

# Nonspecific Immunity, Complement System

Jana Novotná  
Dpt. Of Medical Chemistry and Biochemistry  
The 2nd Faculty of Medicine

# Immunity = protection

- Recognition of “self” and “non-self”
- Specificity of immune response
- Memory – imprinting of some information

# Antigen

A substance that can induce an immune response

# Antibody

A protein produced as a result of introduction of antigen

Antibody has the ability to combine with the antigen that stimulated its production.

# 1. Specific immune response

A contact with antigen lead to antibody production

## **Lymphocytes**

B-cells and T-cells

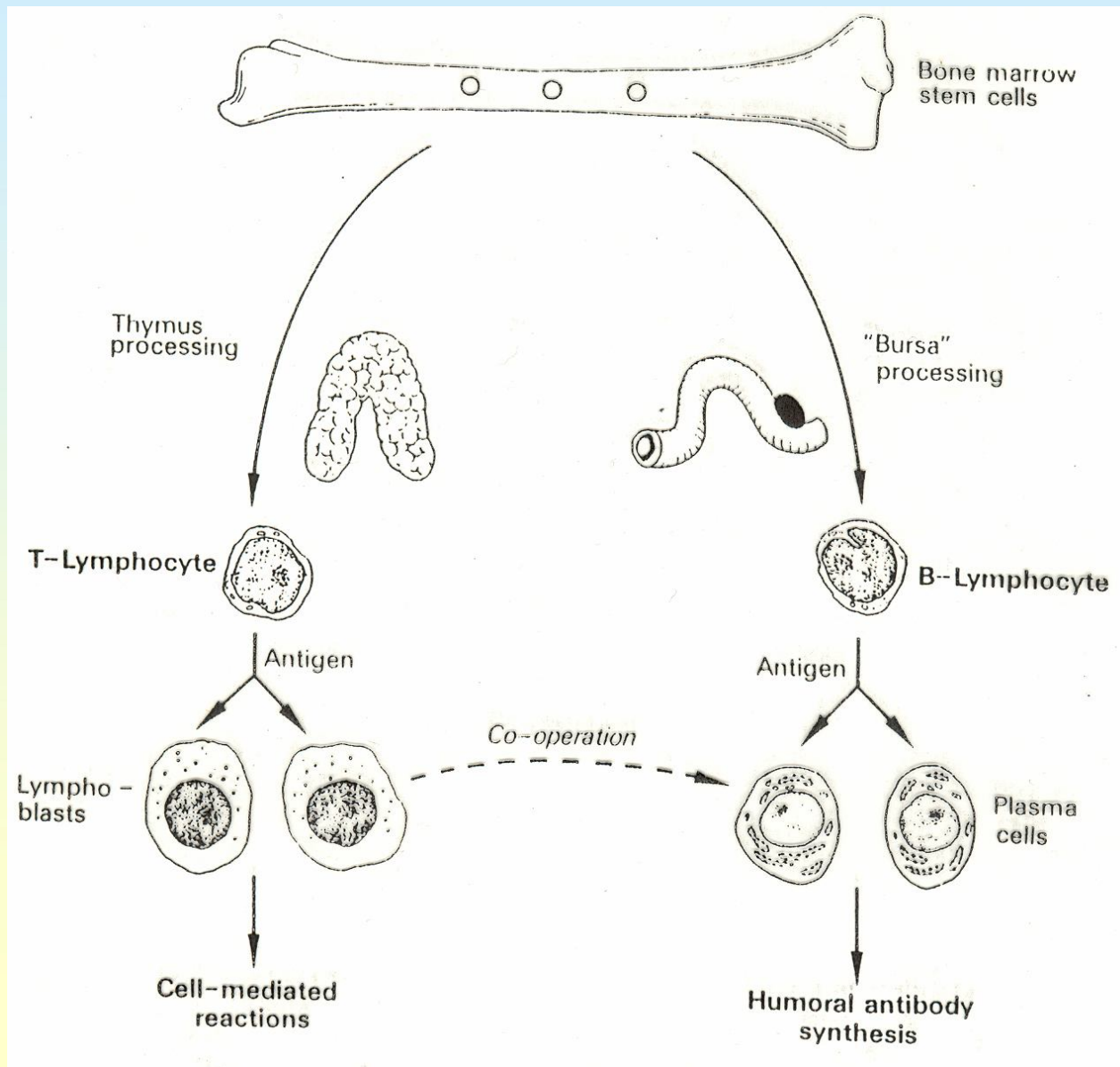
## **Phagocytic cells**

macrophages, granulocytes (neutrophiles)

