The Complement System

Dr. Zahid Khattak

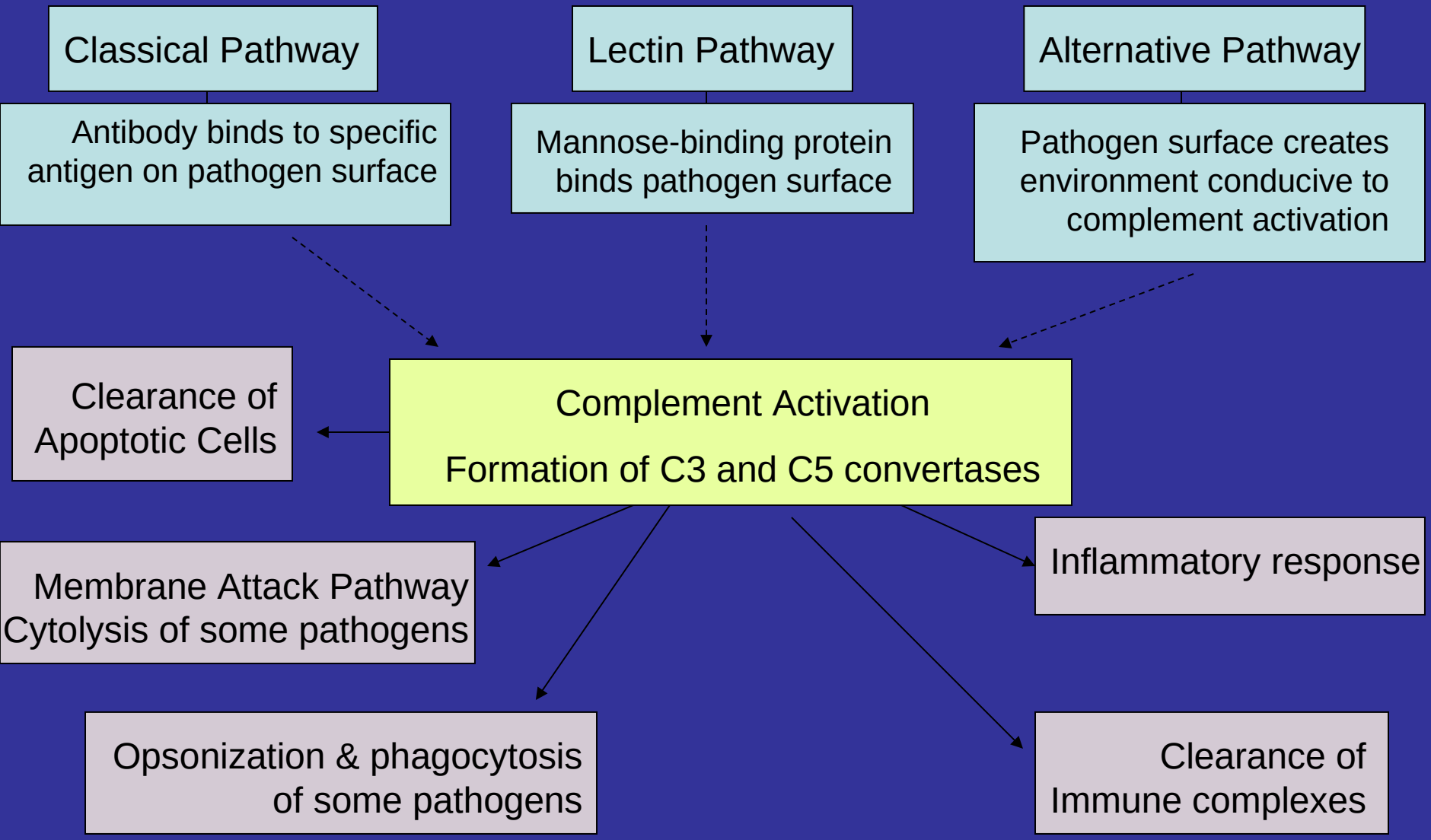
Introduction

- The complement system consists of a group of serum proteins that act in concert and in an orderly sequence to exert their effect

- These proteins are not immunoglobulins and their concentrations in serum do not increase after immunization

- Complement activation (fixation) leads to lysis of cells and to the generation of many powerful biologically active substances

Overview of Complement

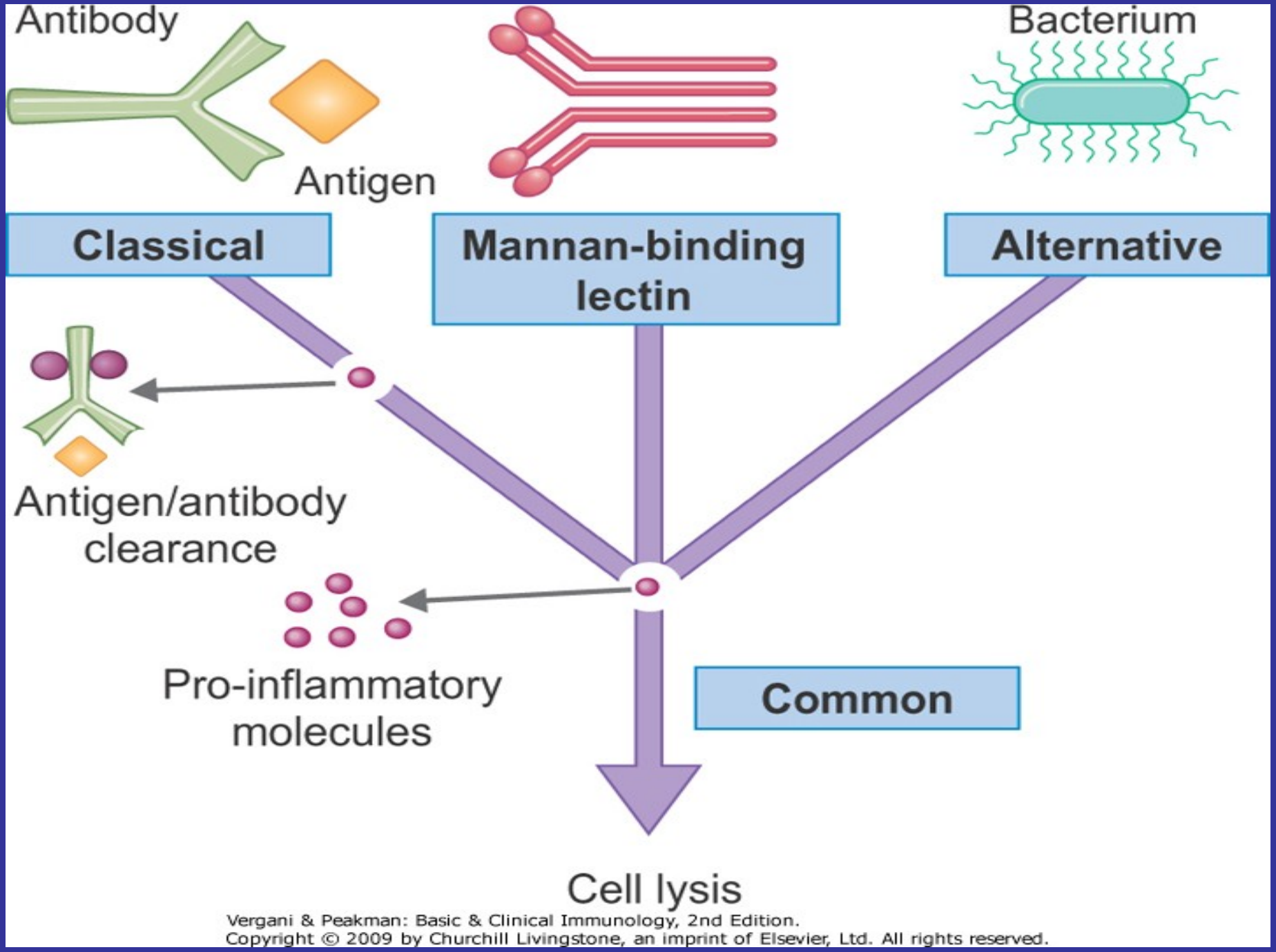


Complement Activation Pathways

- **The Classical Pathway**
  - Ag- Ab complexes

- **The Alternative Pathway**
  - Aggregated immunoglobulins and microbial products

- **The Mannan - Binding Lectin Pathway**
  - Microbial products

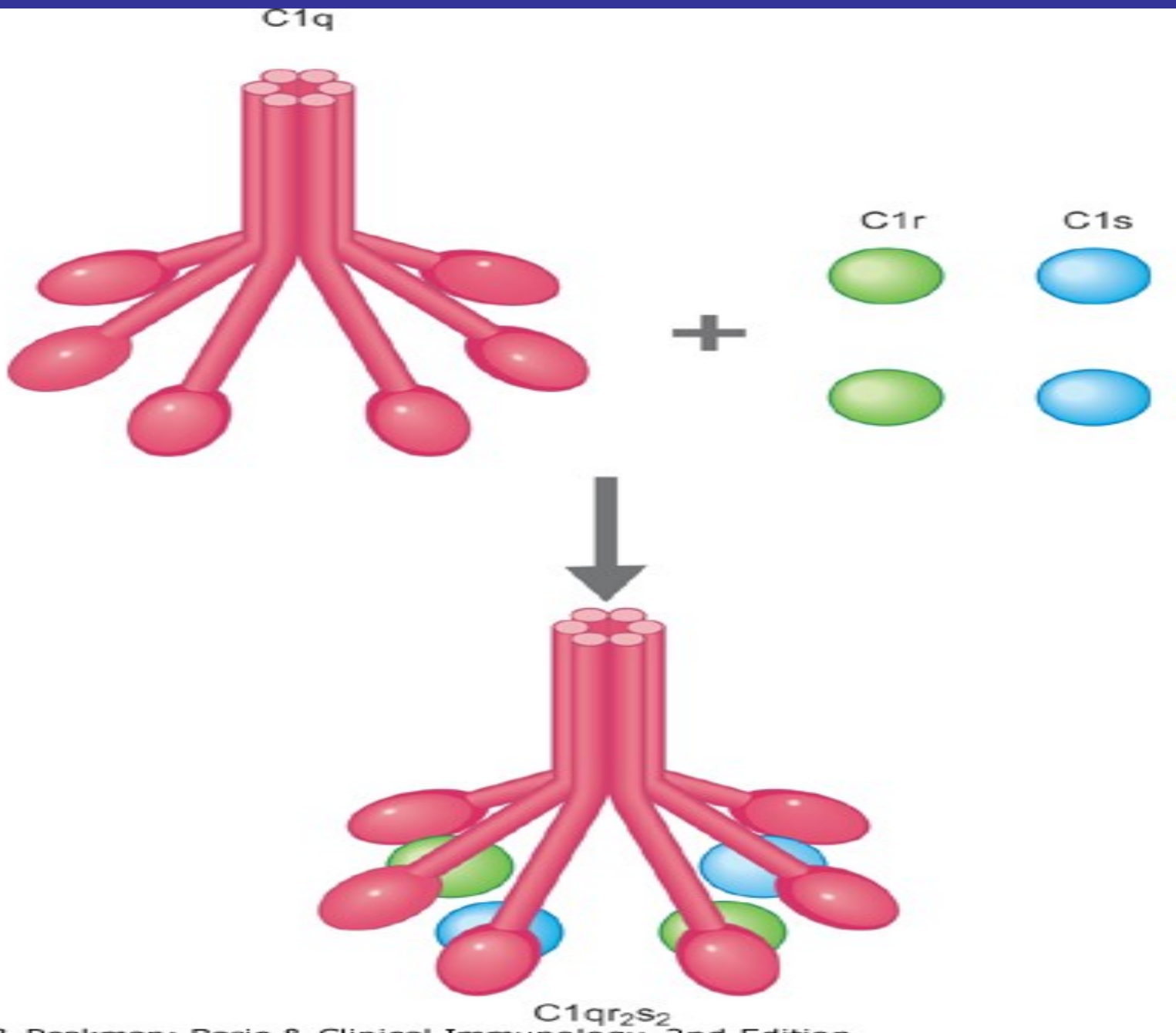


The Classical Pathway

- **Activators**: Ag – Ab complexes
- Antibodies involved: IgG and IgM
- Activation in an orderly fashion of nine major protein components; C1 – C9
- Products of activation are enzymes that catalyze the subsequent step

