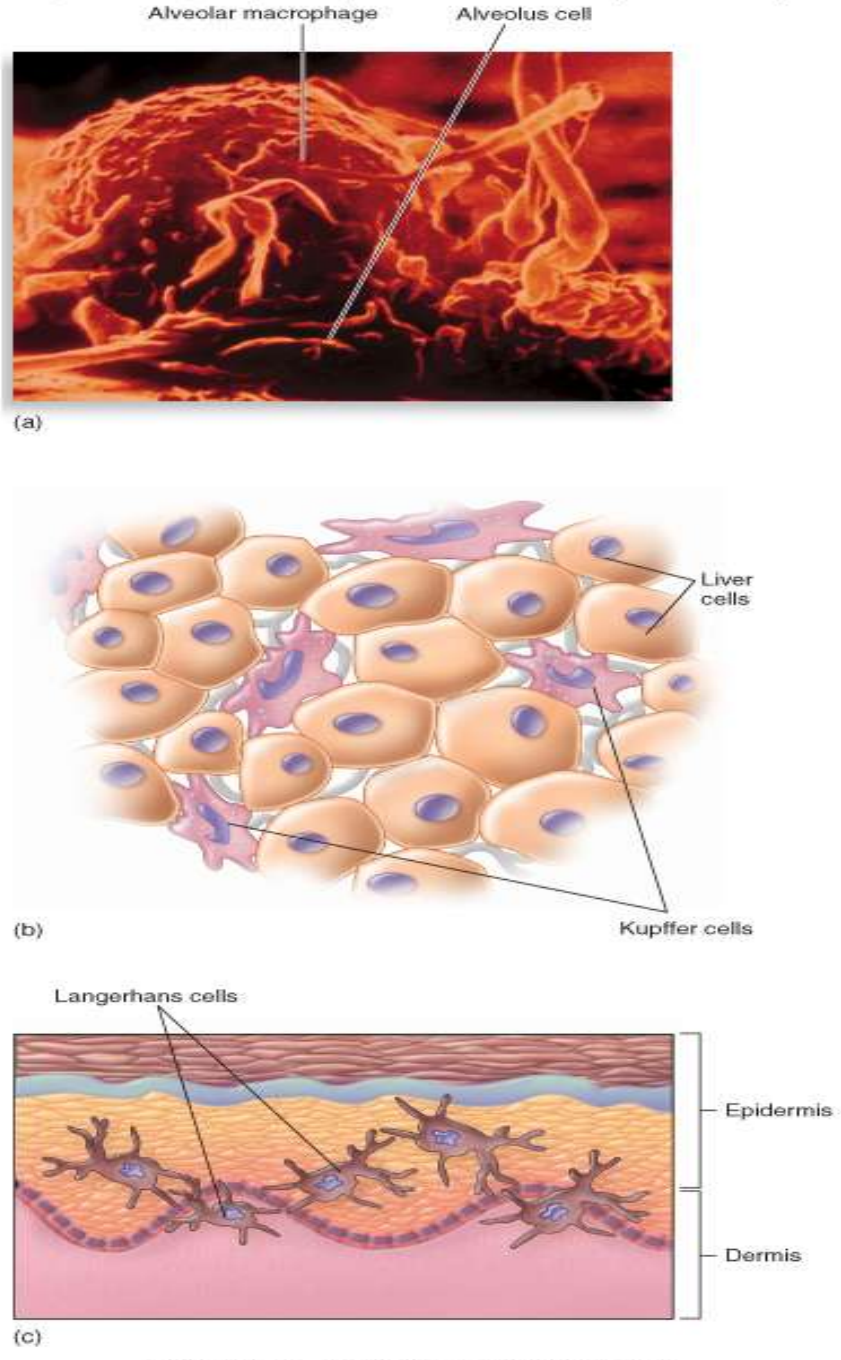
