THE COMPLEMENT SYSTEM

- The complement system is a defensive system consisting of over 30 proteins produced by the liver and found circulating in **blood serum** and **within tissues throughout the body**.
- **Antibodies are not directly toxic or destructive to pathogens, but facilitate host defense through**
  - Neutralizing pathogens – preventing them or toxins they produce from binding to host cells
  - Opsonization – phagocytosis
  - **Complement activation**.

- Together, proteins of the complement *system destroy microbes by :*

  1.Cytolysis

  2.Inflammation

  3.Phagocytosis

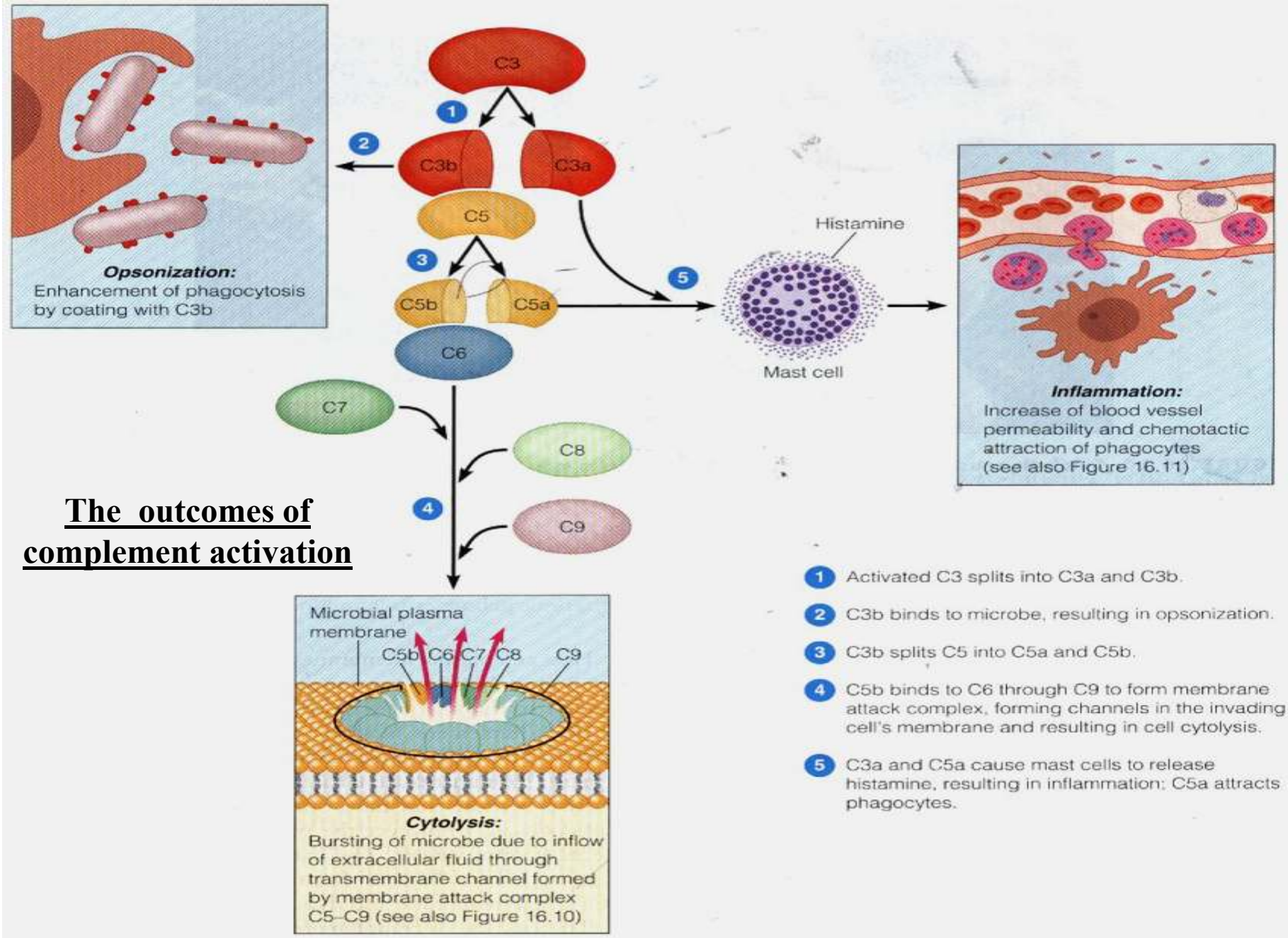
Therefore, complement system:

- Is one of two major **humoral arms of innate immunity**
- Acts in concert with adaptive humoral immunity (antibodies) and innate cellular immunity
- Is a cascade of serine protease pro-enzymes and their substrates.
- **Functions**
  - Inflammation
  - Opsonization (enhance phagocytosis)
  - Lytic activity
  - Antigen-antibody (immune) complex clearance
  - Enhance/modulate antibody production by B cells.

Naming of complement proteins:

- Complement proteins are usually designated by an **uppercase letter C** and are **inactive** until they are split into fragments (products).
- The proteins are numbered **C1 through C9**, named for the order in which they were discovered.
- The fragments are **activated proteins** and are indicated by the **lowercase letters a and b**.
- For example, inactive complement protein C3 is split into two activated fragments, C3a and C3b.

- The activated fragments carry out the destructive actions of the C1 through C9 complement proteins.
- Complement proteins act in a cascade, that is, one reaction triggers another, which in turn triggers another, and so on.
- Also, as part of the cascade, more product is formed with each succeeding reaction so that the effect is amplified many times as the reactions continue.



The outcomes of complement activation

THE OUTCOMES OF COMPLEMENT ACTIVATION

- When C3 is activated, it splits into **C3a** and **C3b**. **C3b binds to the surface of a microbe** and receptors on phagocytes attach to the C3b.
- Thus C3b enhances phagocytosis by coating a microbe, a process called **opsonization**, or immune *adherence.*
- ***Opsonization promotes attachment of a phagocyte to a microbe.***
- C3b also initiates a series of reactions that result in **cytolysis**.

- First, C3b splits C5. Fragment C5b then binds to C6 and C7, which attach to the invading cell plasma membrane.
- Next, C8 and several C9 molecules join the other complement proteins and together form a cylinder-shaped **Membrane Attacking Complex (MAC)**, which inserts into the membrane.
- The MAC creates **transmembrane channels** (holes) in the membrane that result in **cytolysis**, the bursting of the microbial cell due to the **inflow of extracellular fluid** through the channels.

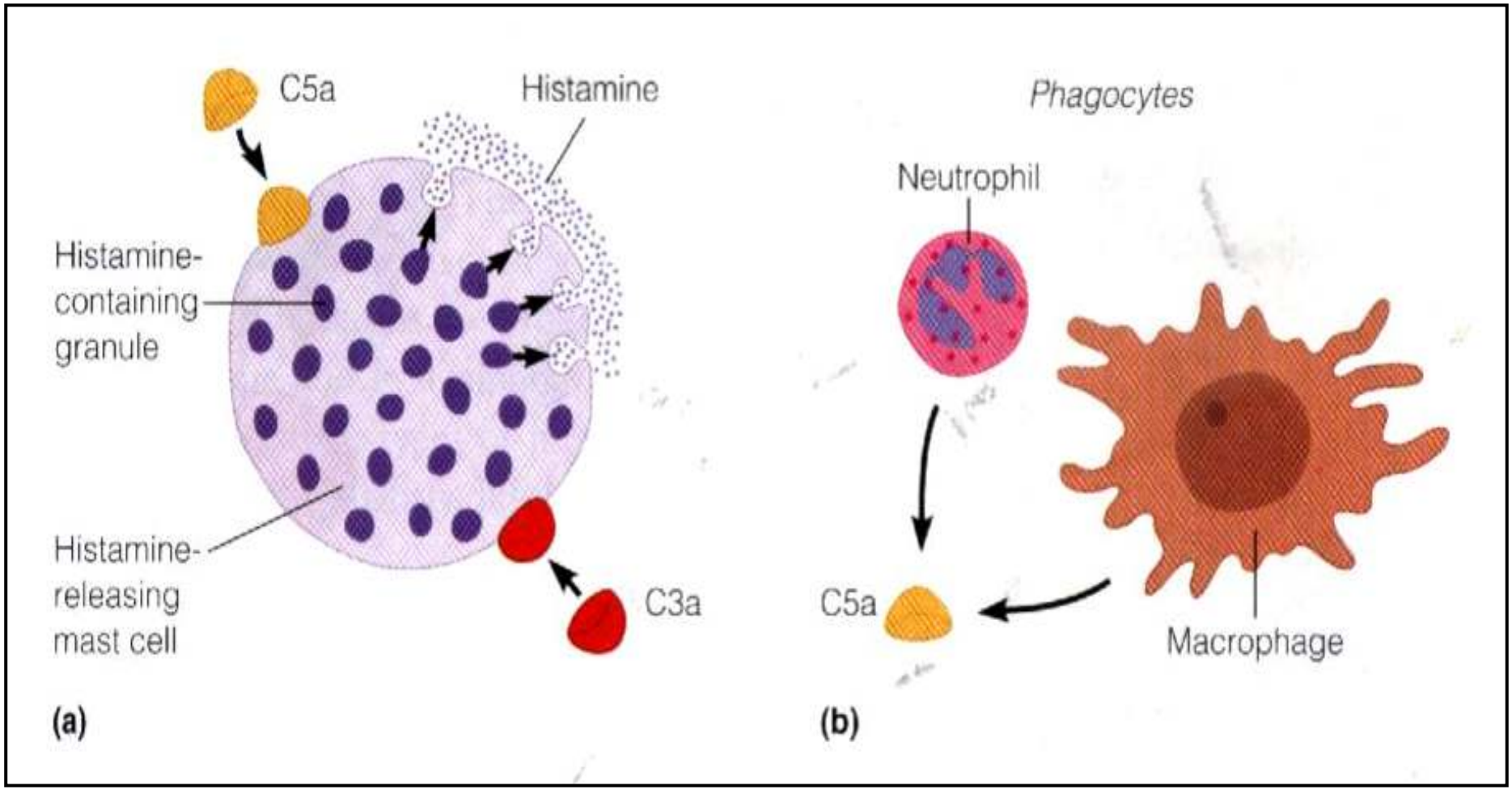
On the other hand:

- C3a and C5a bind to mast cells and cause them to release histamine and other chemicals that increase blood vessel permeability during inflammation.

- C5a also functions as a very powerful chemotactic factor that attracts phagocytes to the site of an infection.

9

INFLAMMATION STIMULATED BY COMPLEMENT SYSTEM



10

PATHWAYS FOR COMPLEMENT ACTIVATION.

1. The Classical pathway
2. The Alternative pathway
3. The Lectin pathway

A) THE CLASSICAL PATHWAY.

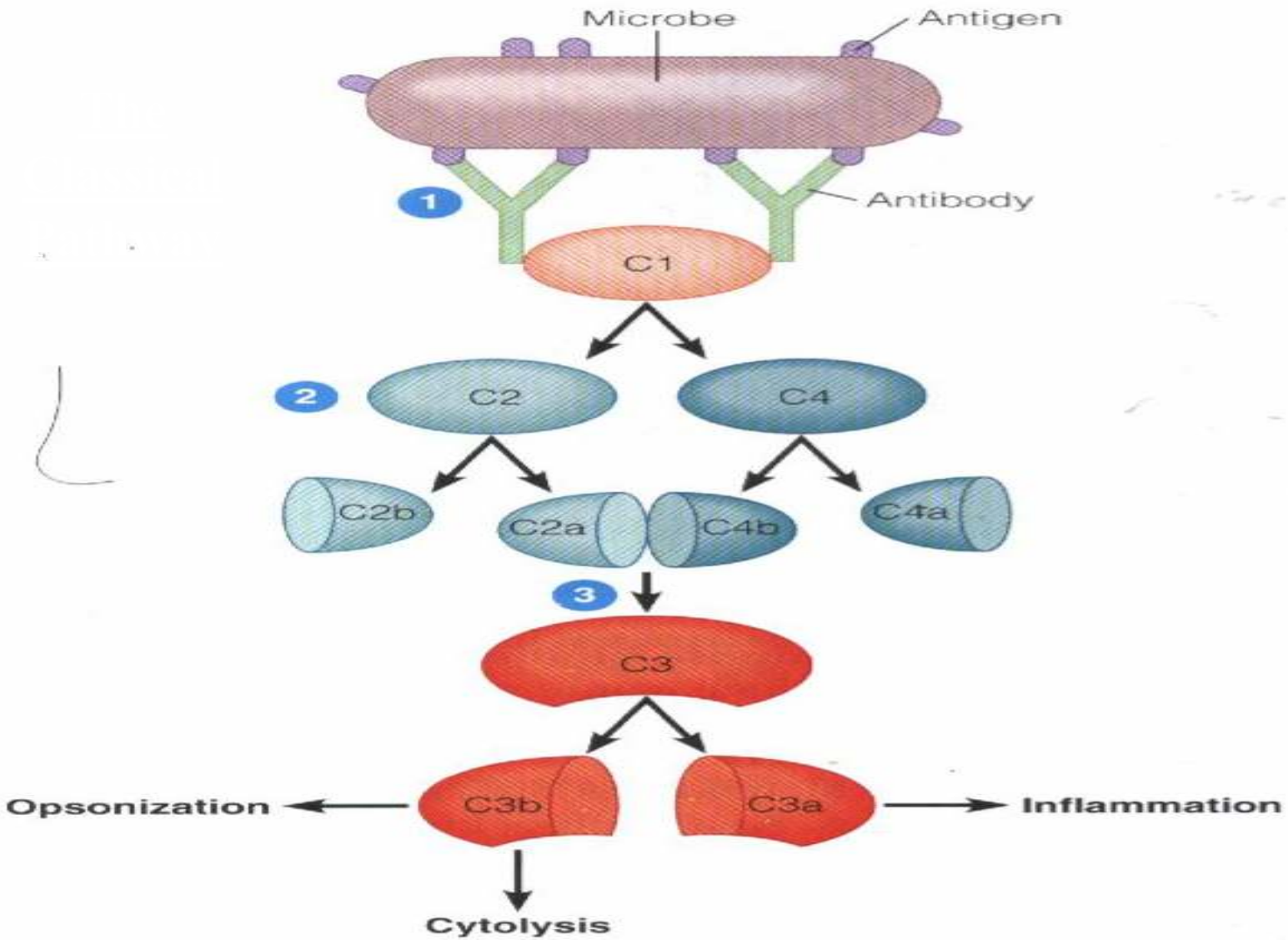
- The classical pathway, so named because it was the first to be discovered, is initiated when antibodies bind to antigens (microbes) and occurs as follows:
  - Antibodies attach to antigens, forming **antigen-antibody complexes**.
    - *Example of antigens:* ***proteins or large polysaccharides on the surface of a bacterium or other cell.***
  - The antigen-antibody complexes bind and activate C1.

- Next, activated C1 activates C2 and C4 by splitting them.

- C2 is split into fragments called C2a and C2b. and C4 is split into fragment, called C4a and C4b.

- **C2a and C4b** combine and together they activate C3 by splitting it into C3a and C3b.

- The C3 fragments then initiate **cytolysis, inflammation, and opsonization**.