The Classical Pathway

- **Activation of C1:**
- C1 consists of C1q (400.000 Daltons), C1r (95000 Daltons), and C1s (85000 Daltons)
- Subunits are held together by Calcium ions
- C1q is a polymer of 6 identical units
- C1q activation requires binding to a c1q- specific receptor on the FC region of at least 2 adjacent molecules of IgG or a single molecule of IgM, a reaction that requires Calcium ions



Molecular structure of C1

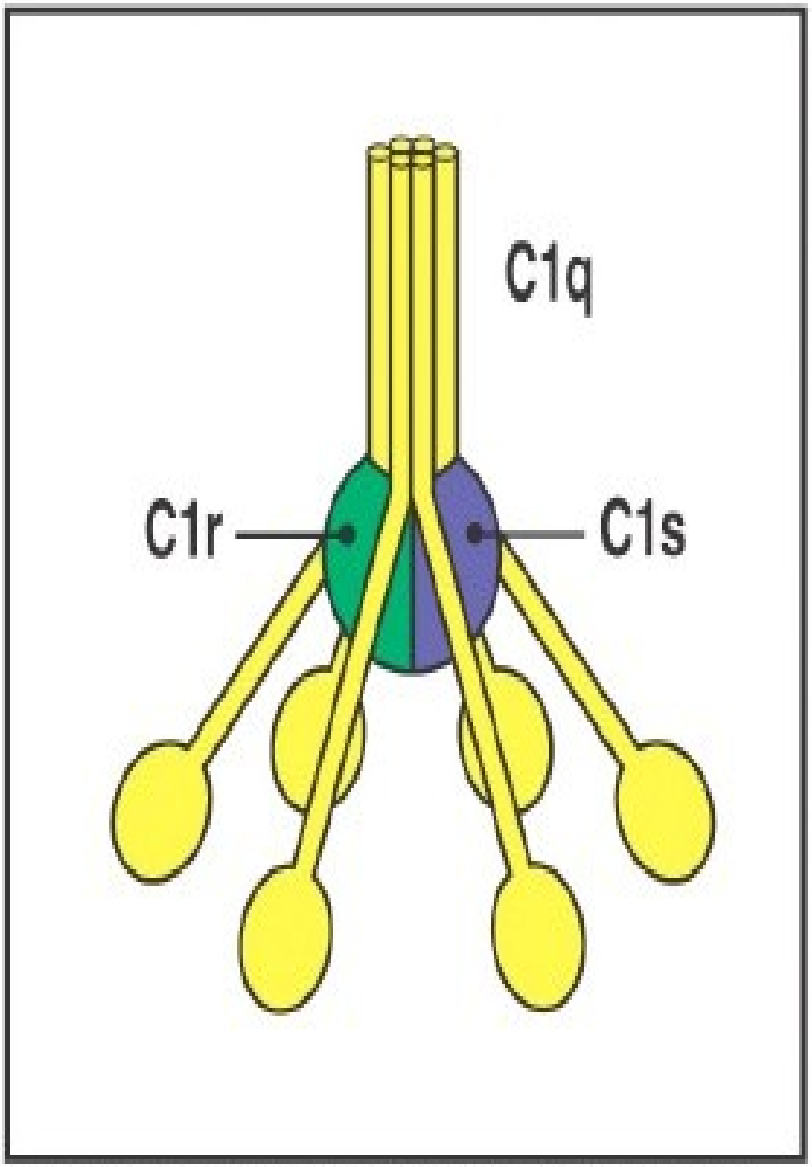
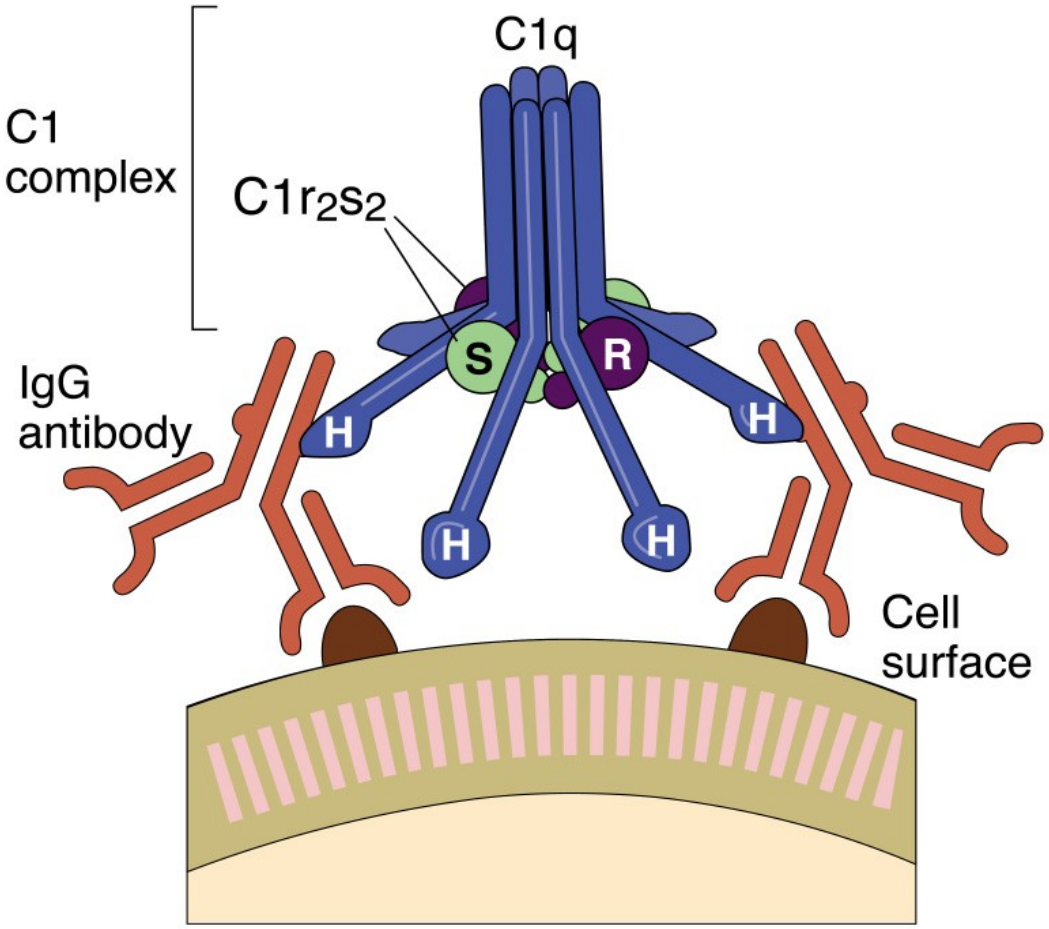


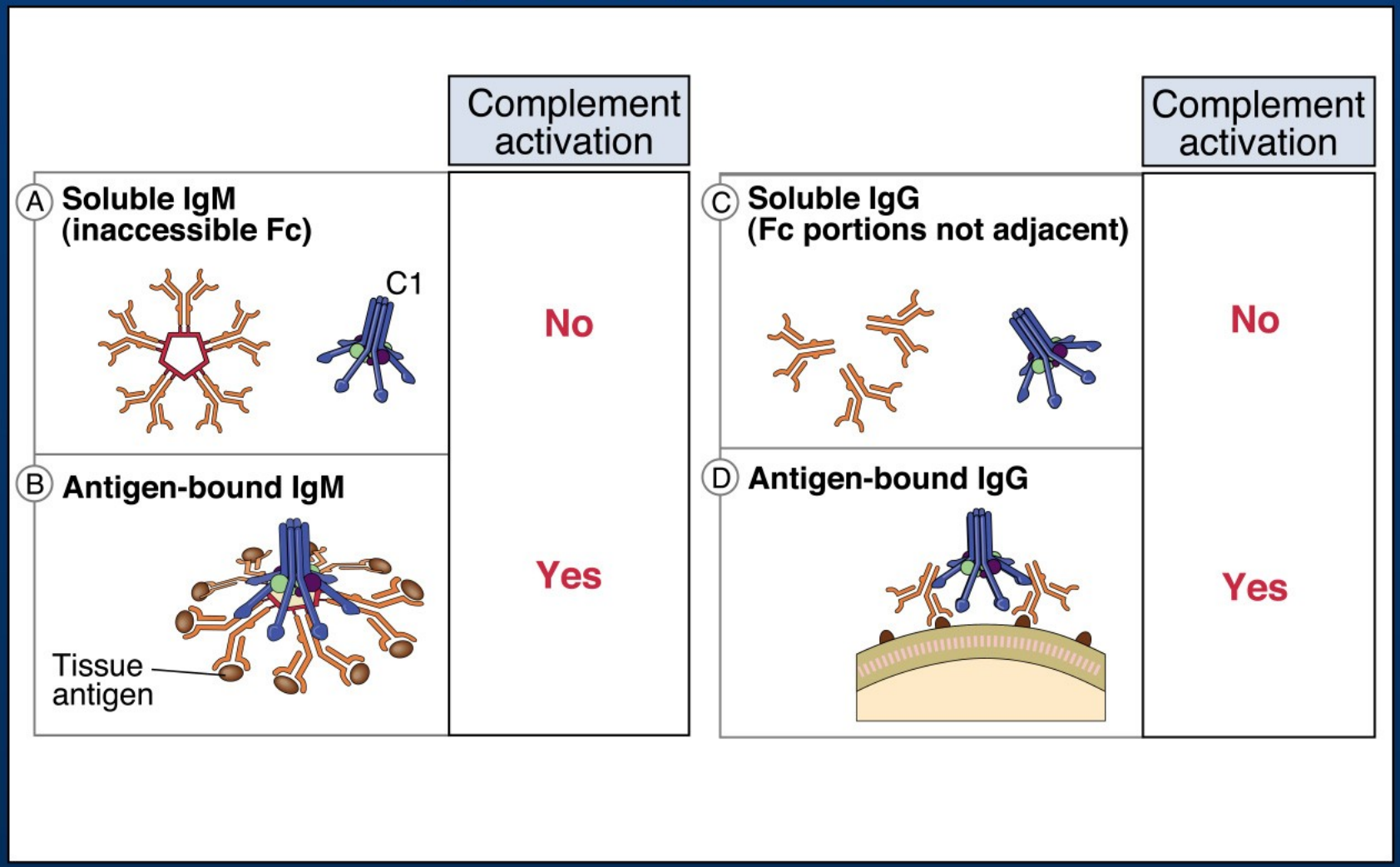
Figure 7-31 The Immune System, 2/e (© Garland Science 2005)

The C1 component of complement



From Abbas, Lichtman, & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1999, Fig. 14-9

Activation of complement by IgM and IgG antibodies



From Abbas, Lichtman, & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1999, Fig. 14-10