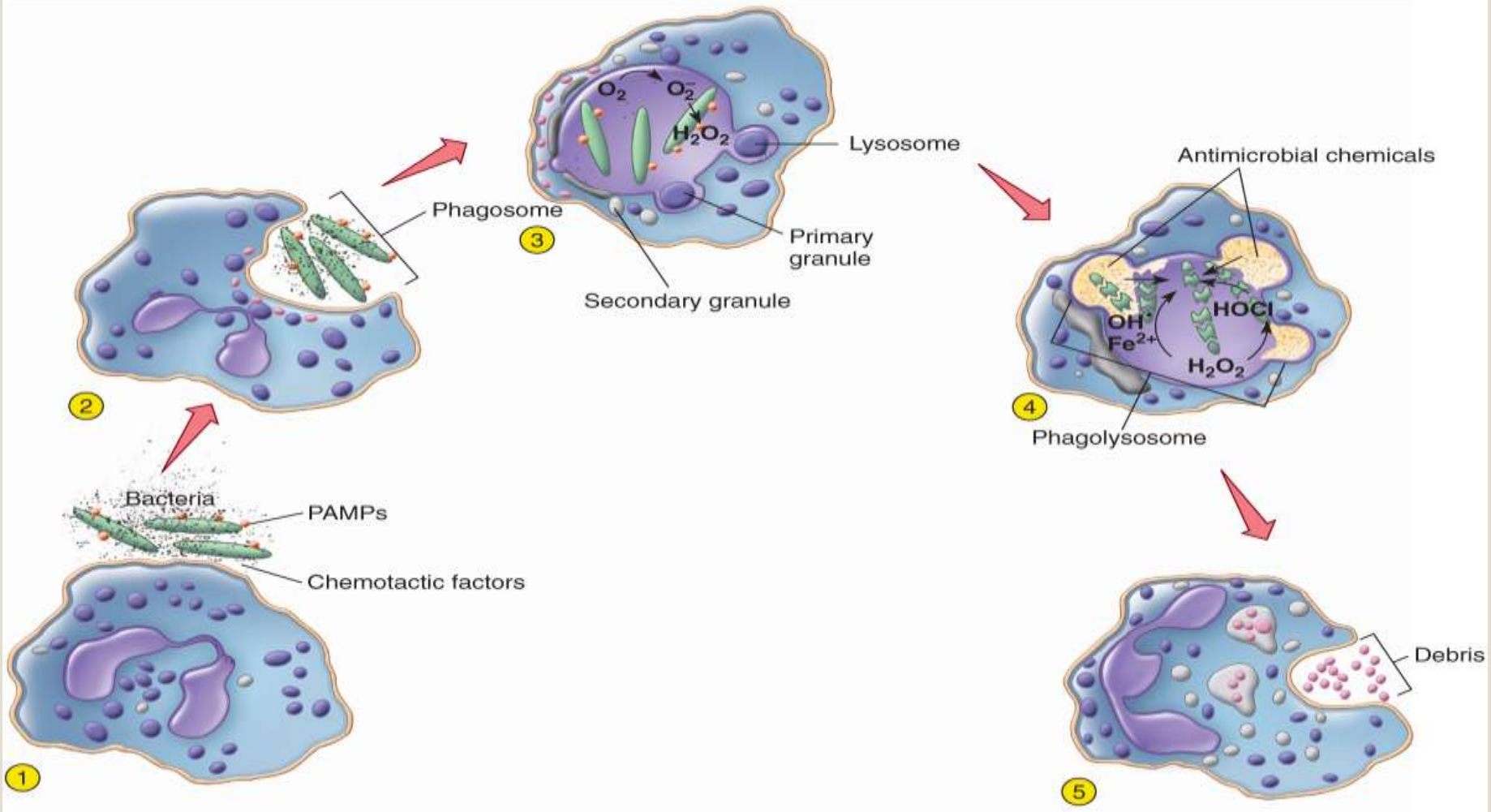