# 2. Nonspecific immune system

*Complement system*

# Specific immunity



# Lymphocytes

Antigen-specific cells

Act via receptors on surface membrane

Produce specific antibodies

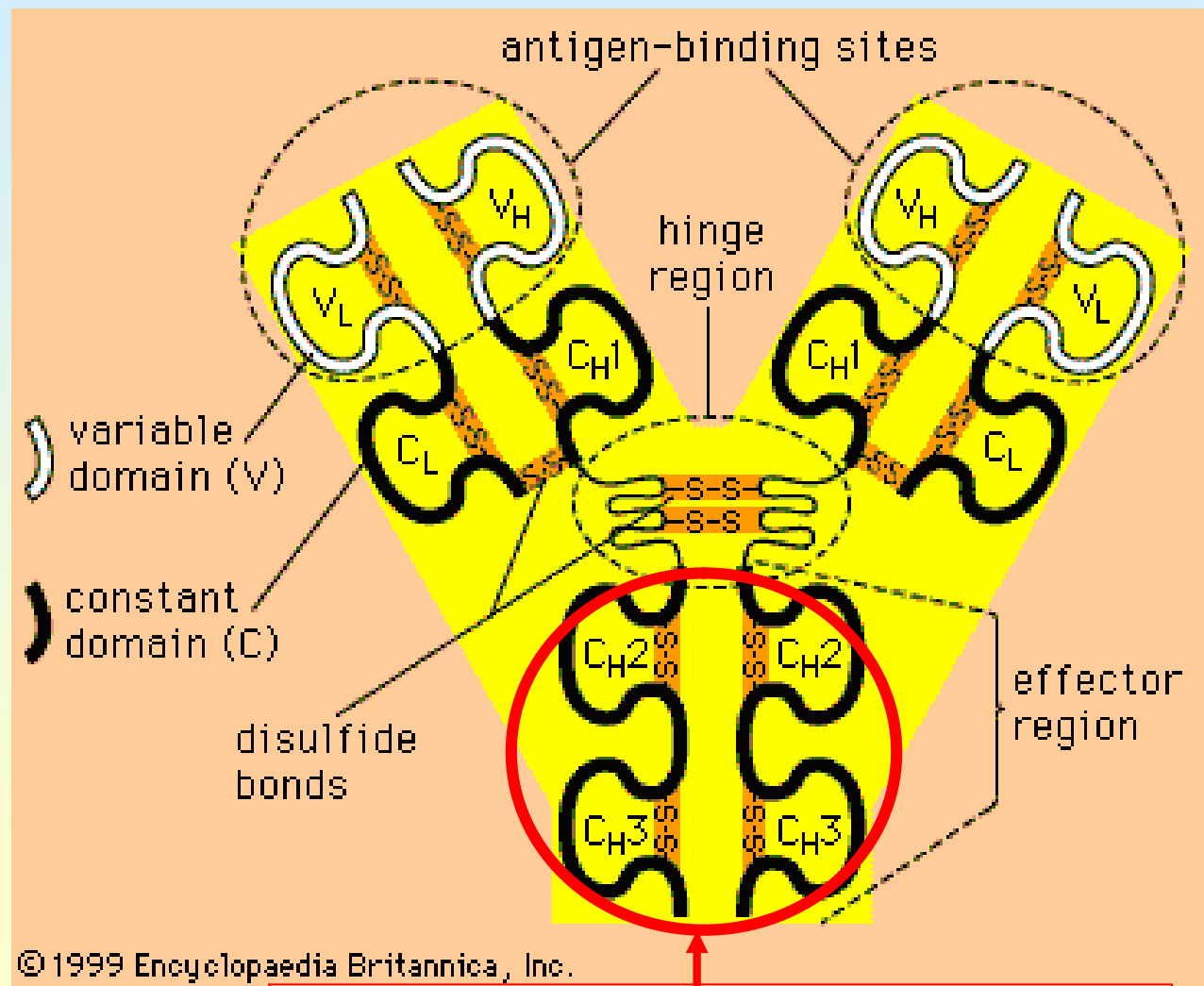
# Macrophages

Regulates lymphocyte response.

Secretes several biologically active mediators which regulate lymphocyte response (enhance or suppression of lymphocyte division or differentiation).

Macrophage-derived cells in tissues – histiocytes in connective tissue, alveolar macrophages in lung, Kupffer cells in liver, osteoclasts in bone.

# Basic structure of IgG



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**Binding site for complement component C1q**