IgA and IgE cannot activate complement

The Classical Pathway

- IgG4, IgA, and IgE do not have complement receptors
- Activated C1q activates C1r which in turn activates C1s
- Activated C1s has esterolytic and proteolytic properties which acts on C4 splitting it into two fragments; C4a and C4b
- C4b complexes with C1s forming an active component that acts on C2 splitting it into C2a and C2b
- C2a binds to C4b creating a very active complex called the C3 convertase, where a single molecule can activate hundreds of C3 molecules

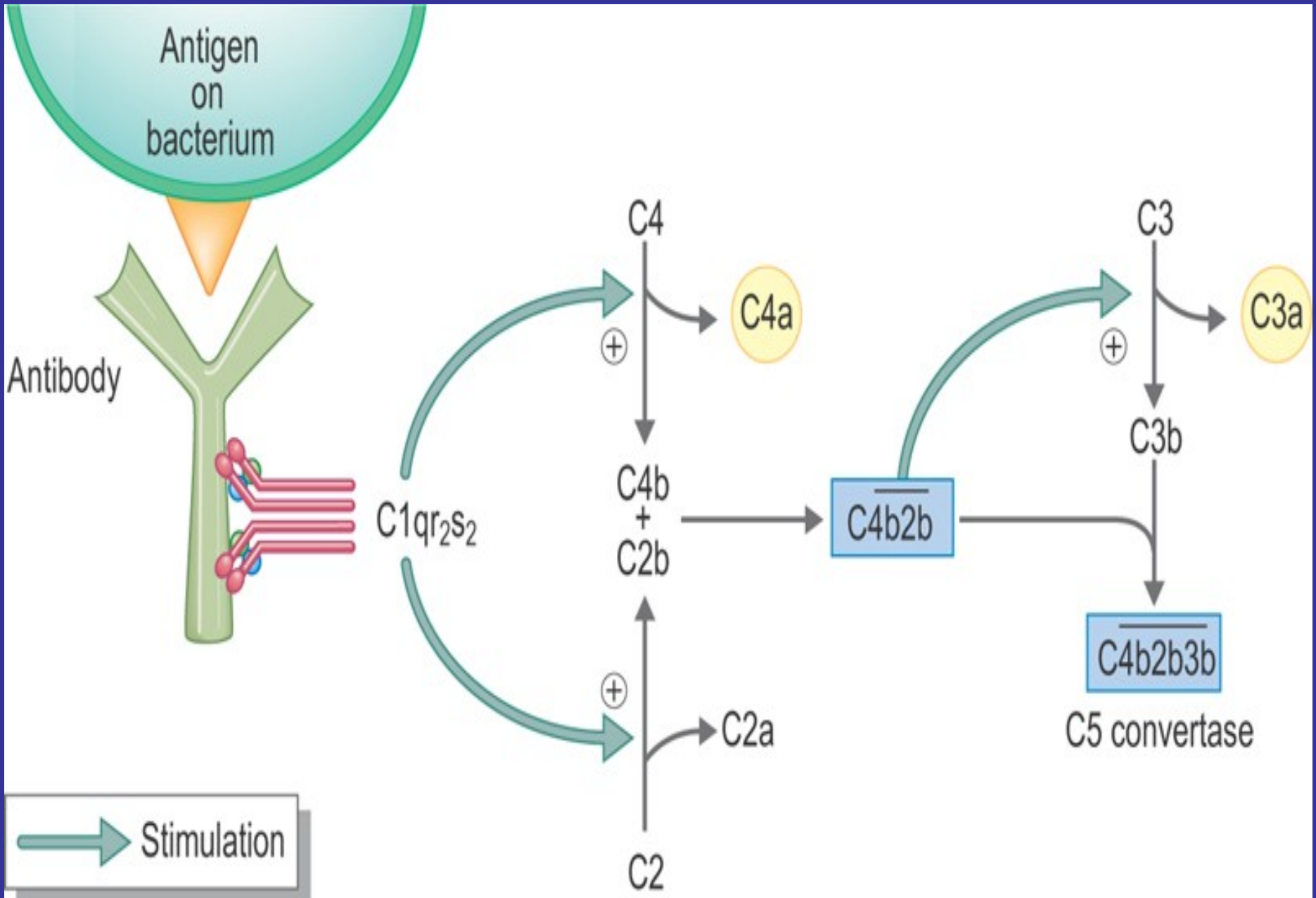
The Classical Pathway

- C3 is split by C4b2a into C3a and C3b
- C3b binds to cells and to C4b2a to generate C5 convertase which splits C5 into C5a and C5b
- C5b binds to cells and activates C6 and C7
- The complex C5b67 activates C8 and C9 forming a giant molecule with a molecular weight of 10^6 Daltons called the membrane attack complex (MAC)

The Classical Pathway

- C5b6789 bound to cells insert themselves into the cell membrane and produce transmembrane channels allowing ions to pass through

- The osmotic equilibrium of the cell is disturbed with rapid influx of water into the cell which swells and lyses



The Alternative (properdin) Pathway

- **Activators**: Bacterial LPS, cell wall of some bacteria, some yeast cells, aggregated IgA, and a factor present in cobra venom