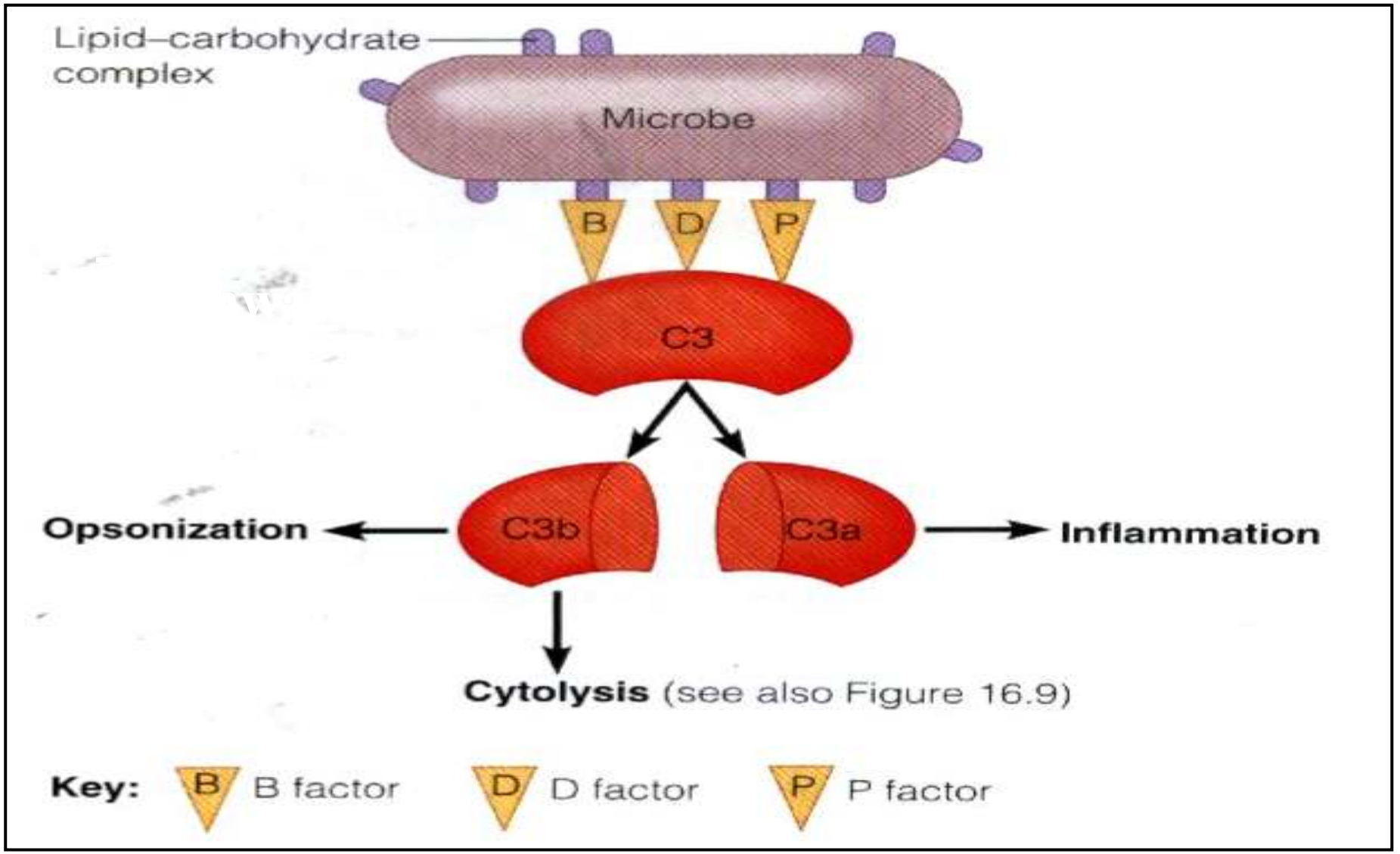


1. C1 is activated by binding to antigen–antibody complexes.
2. Activated C1 splits C2 into C2a and C2b and C4 into C4a and C4b.
3. C2a and C4b combine and activate C3, splitting it into C3a and C3b

B) THE ALTERNATIVE PATHWAY.

- The alternative pathway is so named because it was discovered after the classical pathway.
- Unlike the classical pathway, the alternative pathway does not involve antibodies.
- The alternative pathway is activated by contact between certain complement proteins and a pathogen.

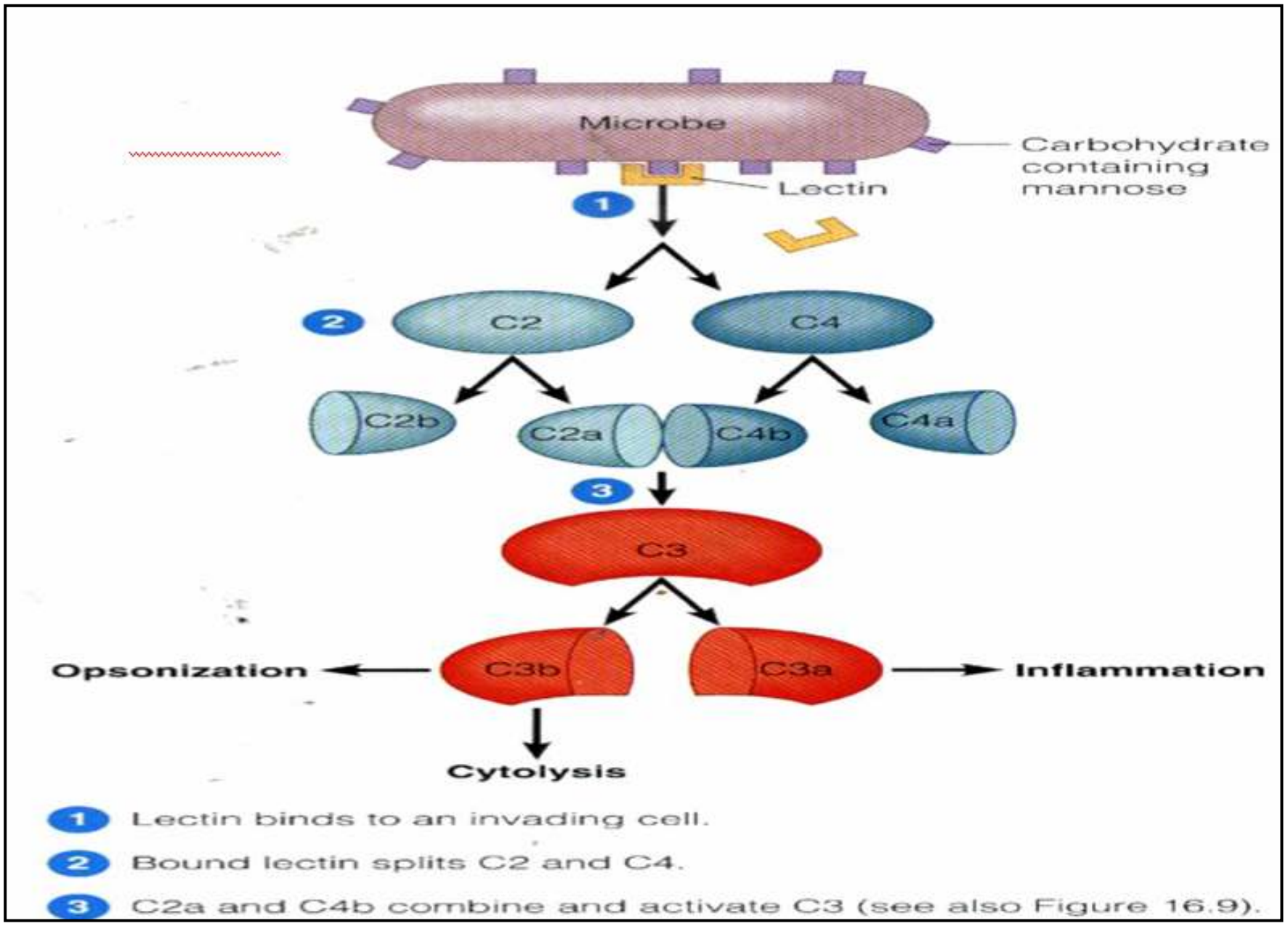
- C3 is constantly present in the blood.
- It combines with complement proteins called factor B, factor D, and factor P (properdin) on the surface of a pathogen.
- The complement proteins are attracted to microbial cell surface material (mostly lipid-carbohydrate complexes of certain bacteria and fungi).
- Once the complement proteins combine and interact, C3 is split into fragments C3a and C3b.
- As in the classical pathway, C3a participates in inflammation, and C3b functions in cytolysis and opsonization.


Lipid–carbohydrate complex
Microbe
B
D
P
C3
C3b
C3a
Opsonization
Inflammation
Cytolysis (see also Figure 16.9)
Key:
B B factor
D D factor
P P factor

C) THE LECTIN PATHWAY.

- The lectin pathway is the most recently discovered mechanism for complement activation.
- When macrophages ingest bacteria, viruses, and other foreign matter by phagocytosis, they release chemicals that stimulate the liver to produce lectins, proteins that bind to carbohydrates.
- One such lectin, mannose-binding lectin (MBL), binds to the carbohydrate mannose.

- MBL binds to many pathogens because the MBL molecules recognize a distinctive pattern of carbohydrates that includes mannose, which is found in bacterial cell walls and on some viruses.
- As a result of binding, MBL functions as an opsonin to enhance phagocytosis and activates C2 and C4.
- C2a and C4b activate C3.


Microbe
Carbohydrate containing mannose
Lectin
1
2
C2
C4
C2b
C2a
C4b
C4a
3
C3
Opsonization
C3b
C3a
Inflammation
Cytolysis
1 Lectin binds to an invading cell.
2 Bound lectin splits C2 and C4.
3 C2a and C4b combine and activate C3 (see also Figure 16.9).