# Complement system

- Distinguishes self from non-self
- It is the innate immunity system (the immunity one is born with).
- It is the initial response by the body to eliminate microbes and prevent infection.
- It is one of the major effector pathway of the inflammation.
- It is the biochemical cascade of proteins (enzymes) normally found in serum in constant concentration (each enzyme acts as a catalyst for the next)
- It interacts with antibody, and with cell membrane



# Complement components are produced by:

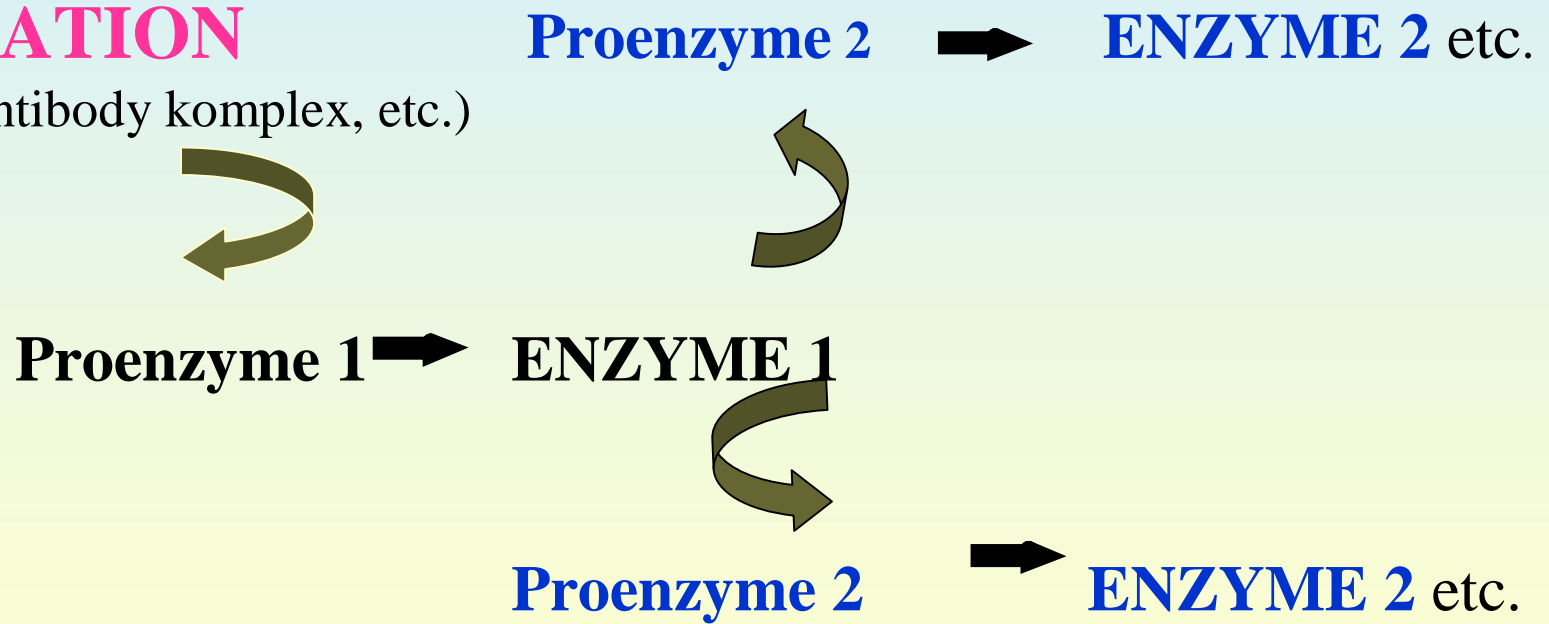
- liver (parenchyma)
- macrophages
- monocytes
- G.I. and urinary tract
- neutrophils store large quantities of some complement components