- **Components**: C3 – C9, factor B, factor D, and Properdin

- C3b present in trace amounts in serum combines with factor B forming C3bB

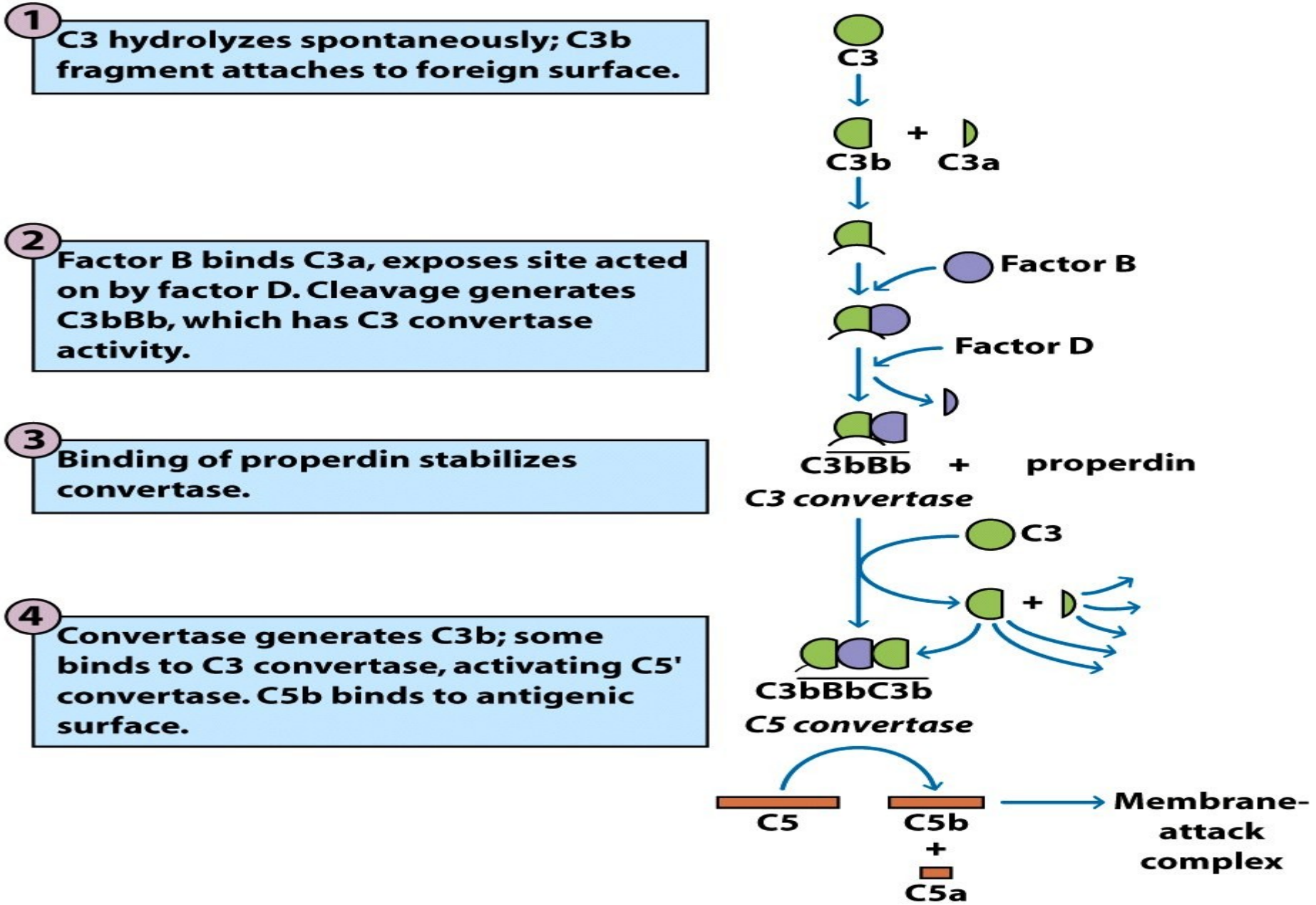


Figure 7-7
Kuby IMMUNOLOGY, Sixth Edition

Alternative Pathway

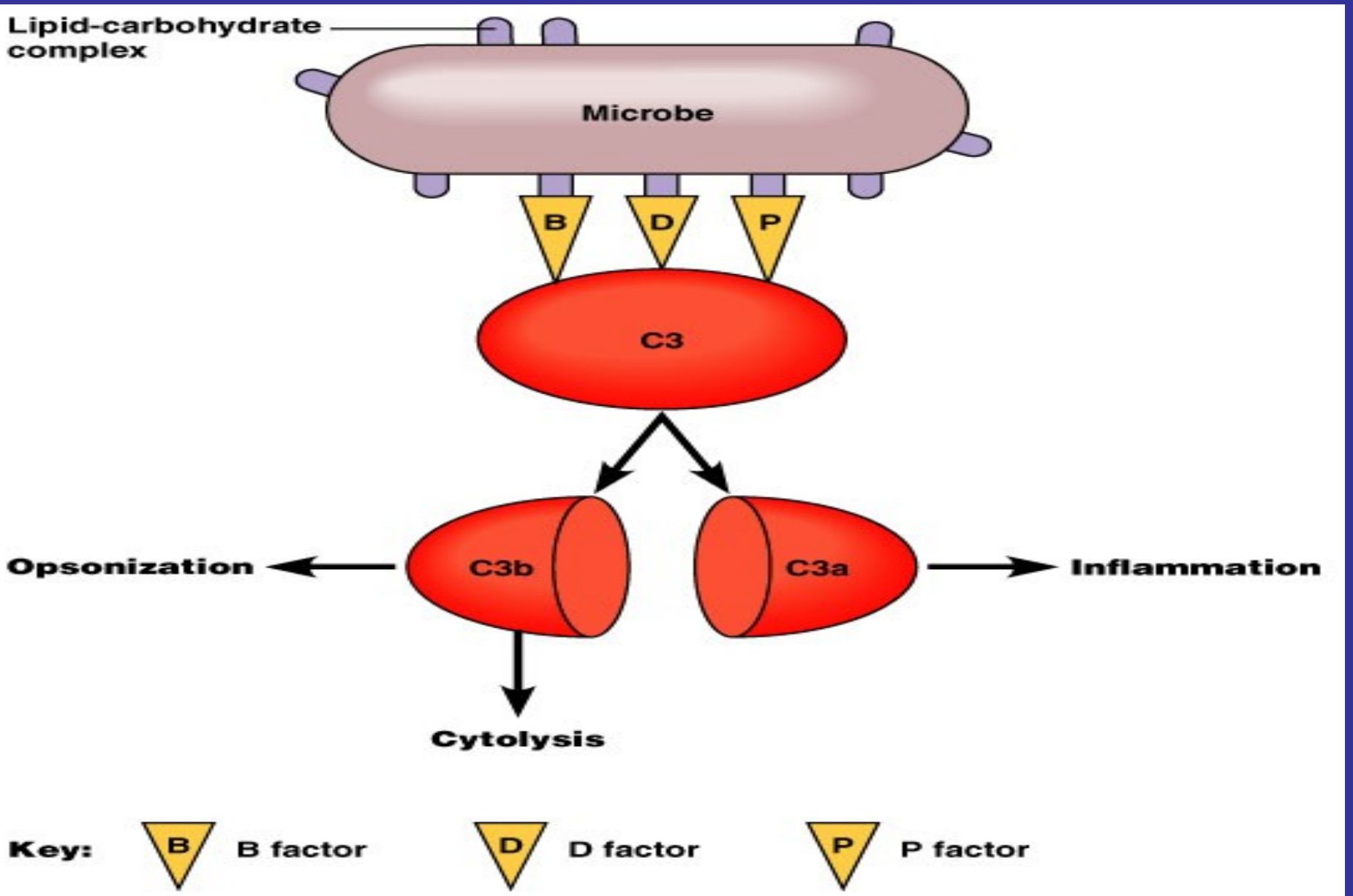


Figure 16.14

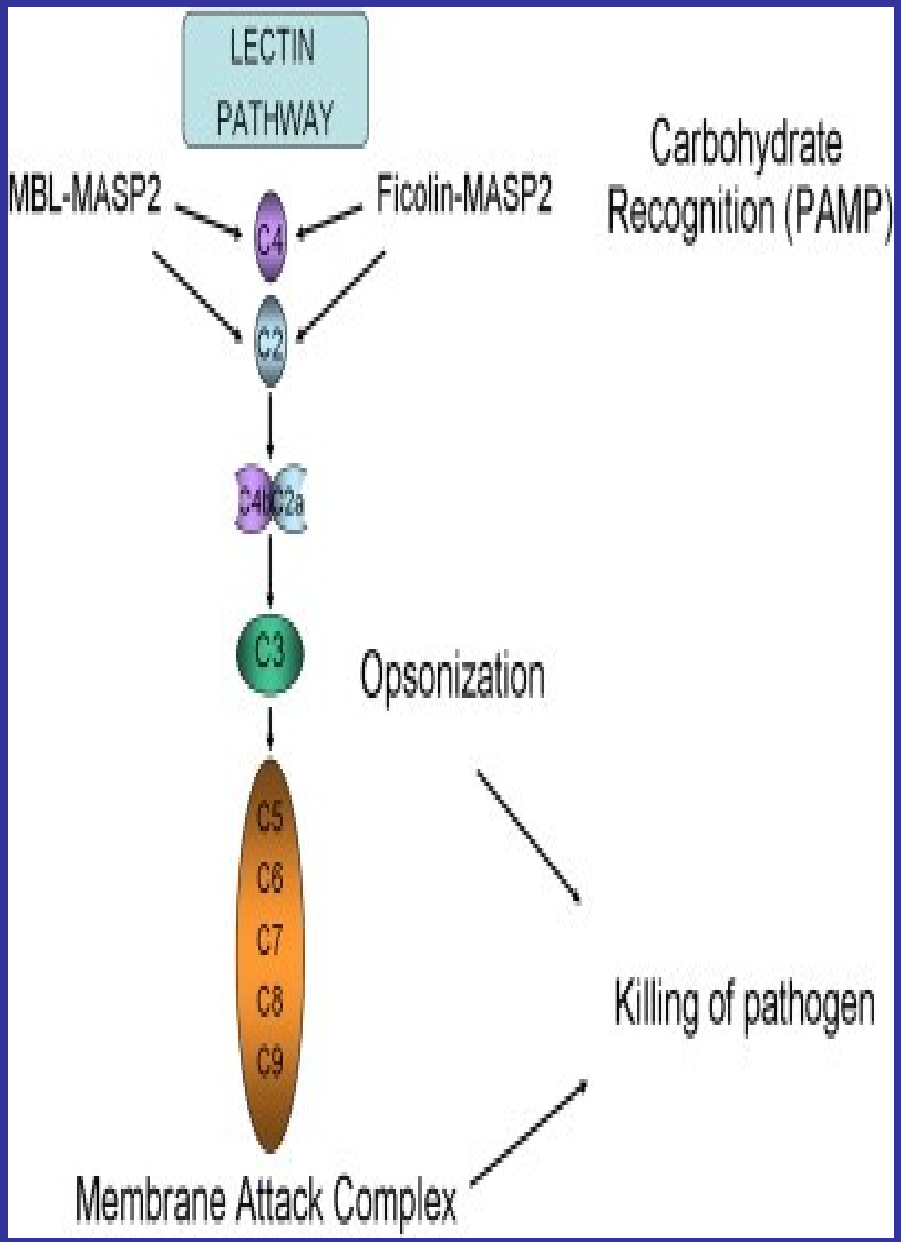
The Mannan Binding Lectin (MBL)

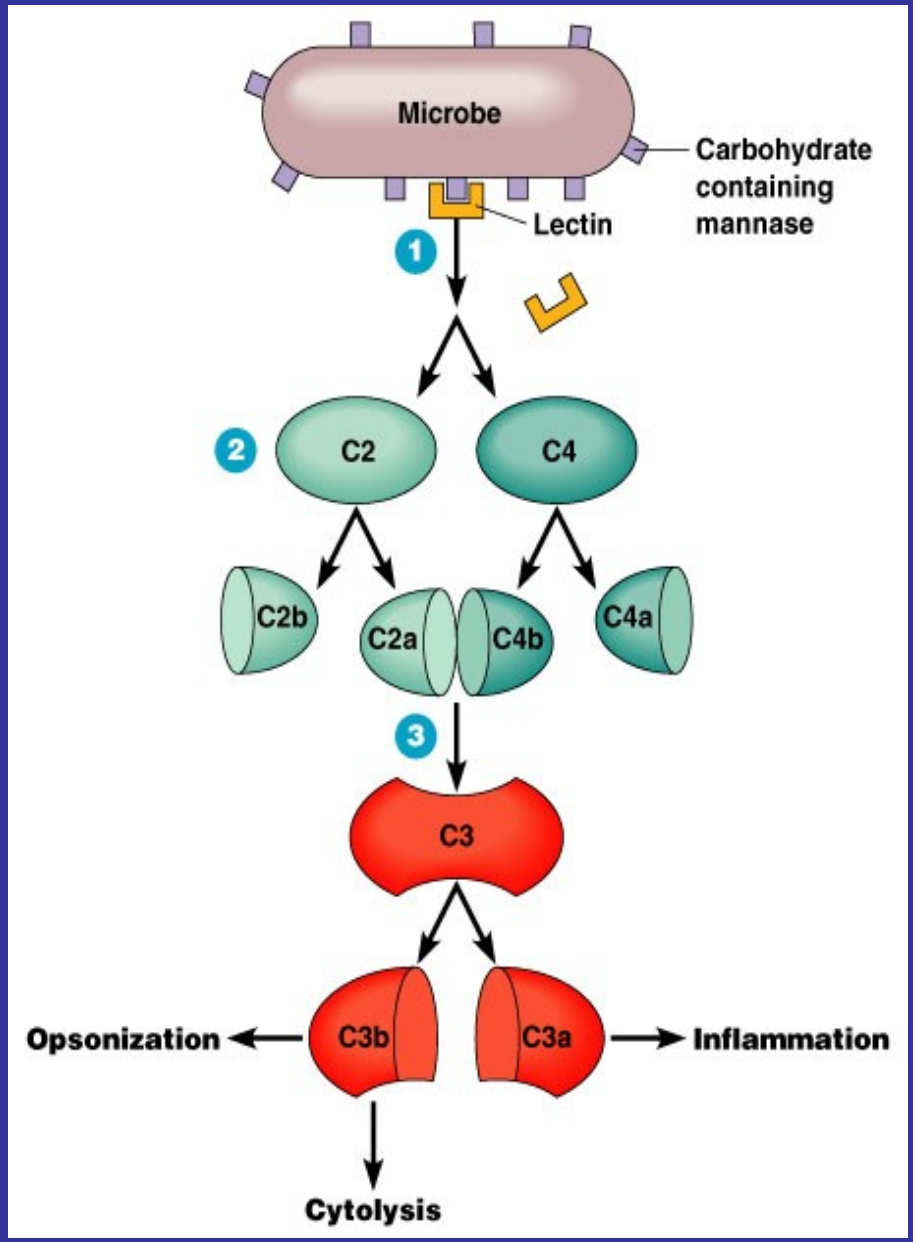
- **Activators**: microorganisms and foreign invaders

- **Components**: C2 – C9, MASP

- MBL recognizes carbohydrate structures through its carbohydrate – recognizing domain (CRD) and then it can interact with an enzyme called MBL – activated serine protease (MASP)