Three Points of Entry into the Complement Cascade

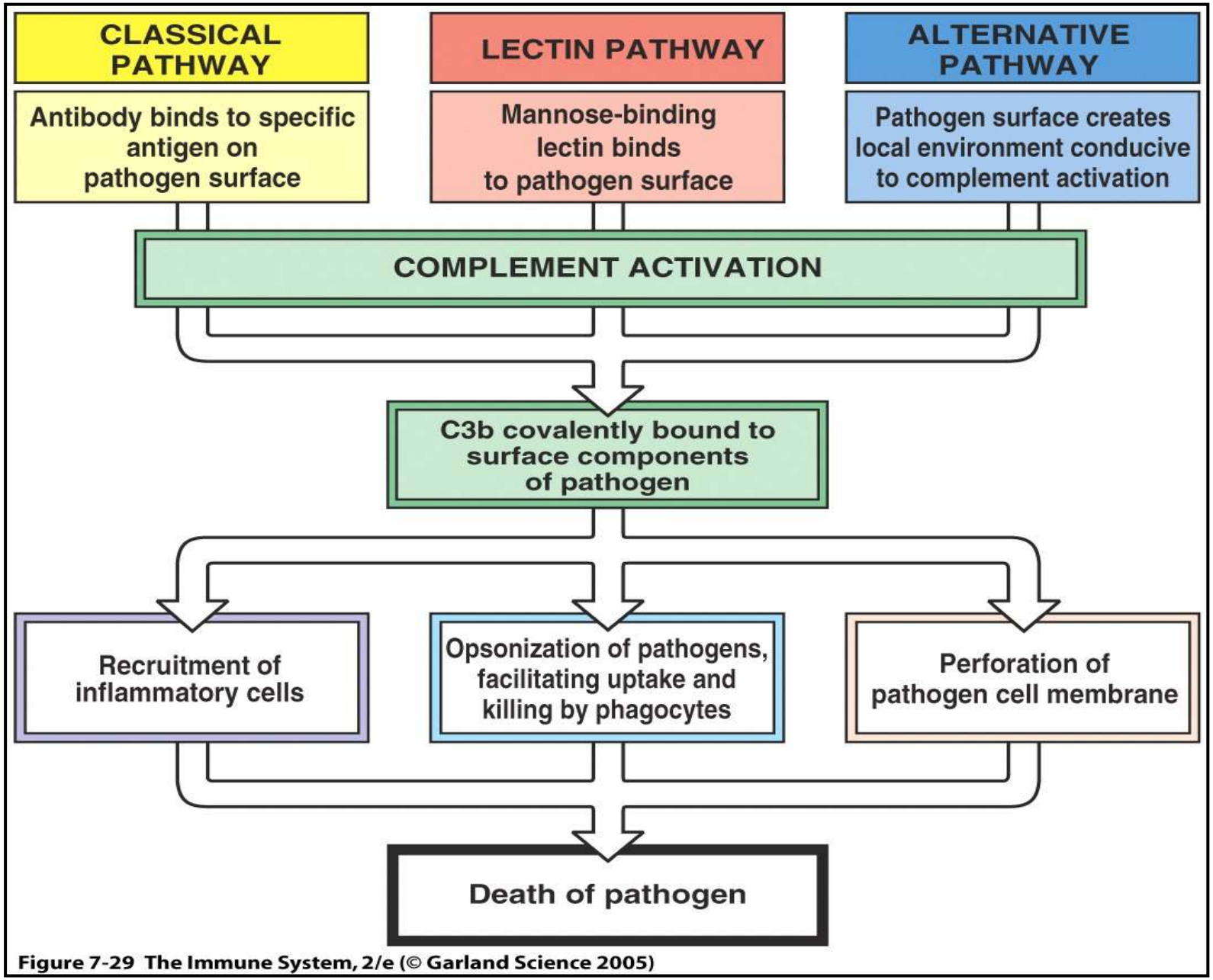
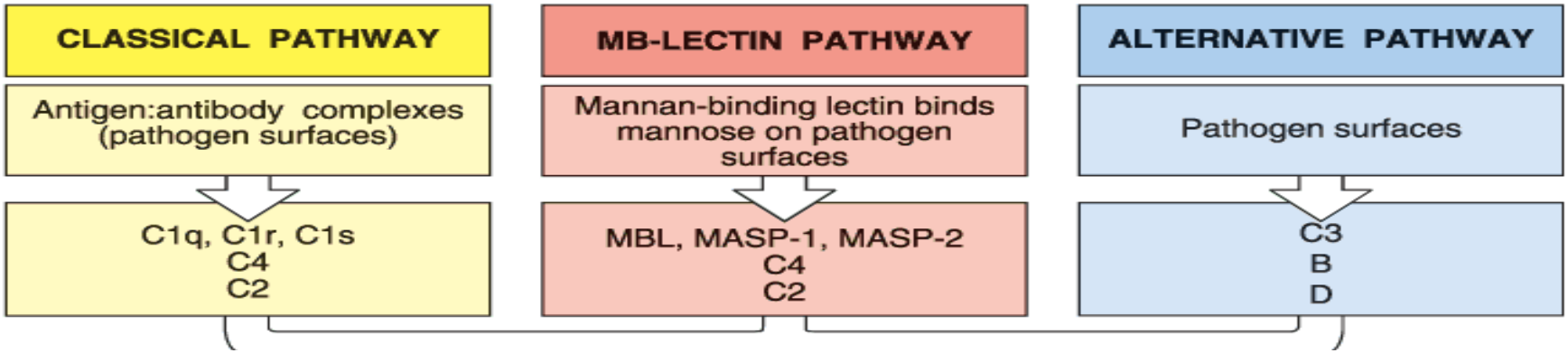
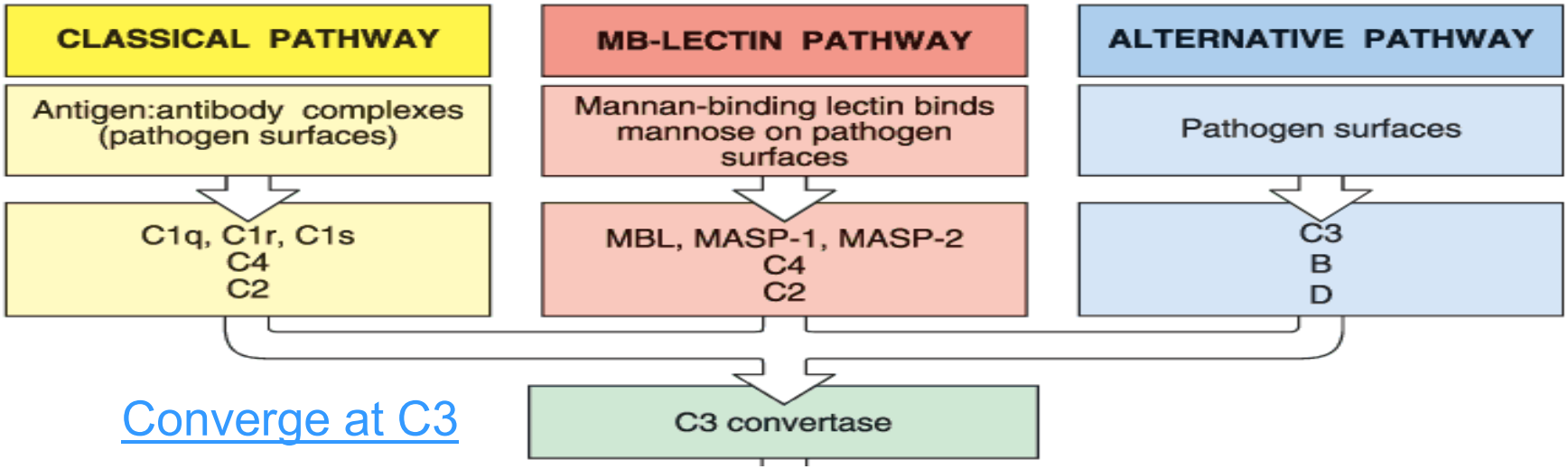


Figure 7-29 The Immune System, 2/e (© Garland Science 2005)