Complement components can be inactivated by heating serum at 56°C for 30 minutes (antibodies not destroyed at this temperature).

# Complement activation cascade

## ACTIVATION

(Antigen-antibody complex, etc.)



# Complement activation may occur via three pathways:

## *classical pathway*

is activated by antigen-antibody complex

## *alternative pathway*

is activated by C3b binding to microbial surfaces and to antibody molecules .

## *mannose-binding lectin pathway (MBL)*

is activated by interaction of microbial carbohydrates with mannose-binding lectin (MBL) in the plasma and tissue fluids.

# Complement system consists of about 19 proteins:

individual proteins are designated numerically with a prefix **C**: **C1** to **C9** in classical pathway

or

alphabetically: **factor B, D** in alternative pathway.

Complement proteins in classical pathway  
are called components

**C1(C1q, C1r and C1s),  
C2, C3, C4, C5, C6, C7, C8, C9**

Complement proteins in alternative pathway  
are called factors

**C3, B, D, C5, C6, C7, C8, C9**

Complement proteins in mannose-lectin binding pathway are  
called collectins (collagen like region and lectin region)

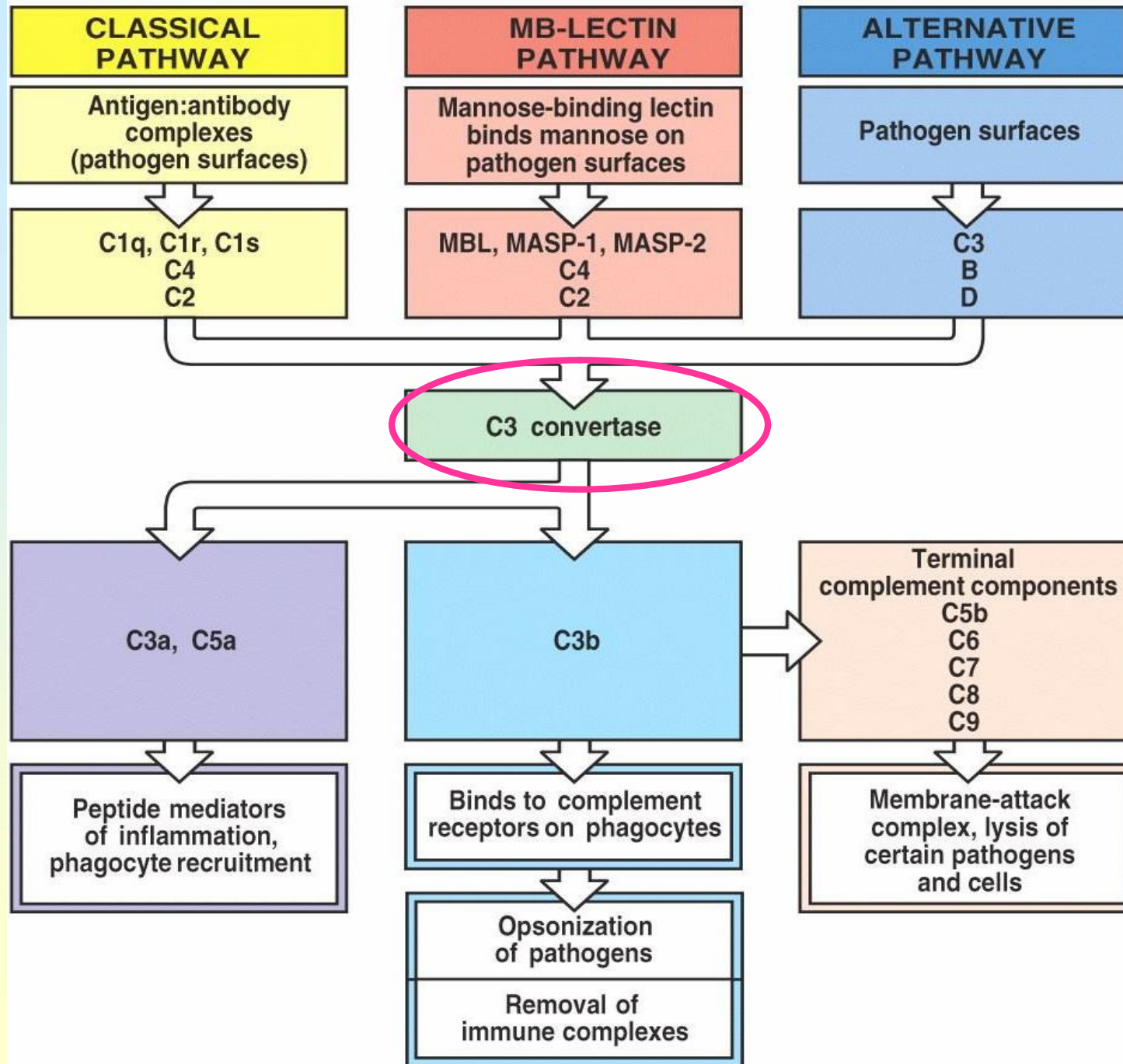


Figure 2-19 Immunobiology, 6/e. (© Garland Science 2005)



**plays the central role in  
complement activation and the  
most important thing the  
complement system does is form  
C3b from C3**

**C3** possesses internal thioester bond between cysteine (Cys 1010) and the  $\gamma$ -carboxyl of glutamate residue (Glu 1013).

**The thioester is reactive in two ways:**

1. It can be hydrolyzed by water via the „thioester mechanism“.
2. It can be hydrolyzed by reactive groups, such as amines and hydroxyls in proteins or carbohydrates – major constituents of biological surfaces.