Lectin Pathway





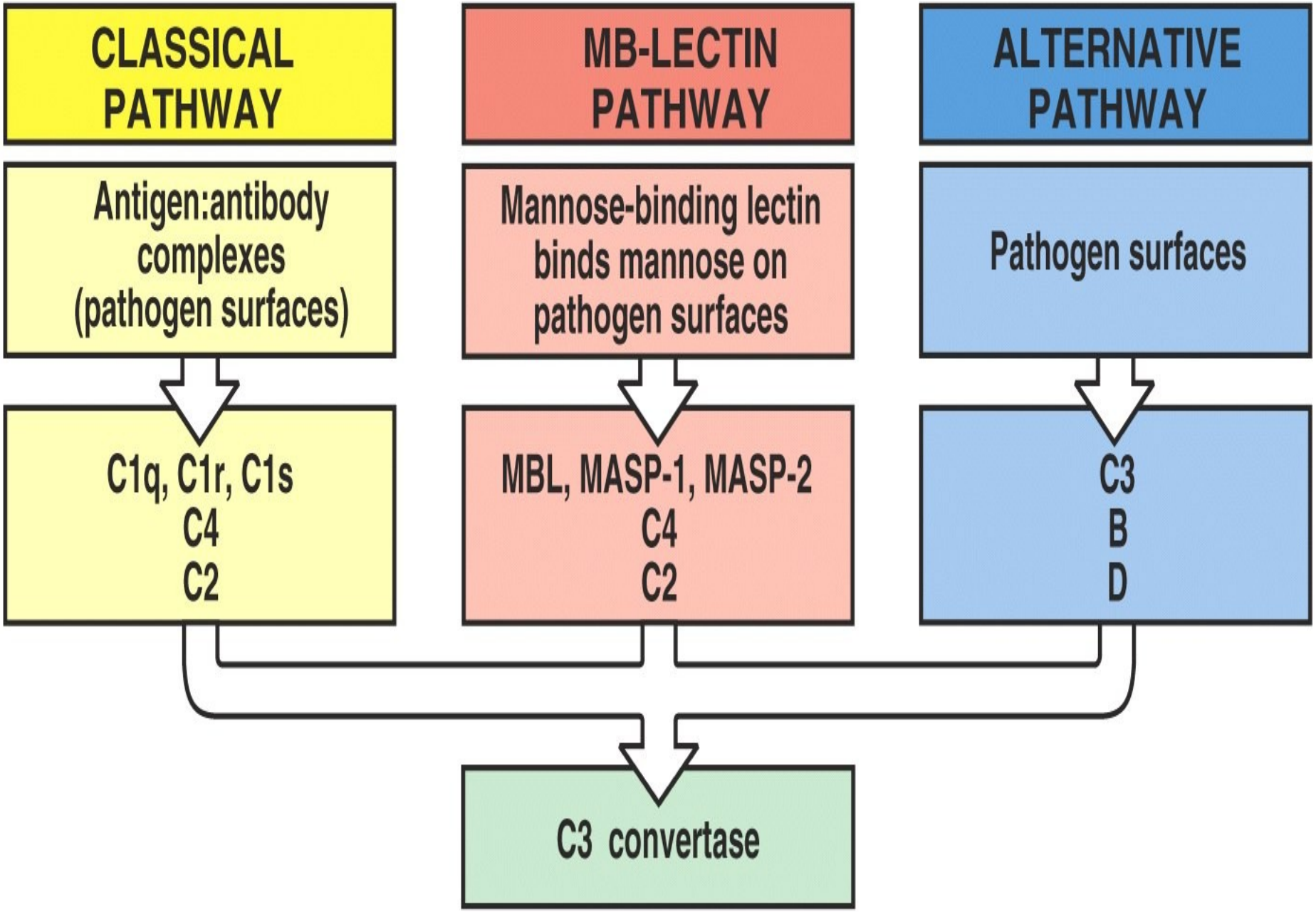


Figure 2-19 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

General Functions of Complement

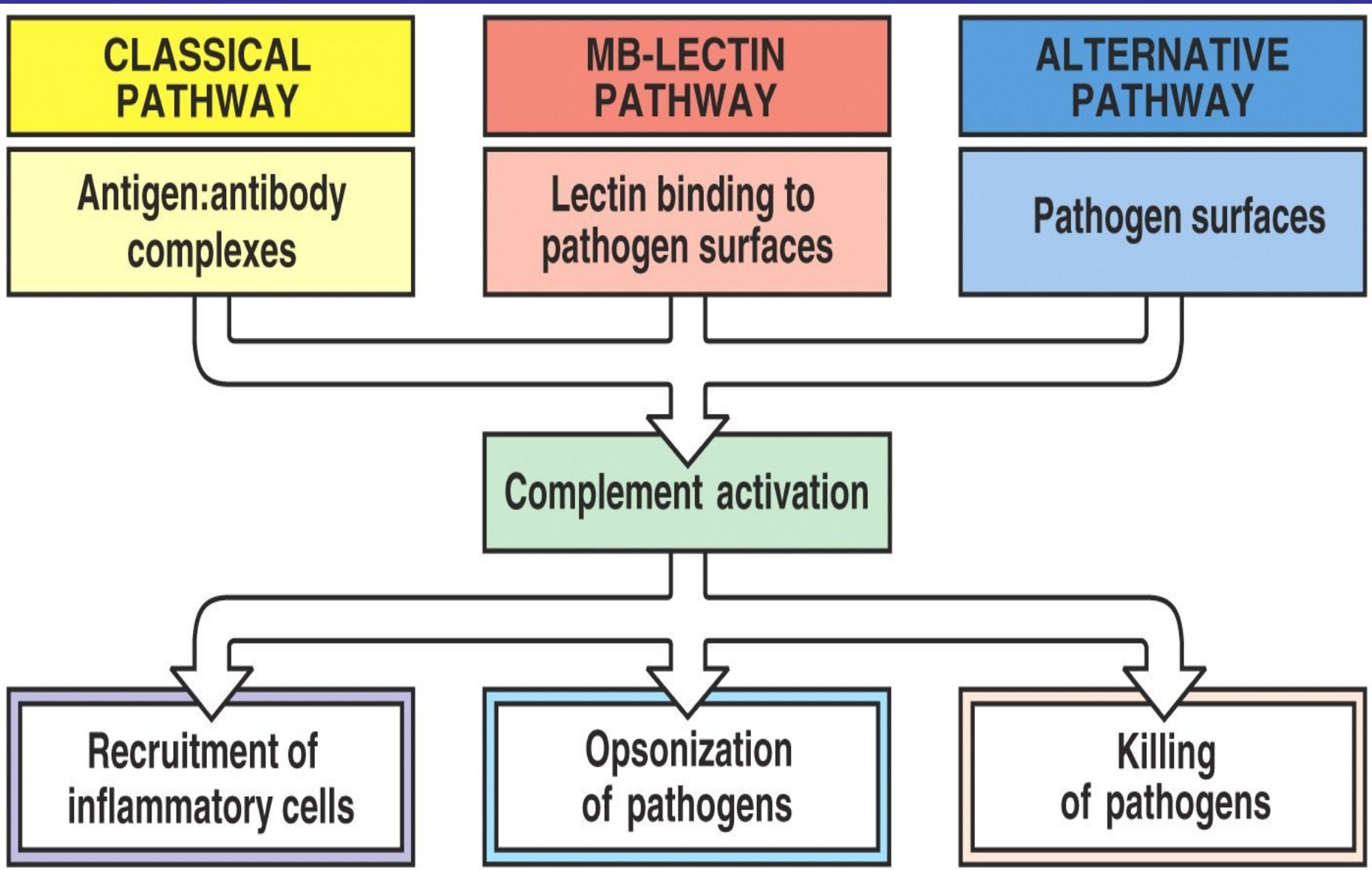
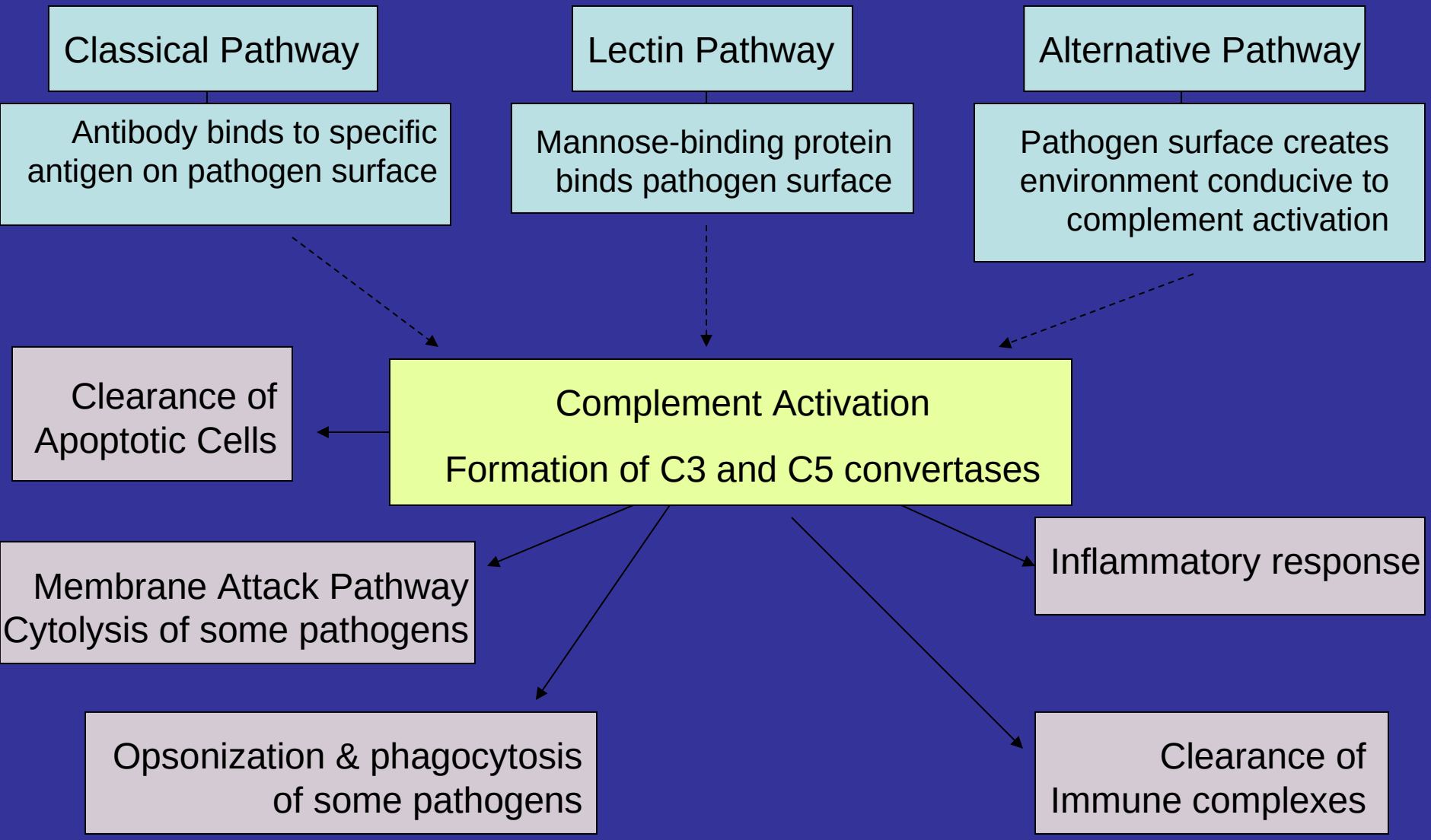


Figure 2-18 Immunobiology, 6/e. (© Garland Science 2005)

Overview of Complement



Complement functions related to immune defense

- **Lysis of cells:** This is the original function identified and causes hypotonic cell death by making holes. It is not effective against organisms with rigid cell walls such as fungi