Figure 14.16



Mechanisms of Phagocyte Recognition, Engulfment, and Killing

Figure 14.17

1. To survey tissue compartments & discover microbes, particulate matter & dead or injured cells
2. To infest and eliminate these materials
3. To extract immunogenic information from foreign matter

Activities of phagocytes

Interferon: Antiviral Cytokines and Immune Stimulants

- Interferon (IFN): involved against viruses, other microbes, in immune regulation and intercommunication
- Three major types
  - Interferon alpha
  - Interferon beta
  - Interferon gamma
- All three classes produced in response to viruses, RNA, immune products, and various antigens
- Bind to cell surfaces and induce changes in genetic expression
- Can inhibit the expression of cancer genes and have tumor suppressor effects

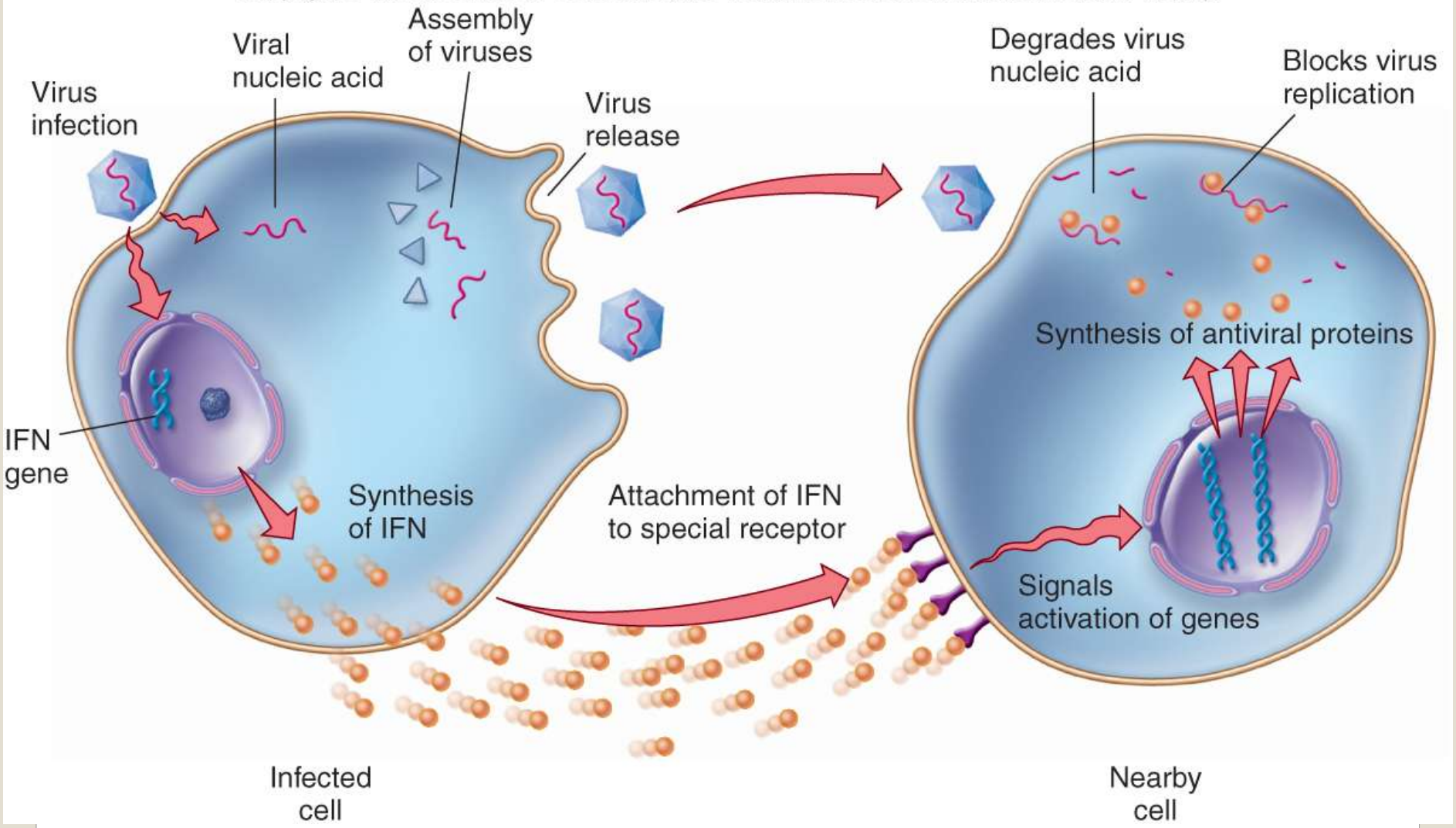


Figure 14.18

Complement

- Consists of 26 blood proteins that work in concert to destroy bacteria and viruses
- Complement proteins are activated by cleavage (cascade reaction)
- Pathways
  - Classical – activated by the presence of antibody bound to microorganism
  - Lectin pathway – nonspecific reaction of a host serum protein that binds mannan
  - Alternative – begins when complement proteins bind to normal cell wall and surface components of microorganisms