# Classical pathway

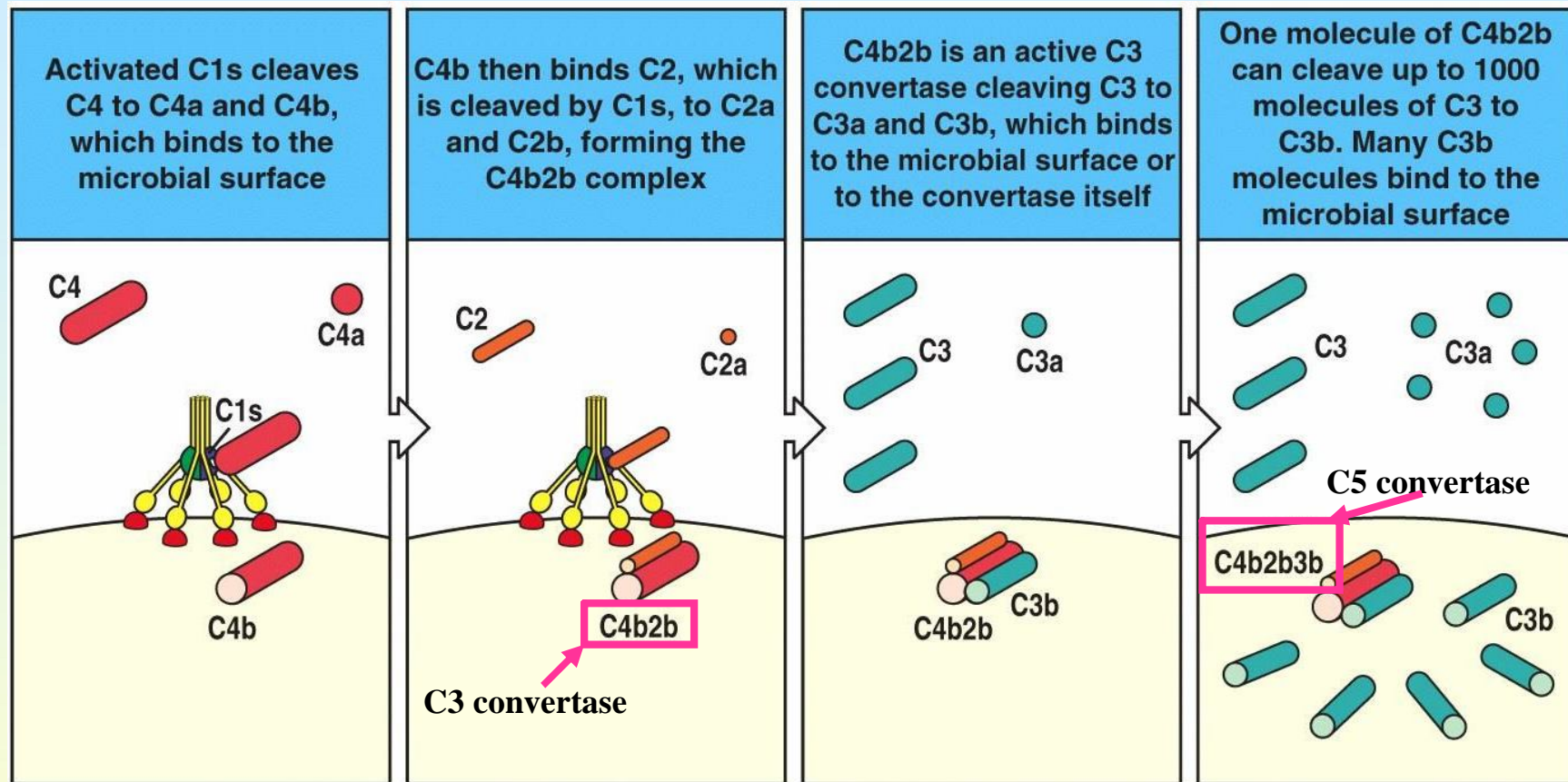