Terminal complement components and the formation of the membrane attack complex

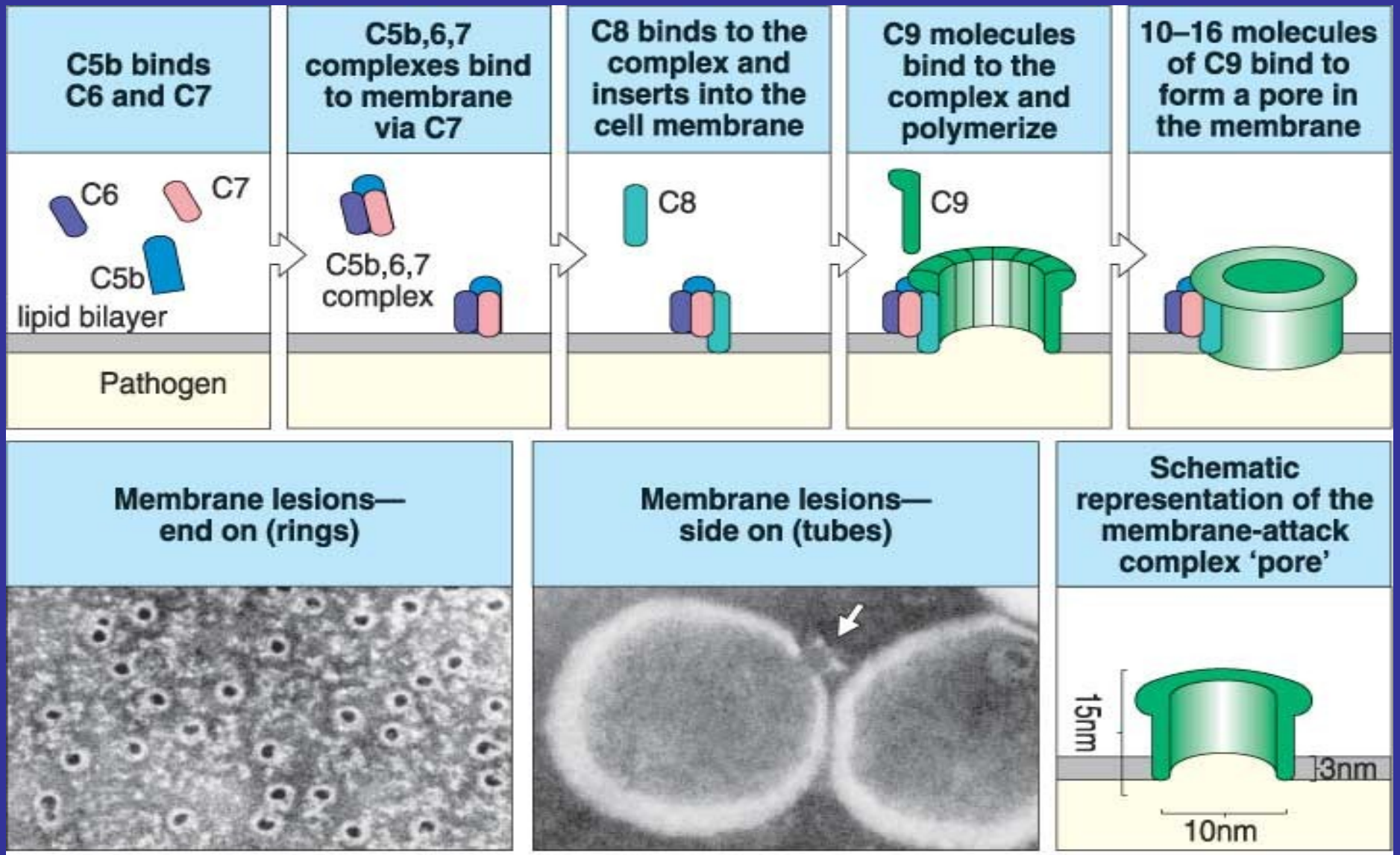
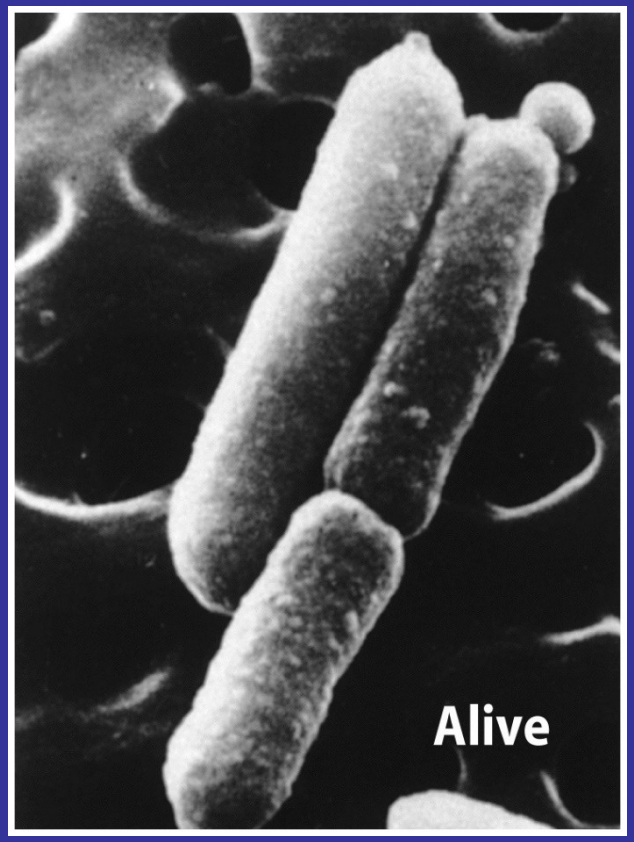
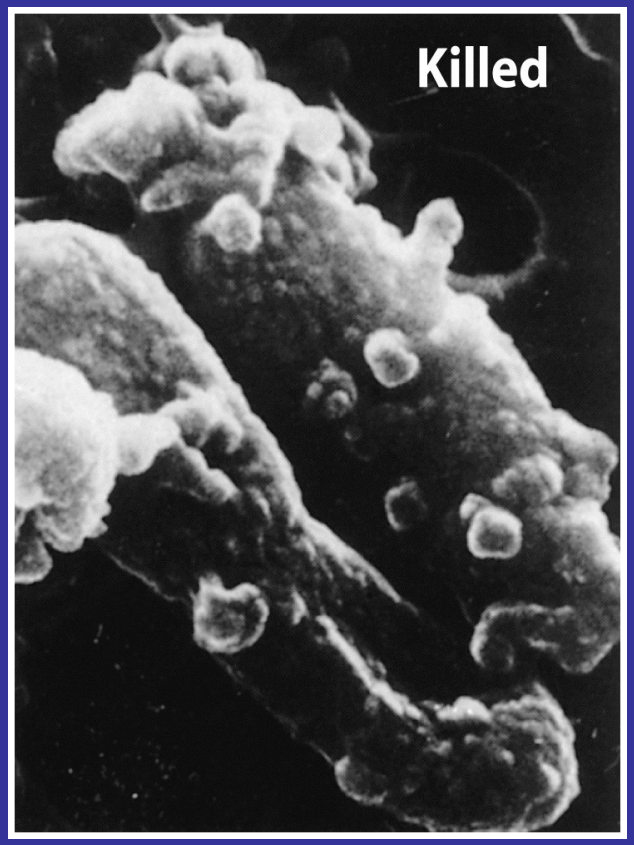
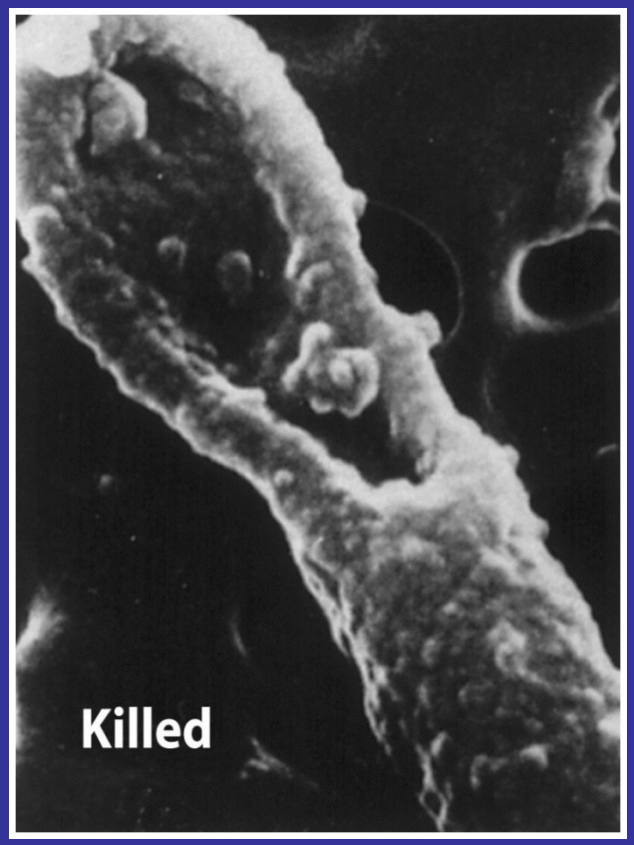


Fig 2.24 © 2001 Garland Science

The contents of the cell leak out through the MAC pore and the cell dies







Before complement

After complement treatment

Opsonization: Antigen coated with C3b binds to cells bearing complement receptors and if the cell is a phagocyte, the antigen will be phagocytosed.

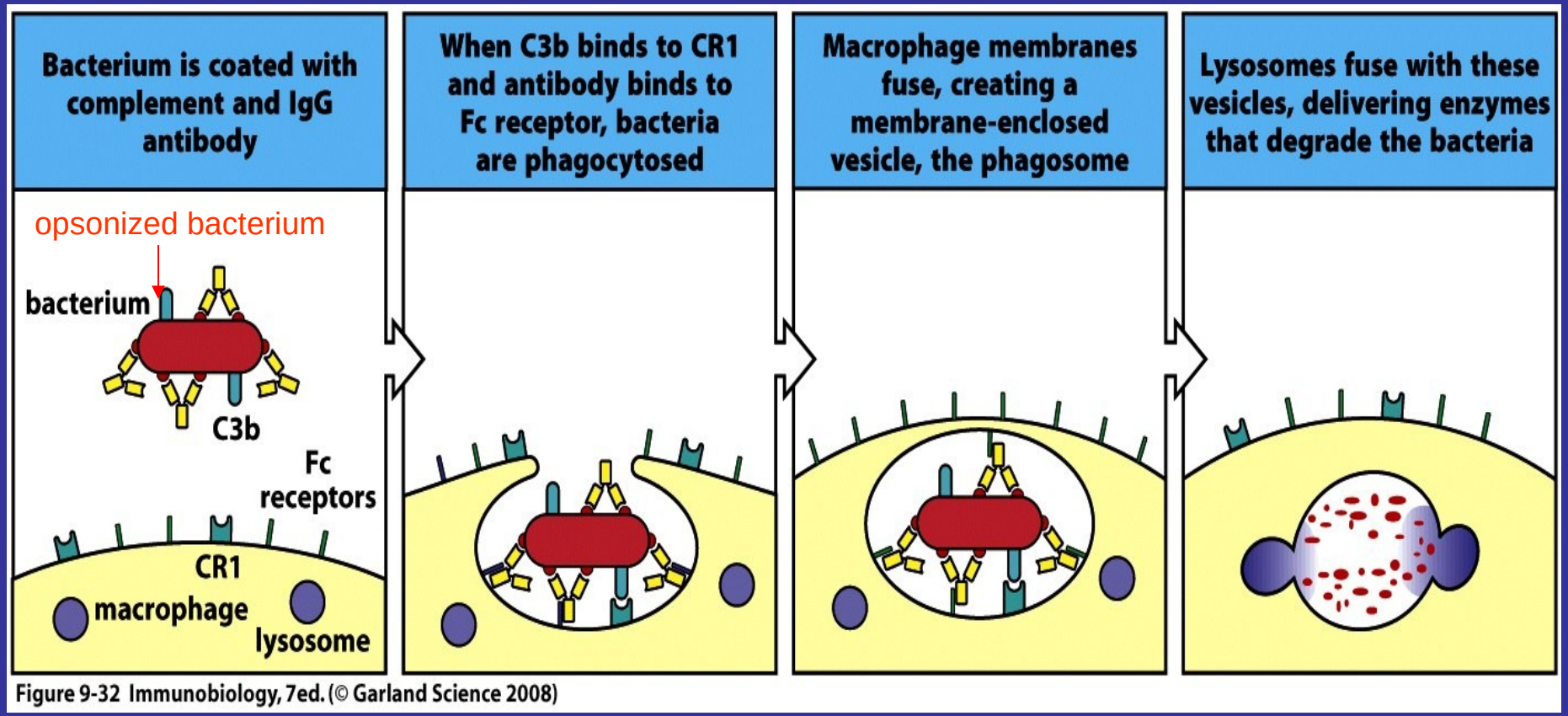


Figure 9-32 Immunobiology, 7ed. (© Garland Science 2008)

- **Inflammation:**

  - **Anaphylatoxins**: C5a, C3a, and C4a of which C5a is the most potent bind receptors on mast cells and basophils and cause degranulation with the release of pharmacologically active mediators which induce smooth-muscle contraction and increases in vascular permeability.

  - **Chemoattractants:** C3a, C5a and C5b67 attract and induce monocytes and neutrophils to adhere to vascular endothelial cells, extravasate through the endothelial lining of the capillaries and migrate to the site of complement activation in the tissue.