Overview of Complement Cascade

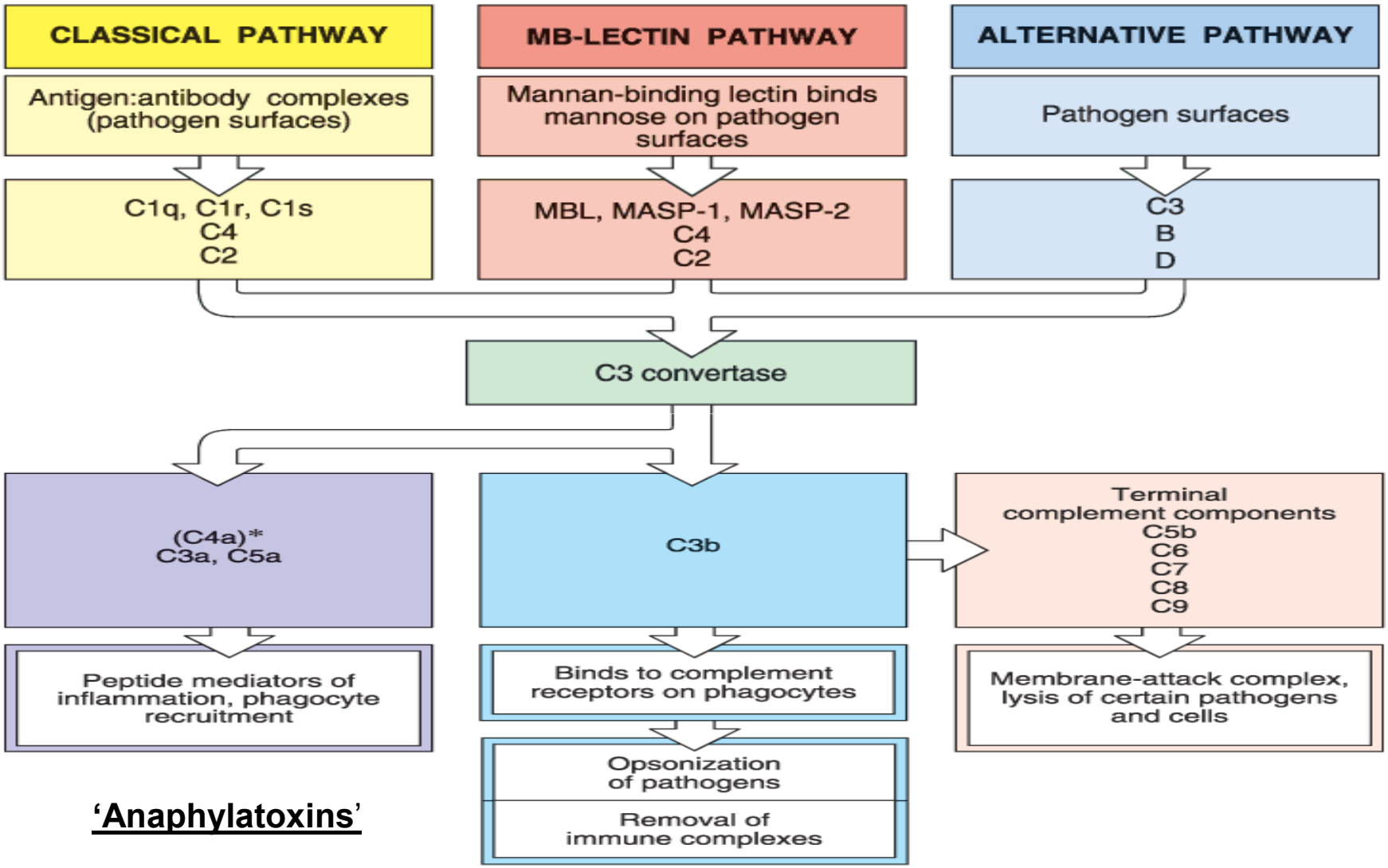


Overview of Complement Cascade



Converge at C3

Overview of Complement Cascade



'Anaphylatoxins'

Common Effector Molecules/Functions

Arcane Nomenclature

- **Classical pathway** components and components shared by all pathways – C followed by number; fragments denoted by lower case letter
  - Examples
  - C4 – C4 protein
  - C4a – smaller soluble fragment
  - C4b – larger fragment binds to surface (of microbe)
  - **There is one exception – for C2, C2b = smaller soluble fragment, C2a = larger fragment that binds to surface of microbe**
- Alternative Pathway Proteins – Upper case letter, fragments denoted by lower case letter
  - Example
  - B $\rightarrow$ Bb

Two Types of C3 Convertase

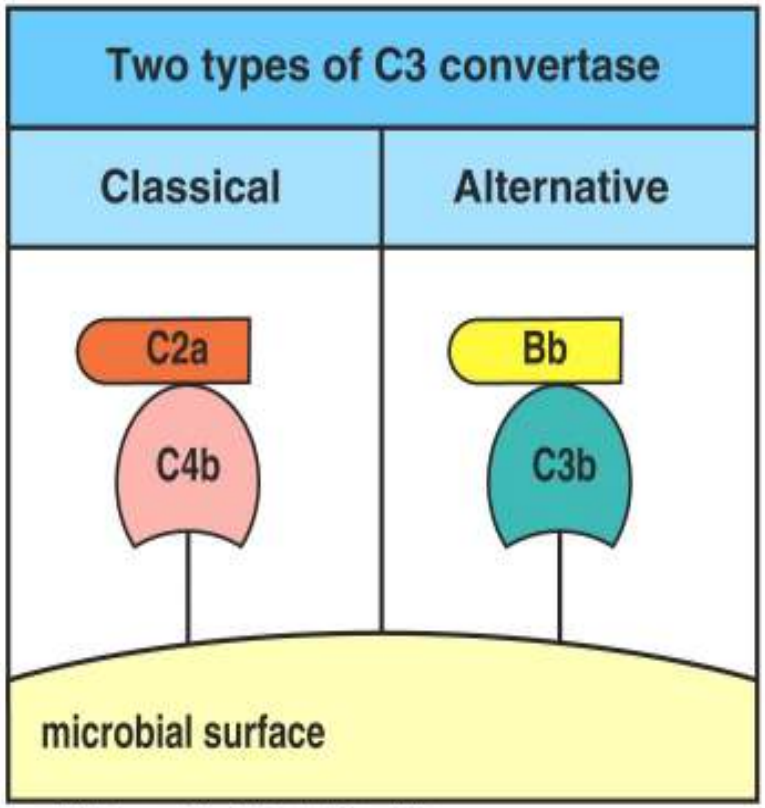


Figure 7-37 The Immune System, 2/e (© Garland Science 2005)

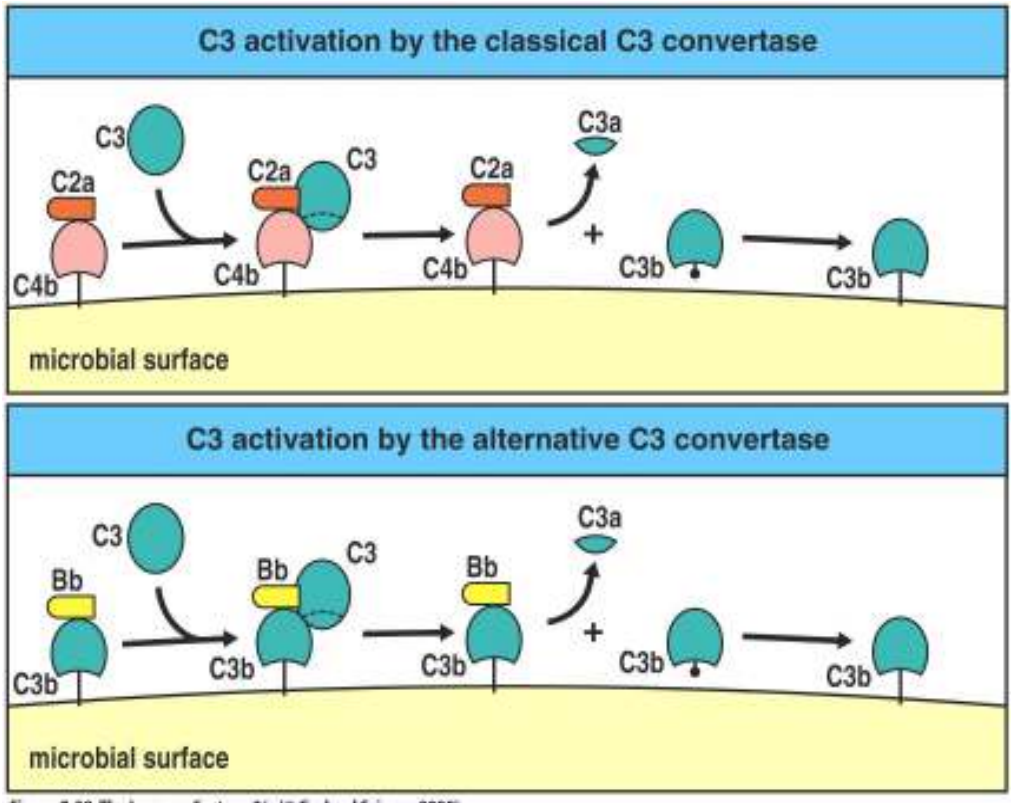
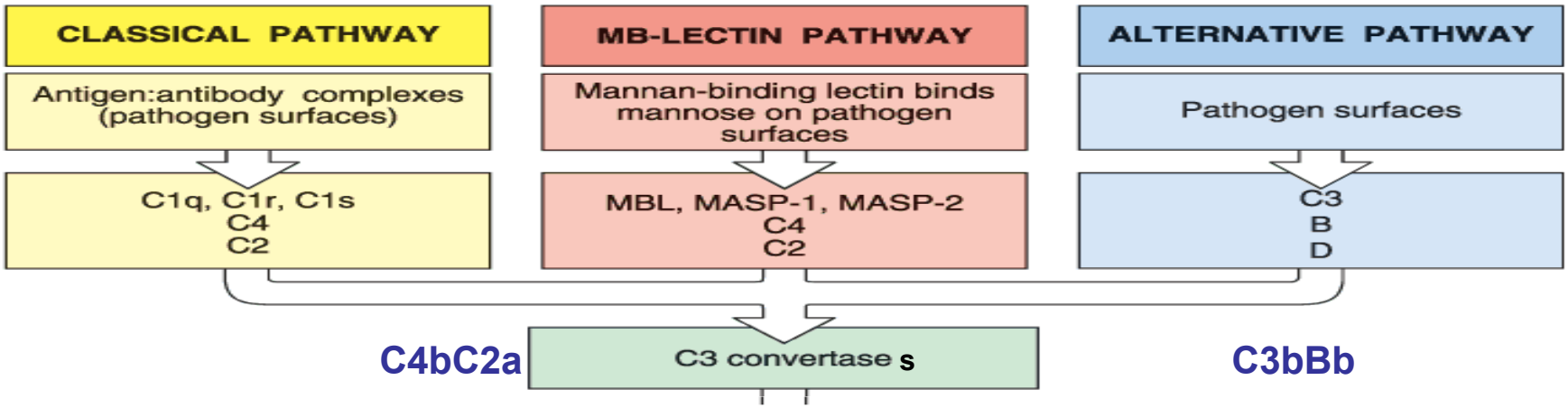