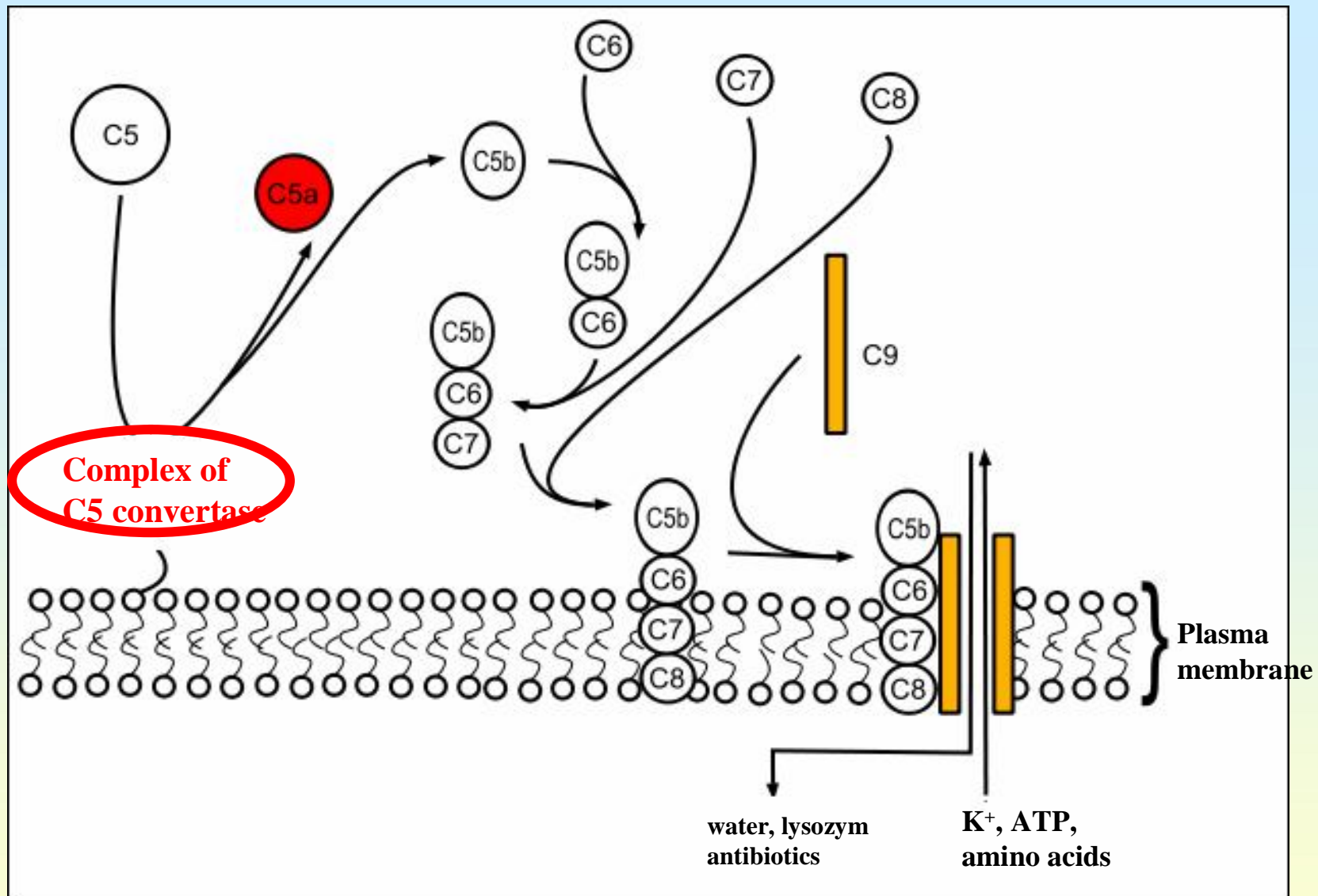