Inflammation

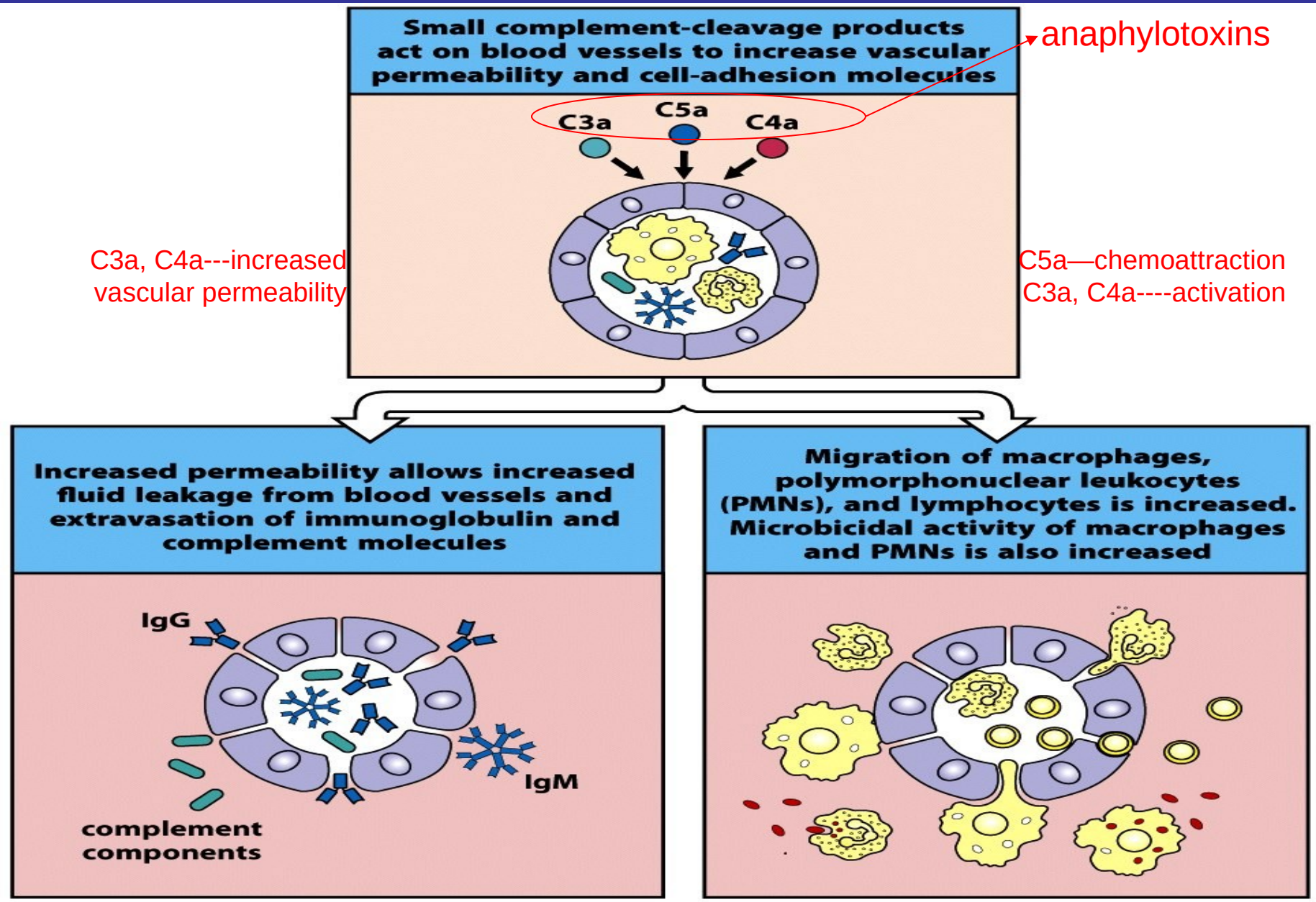


Figure 2-39 Immunobiology, 7ed. (© Garland Science 2008)

- **Immune clearance:** Removes immune complexes from the circulation and deposits them in the liver where they are degraded.

- **Virus neutralization**: Complement mediates viral neutralization by facilitating viral aggregation and by coating the viral surface.

Clearance of Immune Complexes

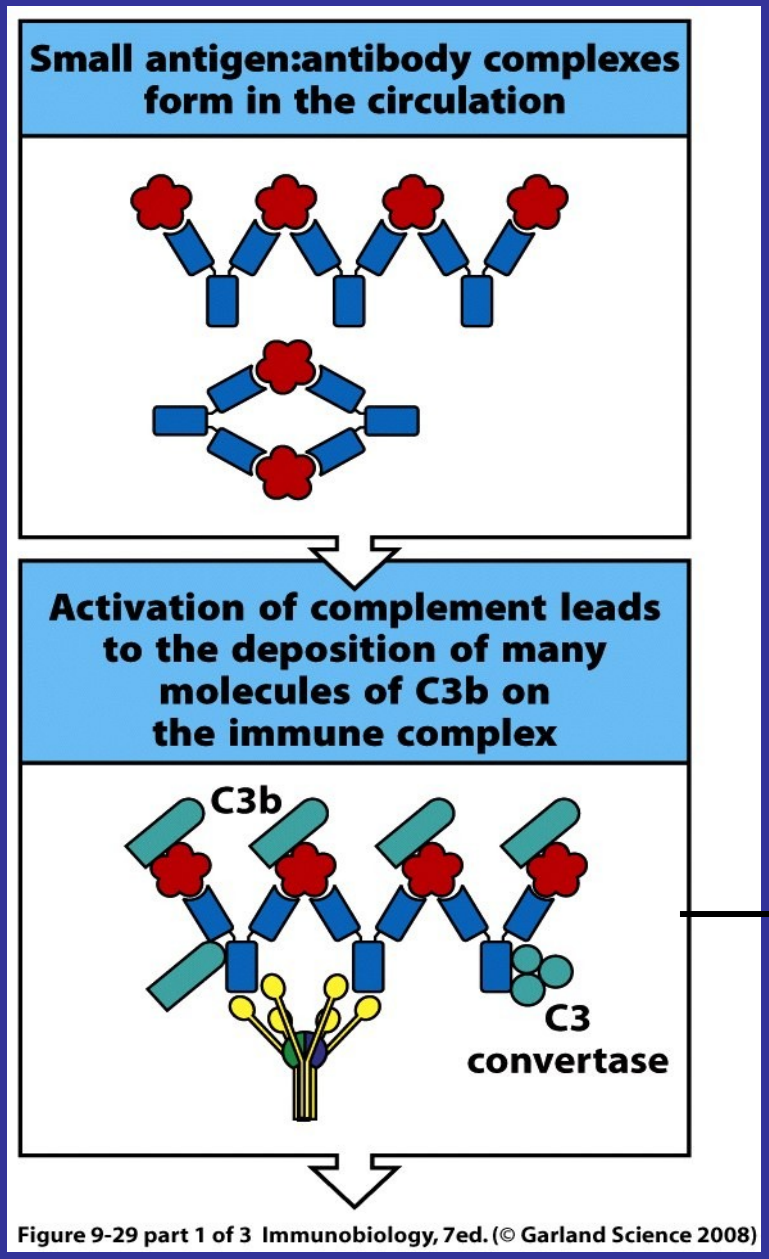
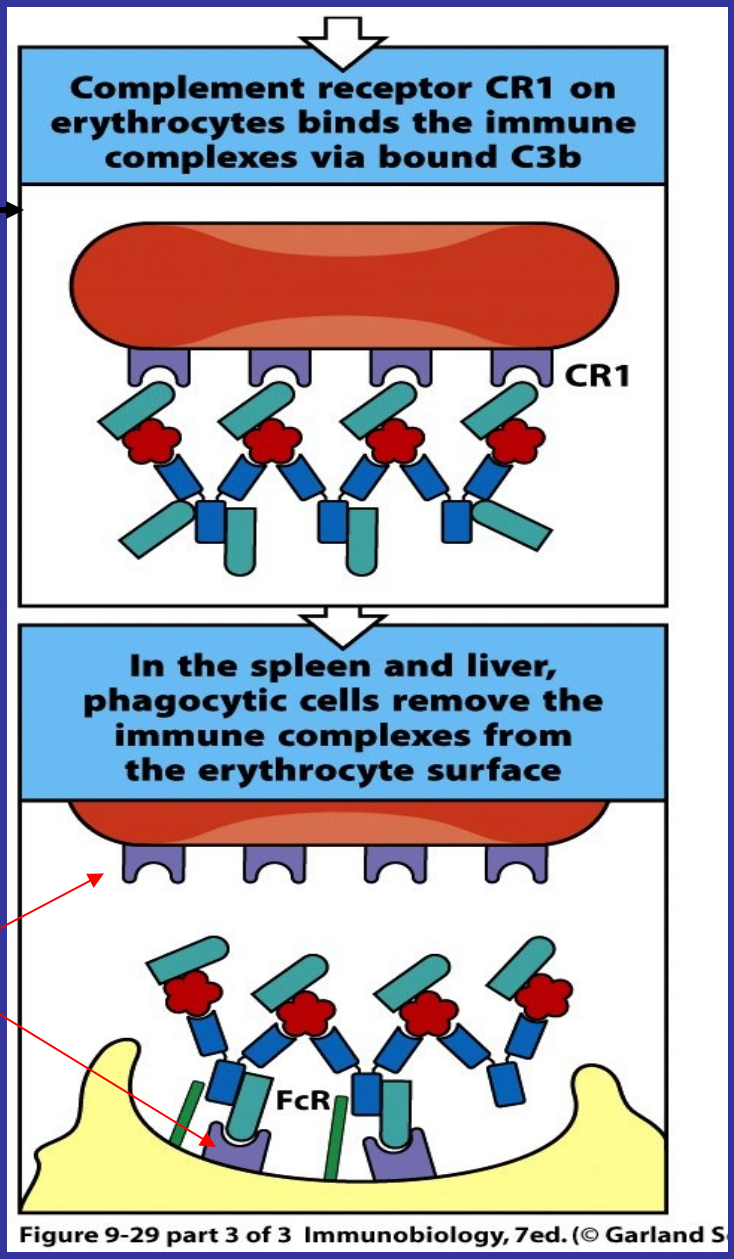


Figure 9-29 part 1 of 3 Immunobiology, 7ed. (© Garland Science 2008)