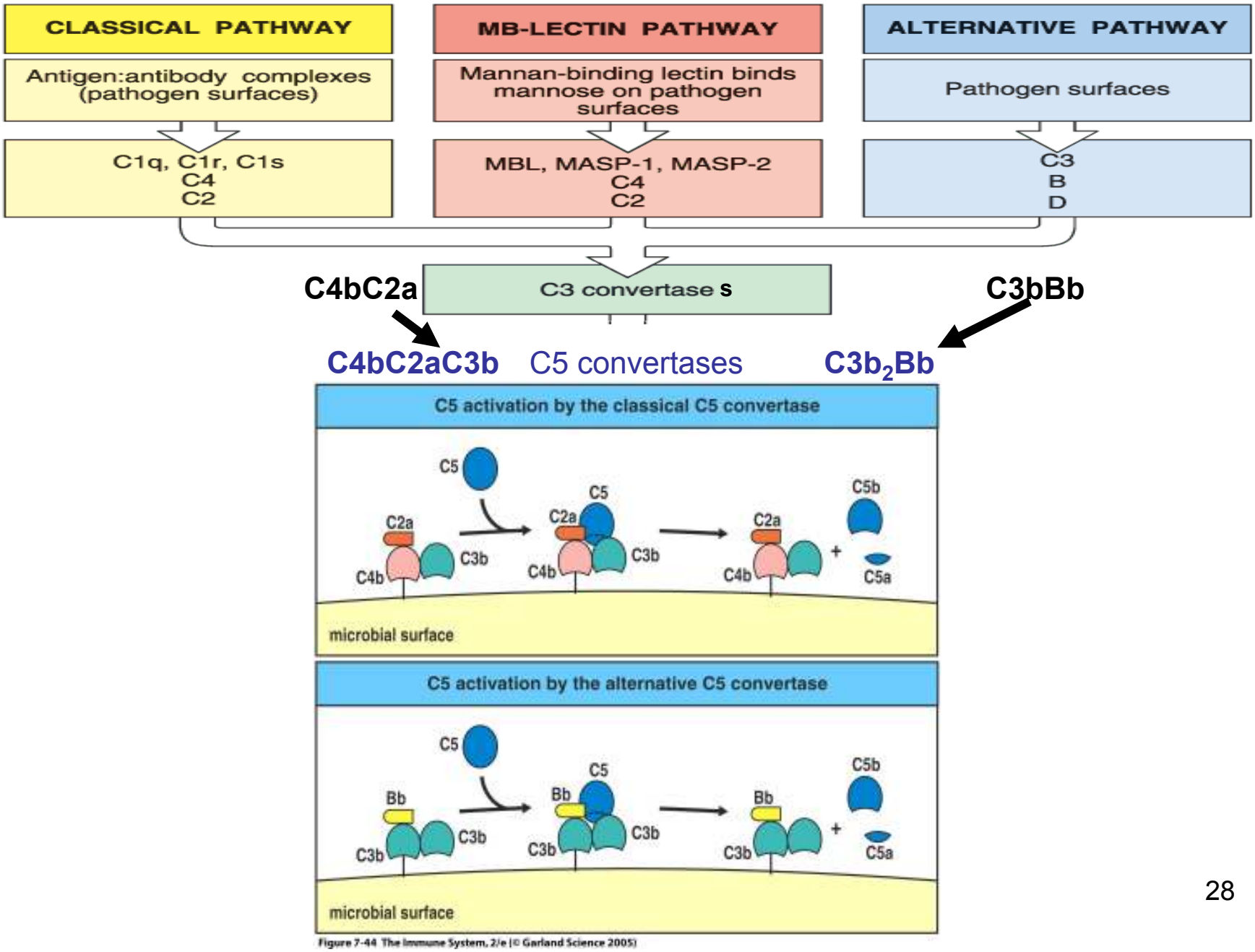
Figure 7-38 The Immune System, 2/e (© Garland Science 2005)

C3b bound to the microbial surface can also bind factor B $\rightarrow$ C3bBb; in other words, the alternative pathway can amplify complement activation by the classical pathway.