- Initiation
- Amplification and cascade
- Polymerization
- Membrane attack

Stages in the Complement Cascade

(a)

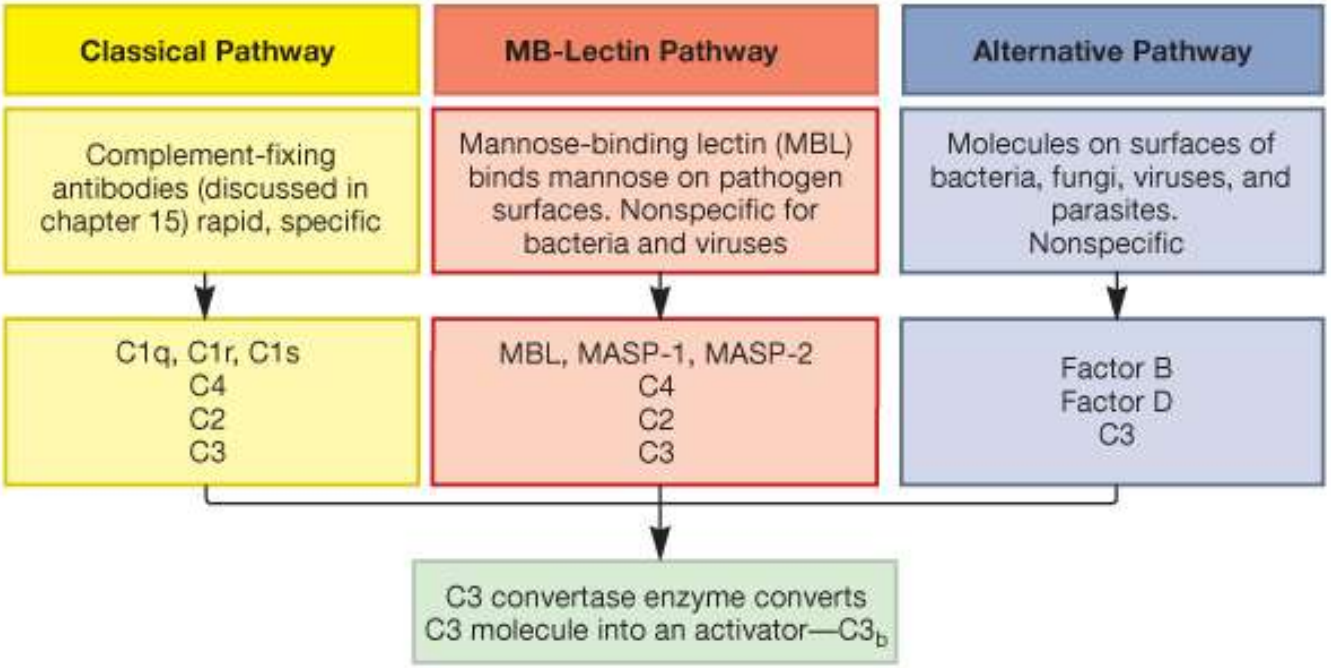
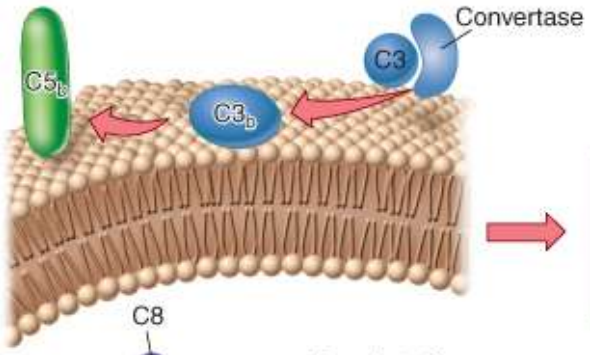