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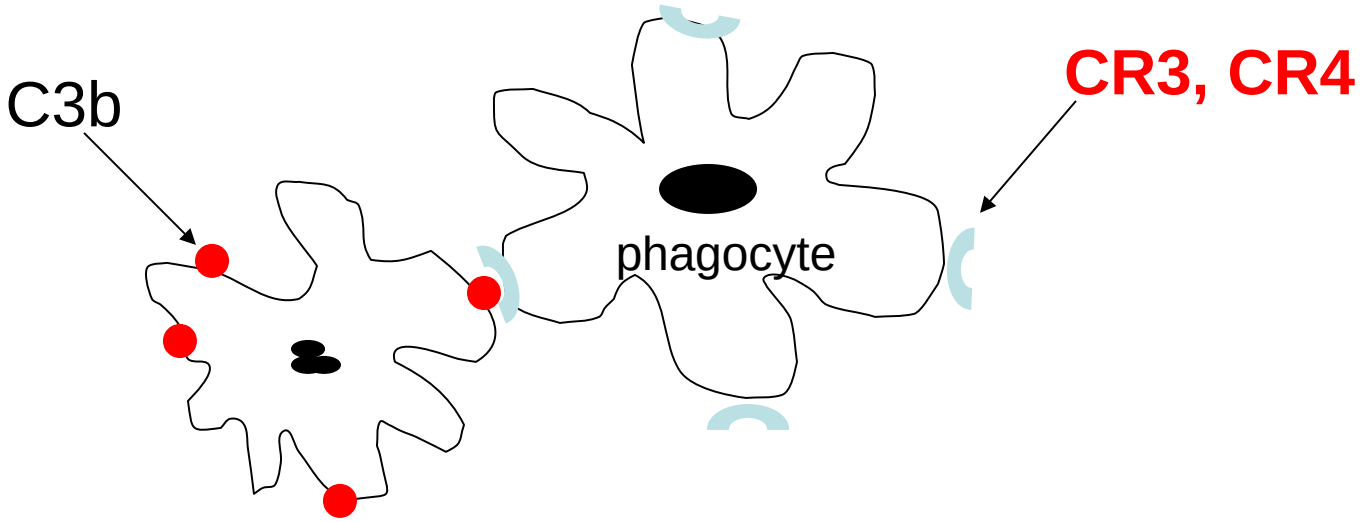
Clearance of Apoptotic Cells



- Phagocyte recognizes C3b deposited on the surface of apoptotic cell
- Apoptotic cell is ingested and destroyed by phagocyte
- This is an important mechanism for clearing self antigens and preventing autoimmune responses
- Uptake of apoptotic cell also induces self tolerance, thereby prevents autoimmune response

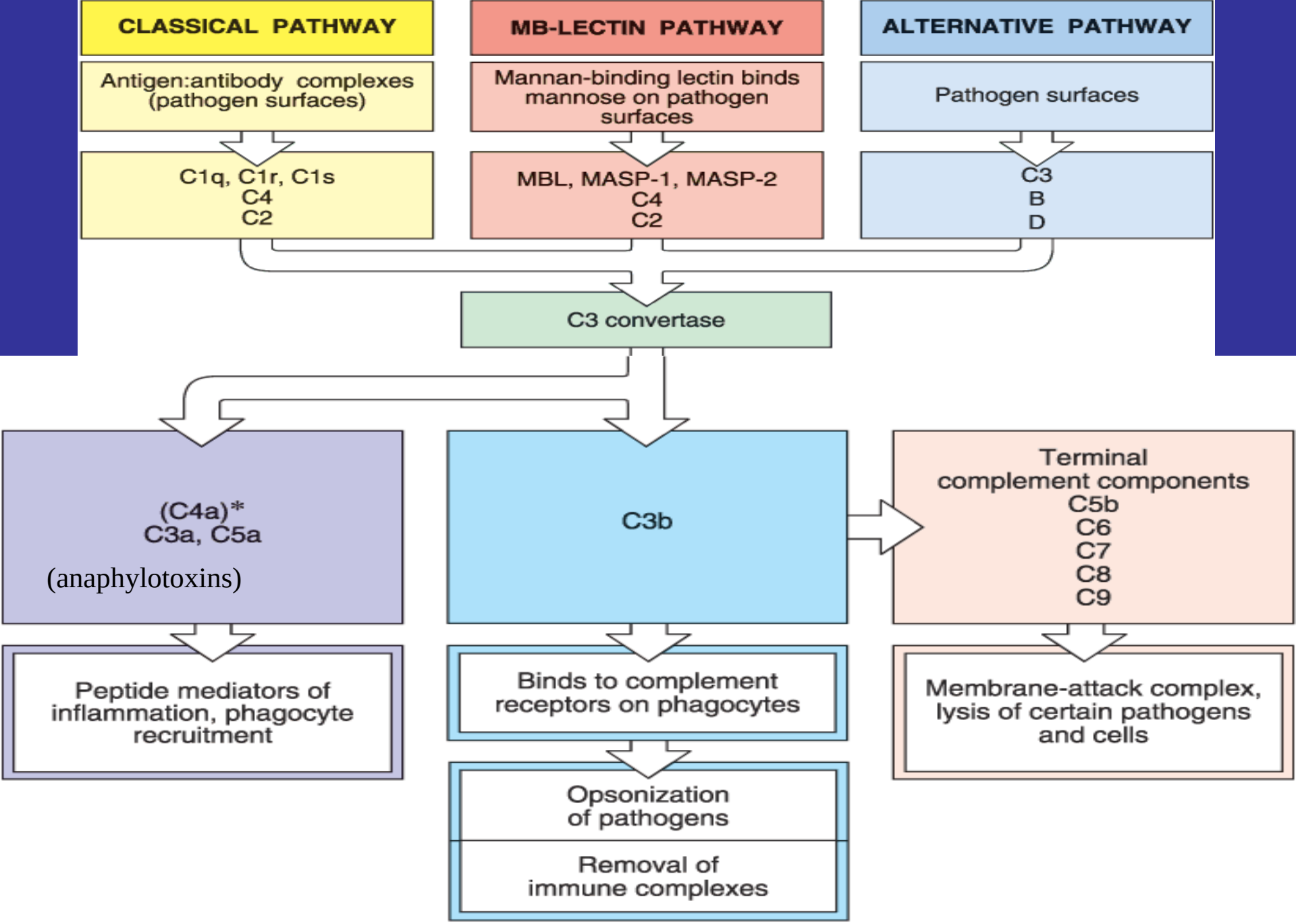


Fig 2.8 part 2 of 2 © 2001 Garland Science

Functional protein classes in the complement system	
Binding to antigen:antibody complexes and pathogen surfaces	C1q
Binding to mannose on bacteria	MBL
Activating enzymes	C1r C1s C2b Bb D MASP-1 MASP-2
Membrane-binding proteins and opsonins	C4b C3b
Peptide mediators of inflammation	C5a C3a C4a

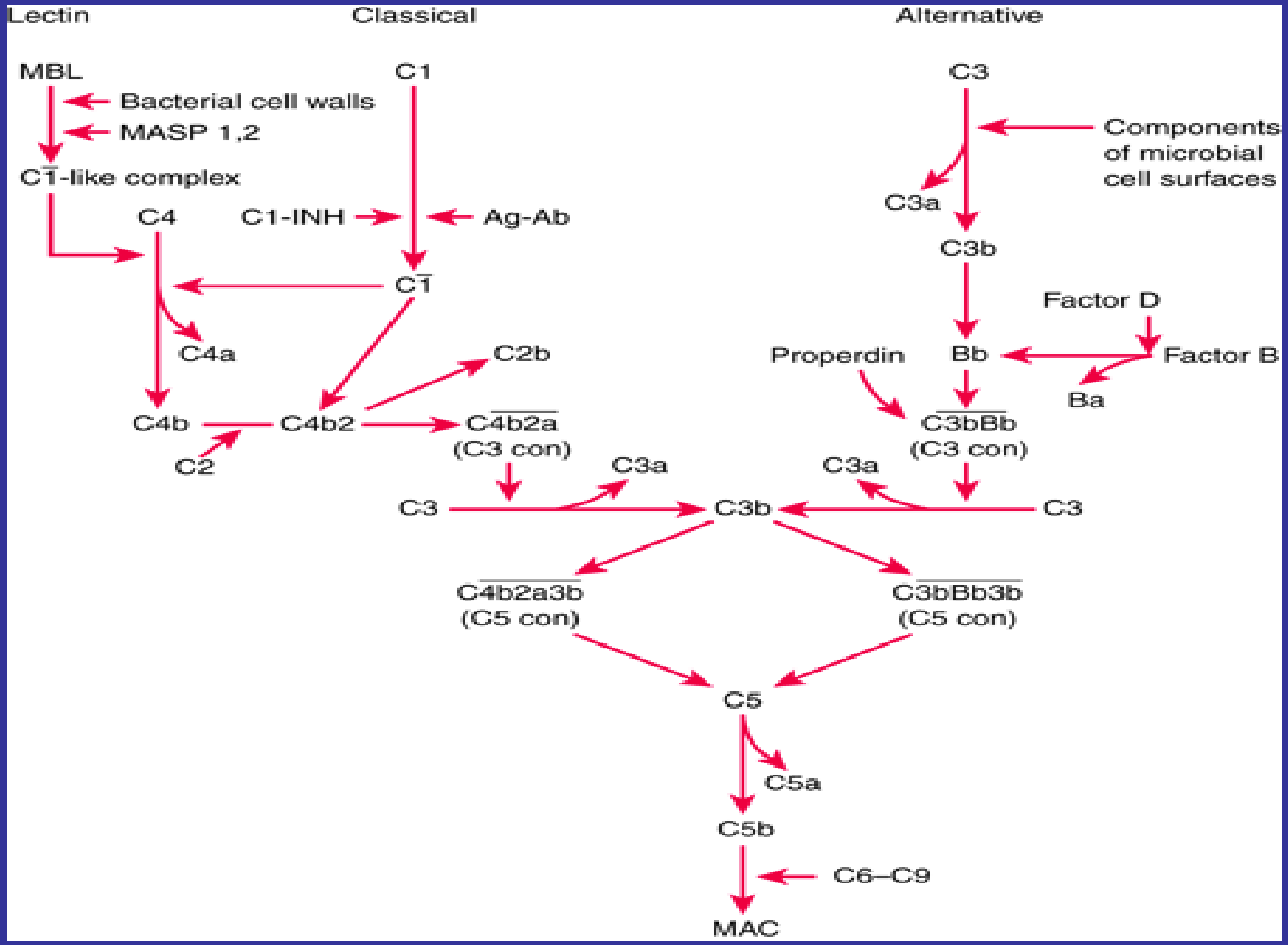
Functional protein classes in the complement system	
Membrane-attack proteins	C5b C6 C7 C8 C9
Complement receptors	CR1 CR2 CR3 CR4 C1qR
Complement-regulatory proteins	C1INH C4bp CR1 MCP DAF H I P CD59

Figure 2-20 Immunobiology, 6/e. (© Garland Science 2005)

Regulatory proteins of the classical and alternative pathways

Name (symbol)	Role in the regulation of complement activation
C1 inhibitor (C1INH)	Binds to activated C1r, C1s, removing them from C1q, and to activated MASP-2, removing it from MBL
C4-binding protein (C4BP)	Binds C4b, displacing C2a; cofactor for C4b cleavage by I
Complement receptor 1 (CR1)	Binds C4b, displacing C2a, or C3b displacing Bb; cofactor for I
Factor H (H)	Binds C3b, displacing Bb; cofactor for I
Factor I (I)	Serine protease that cleaves C3b and C4b; aided by H, MCP, C4BP, or CR1
Decay-accelerating factor (DAF)	Membrane protein that displaces Bb from C3b and C2a from C4b
Membrane cofactor protein (MCP)	Membrane protein that promotes C3b and C4b inactivation by I
CD59 (protectin)	Prevents formation of membrane-attack complex on autologous or allogeneic cells. Widely expressed on membranes

Figure 2-42 Immunobiology, 7ed. (© Garland Science 2008)


Lectin
Classical
Alternative
MBL
Bacterial cell walls
MASP 1,2
C1
C3
Components of microbial cell surfaces
C1-like complex
C4
C1-INH
Ag-Ab
C3a
C3b
C1
Factor D
C4a
C2b
Properdin
Bb
Factor B
Ba
C4b
C4b2
C4b2a (C3 con)
C3bBb (C3 con)
C2
C3a
C3a
C3
C3b
C3
C4b2a3b (C5 con)
C3bBb3b (C5 con)
C5
C5a
C5b
C6–C9
MAC