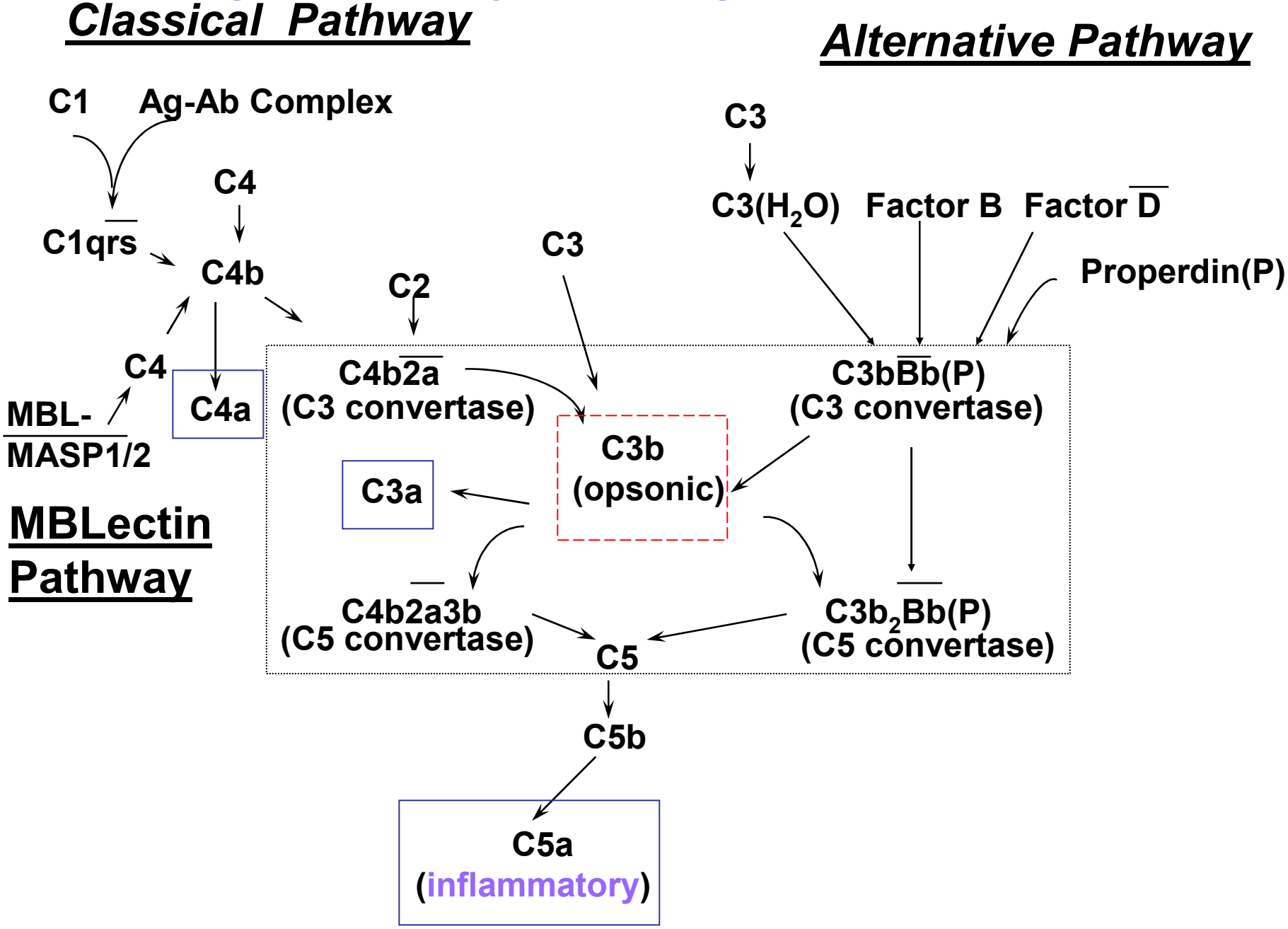
C3 and C5 convertases



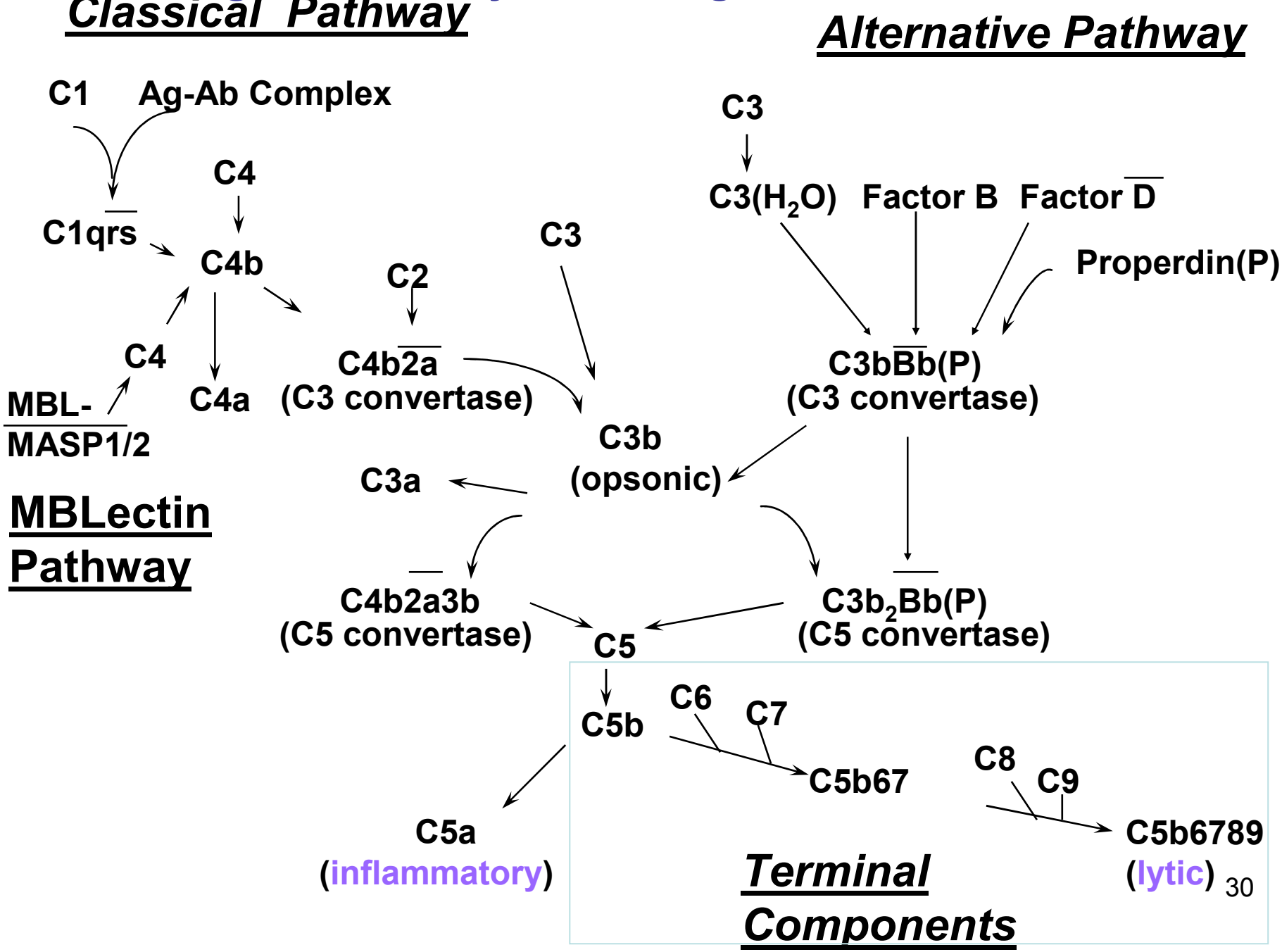
C3 and C5 convertases



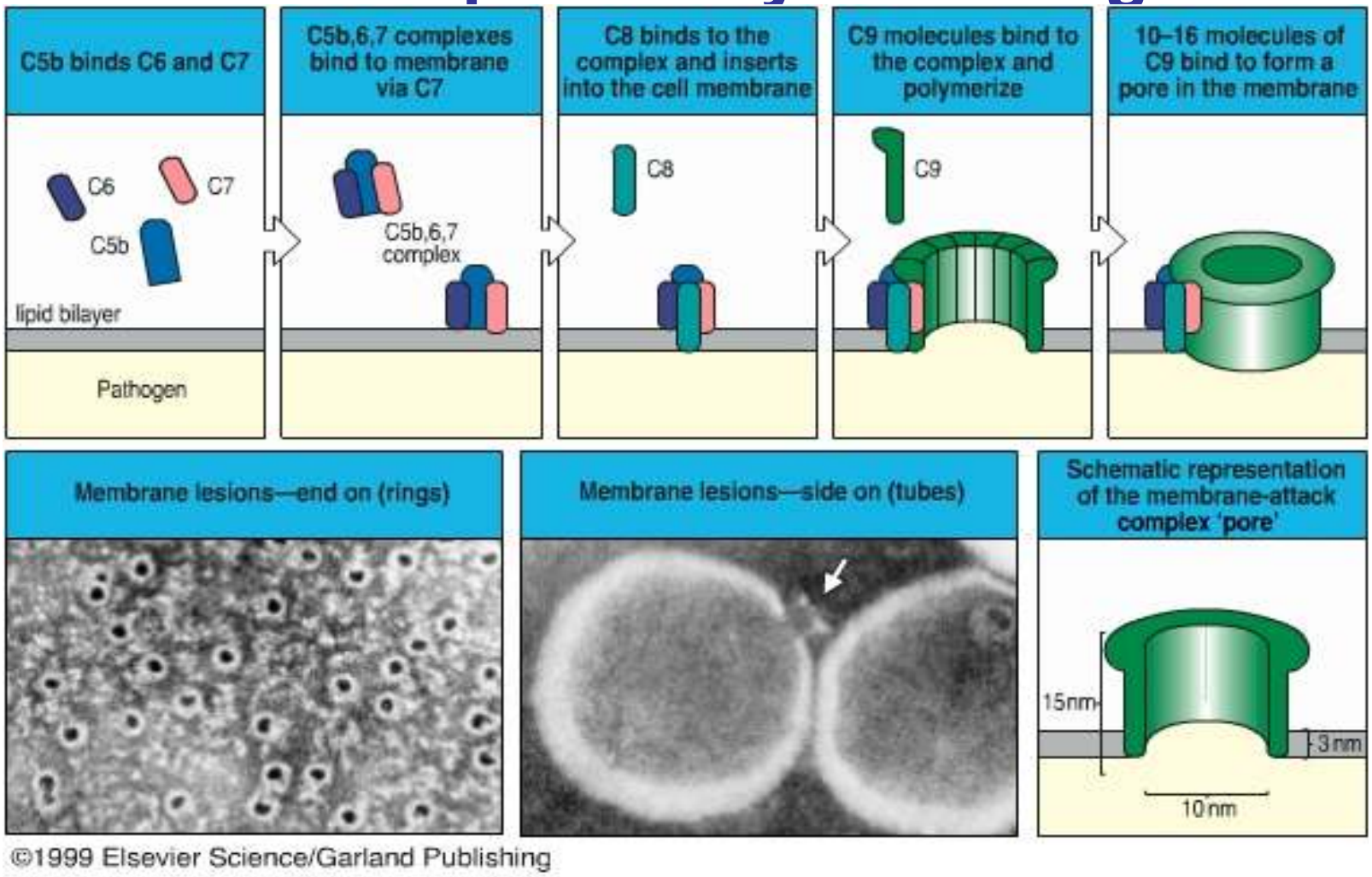
Divergent Pathways Converge for Effector Function



Divergent Pathways Converge for Effector Function



The Terminal Pathway Generates a Membrane Attack Complex to Lyse Pathogens



Pore inserts through lipid layer of membrane - lytic for Gram-negative bacteria and mammalian cells not Gram-positives

Complement Lysis

Complement Ward

- There are inhibitors of complement that prevent it from leading to self-destruction.
- These include the *C1-inhibitor*, the ability to destroy C3 and C5 convertases, and the inhibition of MAC.