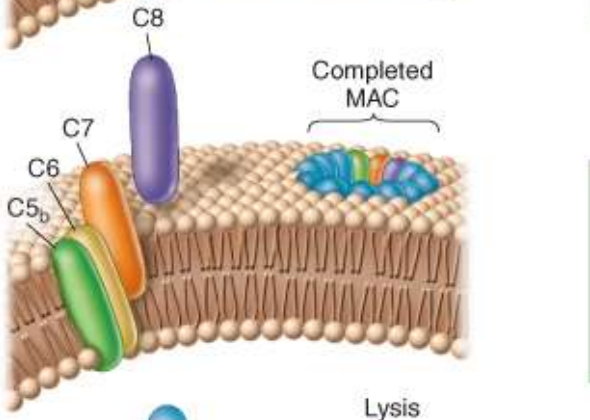
Figure 14.20(b, c, d)

(b) C5 factor is acted on by C3b, which converts it to C5b. C5b becomes bound to the membrane and serves as the starting molecule for the chain of events that assemble the complex in (c) and (d).



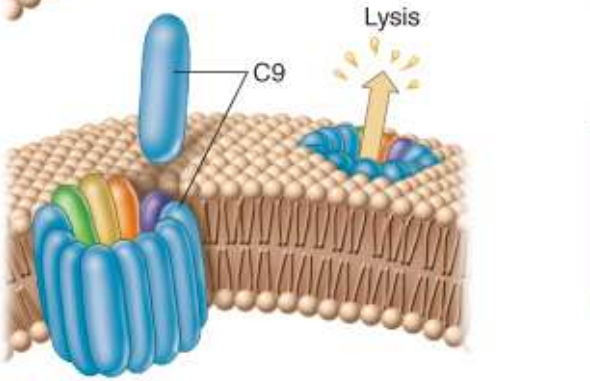
Other molecules given off: C3a, C5a which are peptide mediators of inflammation, phagocyte recruitment

(c) **Polymerization.** $C5_b$ is a reactive site for the final assembly of an attack complex. In series, C6, C7, and C8 aggregate with C5 and become integrated into the membrane. They form a substrate upon which the final component, C9, can bind. Up to 15 of these C9 units ring the central core of the final membrane attack complex (MAC).



Terminal complement components
C5b
C6
C7
C8
C9

(d) Insertion of MACs produces hundreds of tiny holes in the cell membrane. This can cause lysis and death of eukaryotic cells and many gram-negative bacteria.



$\overline{C5b6789}$ Membrane-attack complex, lysis of certain pathogens and cells

Complement: A Versatile Backup System

- At least 26 blood proteins that work in concert to destroy bacteria and certain viruses
- Cascade reaction
- Three different pathways that all yield similar end results
  - Classical pathway
  - Lectin pathway
  - Alternative pathway

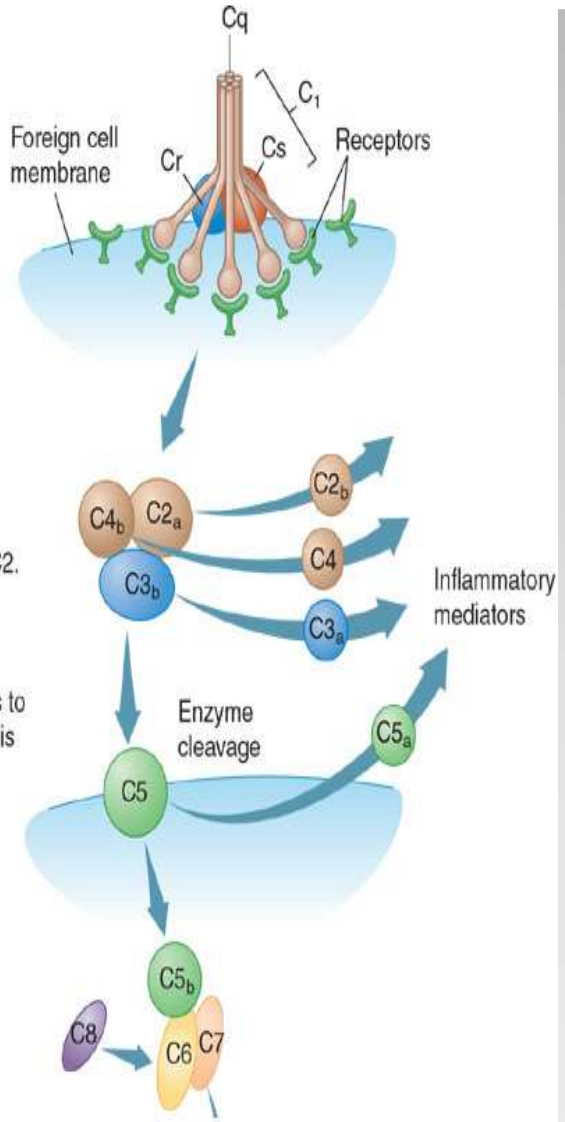
TABLE 14.1 Complement Pathways

Pathway	Activators	Host Components That Initially Bind	Complement Proteins Involved
Classical (Rapid, efficient)	Complement-fixing antibodies (IgG, IgM) (sometimes microbe surface components)	C1 complex	C1 complex C4 C2 C3
Lectin (Enters classical pathway)	Mannans	Mannose-binding lectin	C2 C4
Alternative (Slower, less efficient)	Bacterial or fungal cell wall Viruses Parasite surfaces	C3	C3 Factor B Factor D Properdin

C5, C6, C7, C8, C9, Membrane attack complex

- Initiation
- Amplification and cascade
- Polymerization
- Membrane attack

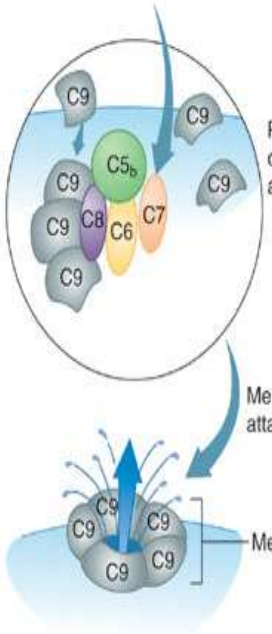
Complement Cascade



(a) **Initiation.** The classical pathway begins when C1 components bind to receptors on a foreign cell membrane.

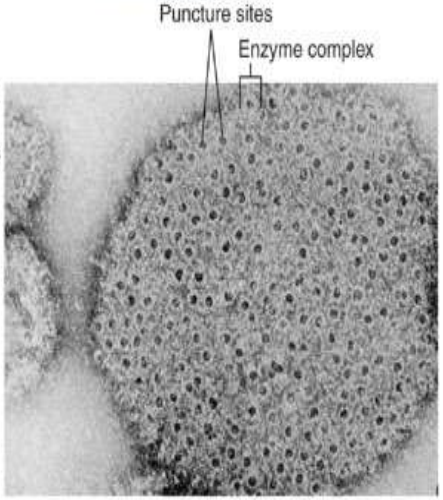
(b) **Amplification and cascade.** The C1 complex is an enzyme that activates a second series of components, C4 and C2. When these have been enzymatically cleaved into separate molecules, they become a second enzyme complex that activates C3. At this same site, C3 binds to C5 and cleaves it to form a product that is tightly bound to the membrane.

(c) **Polymerization.** $C5_b$ is a reactive site for the final assembly of an attack complex. In series, C6, C7, and C8 aggregate with C5 and become integrated into the membrane. They form a substrate upon which the final component, C9 can bind. Up to 15 of these C9 units ring the central core of the complex.



(d) **Membrane attack.** The final product of these reactions is a large, donut-shaped enzyme that punctures small pores through the membrane, leading to cell lysis.

(e) An electron micrograph (187,000×) of a cell reveals multiple puncture sites over its surface. The lighter, ringlike structures are the actual enzyme complex.



Classical PathwayComplement

- B and T lymphocytes
- Specificity and memory

Specific immunities

(a) Specificity: Viruses and other infectious agents contain antigen molecules that are specific to a single type of lymphocyte. One result of binding will be the production of virus-specific antibodies.

(b) Memory: First contact with antigen creates a unique programmed memory cell that provides quick recall upon second and other future contacts with that antigen.