C1-Inhibition

- C1-inhibitor binds to C1 and holds it inactive; if it does become active, C1inhibitor serves as a suicide substrate

Regulatory Proteins Prevent Self Injury by the Complement System at Multiple Steps

C1 Inhibition – C1INH

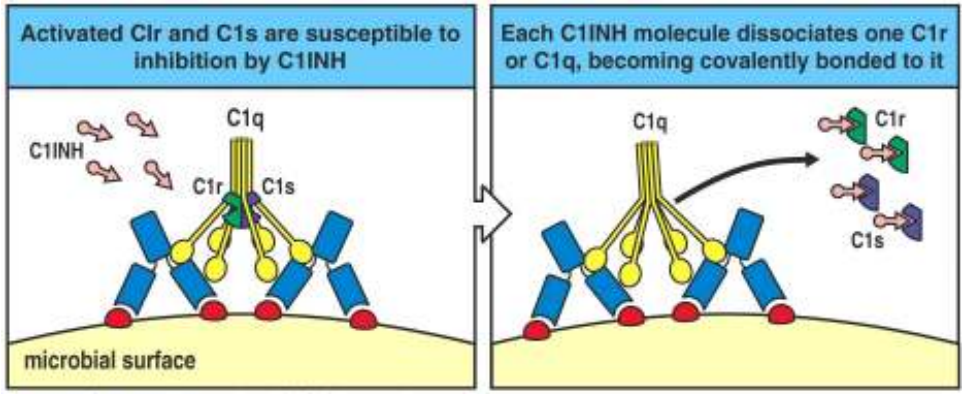


Figure 7-47 The Immune System, 2/e (© Garland Science 2005)

Cleave and Inactivate C3 Factors H and I

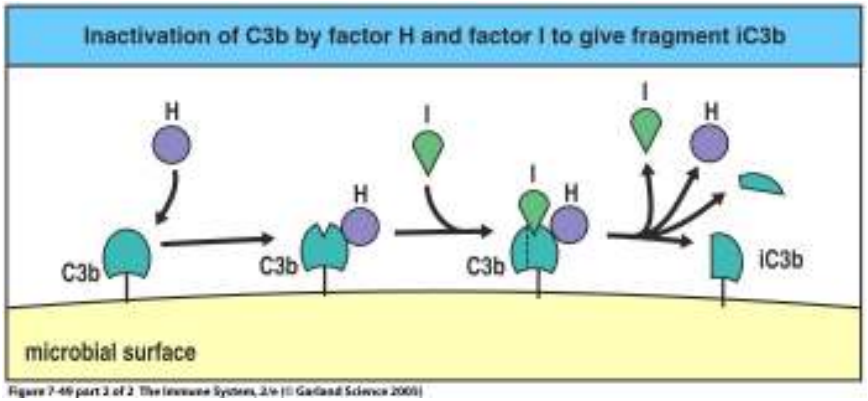


Figure 7-49 part 2 of 2 The Immune System, 2/e (© Garland Science 2005)

Block MAC Assembly – CD59

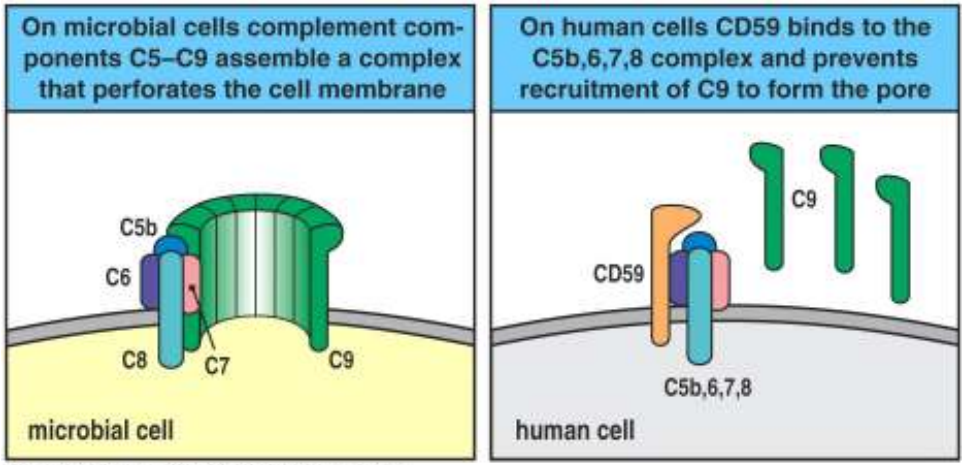


Figure 7-51 The Immune System, 2/e (© Garland Science 2005)

Dissociate C3 Convertase DAF, MCP and Factor I

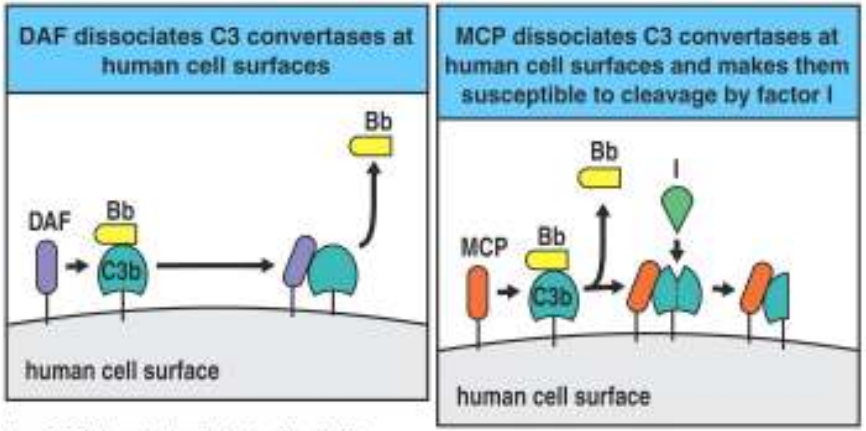


Figure 7-50 The Immune System, 2/e (© Garland Science 2005)

Convertase destruction

- Many things can inactivate the C3 convertase, including *decay accelerating factor* (DAF) on endothelial and blood cells, and CR1 on immune cells. Also, *Factor I* can proteolyze C4b when C4b is complexed with the *membrane cofactor protein* (MCP). Similarly, *Factor H*, DAF, and CR1 can inhibit C3bBbP, ultimately recruiting Factor I.

- All of the fragments released by dissociation or cleavage still encourage immunologically competent cells to proliferate or invade the area.

- Thus, **soluble fragments are chemotactic while bound fragments are opsonic (and/or biochemically active)**.

MAC inhibition

- Protectin (CD59), in the membrane, binds to C8 and C9, blocking the growth of the MAC. *Vitronectin*, in the serum, acts similarly.

Evolution

- Many of the complement proteins are structurally related, consisting of varying numbers of *short consensus repeats* (SCRs). Unfortunately, bacteria and parasites can take advantage of the complement inhibitors or even complement receptors.

Innate-Adaptive Interplay

- B-cells have complement receptors (CR2 in association with CD19) in addition to surface Ig's.
- Cross-linking of CD19 and sIgM in B-cells leads to a 100x-increase in the activation sensitivity of the cells.

Complement Deficiency States

- Increased risk for infection with capsulated bacterial pathogens
  - early classical pathway components (C1, C4 and C2) and C3 – *Streptococcus pneumoniae* – Gram-positive bacterium
  - early classical pathway components, C3, and alternative pathway and terminal components – *Neiserria meningitidis* – Gram-negative bacterium

Summary: COMPLEMENT SYSTEM

- Complement bridges the innate and the adaptive immune systems.
- It leads to chemotaxis.
- It opsonizes pathogens.
- It is a proteolytic cascade, much like blood clotting.