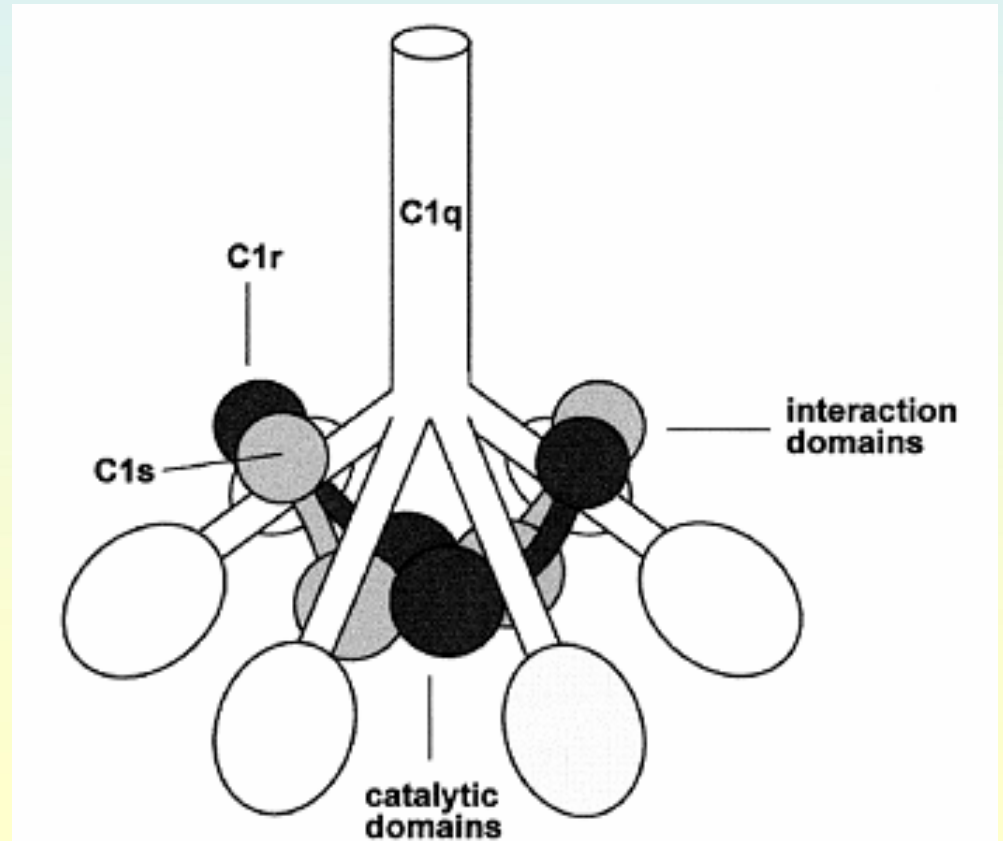
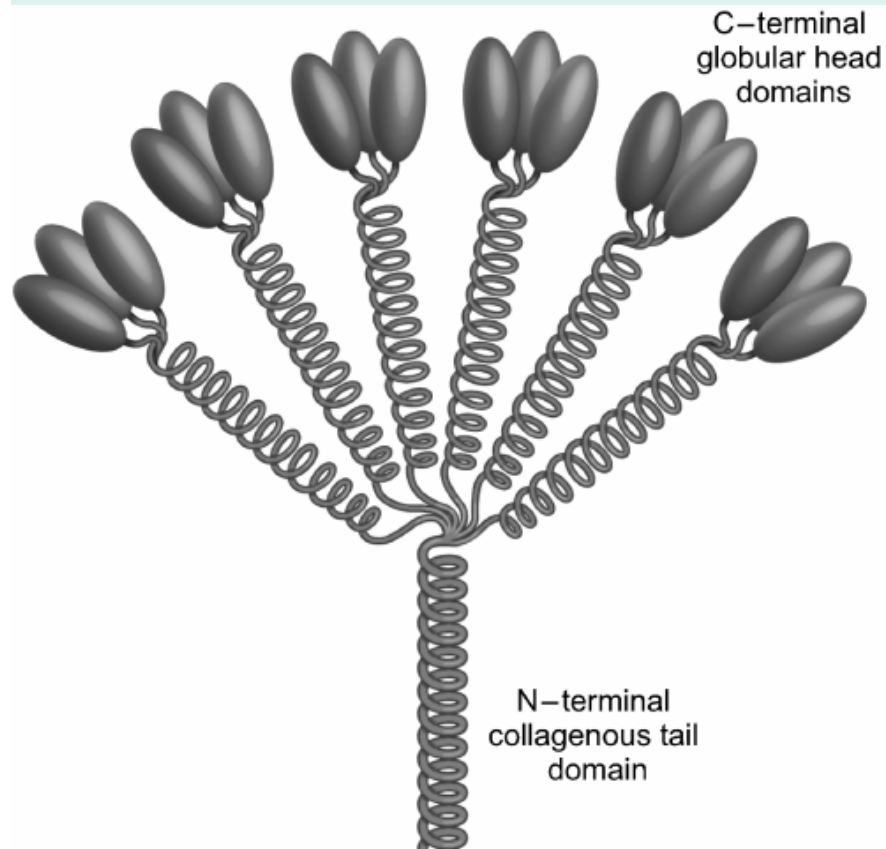
Figure 2-22 Immunobiology, 6/e. (© Garland Science 2005)

1. **C1** binds to antibody in cell membrane , **C1** = esterase which cleavages **C4** to **C4a** and **C4b**.
2. **C4b** = esterase which cleavages **C2** to **C2a** and **C2b** .
3. **C4b** and **C2b** form complex enzyme which cleavages **C3** (convertase. **C4b2b**)  
**C3a** is anaphylatoxin, i.e., hormone-like peptide induces smooth muscle contraction, enhance vascular permeability, release vasoactive amines such as histamin.

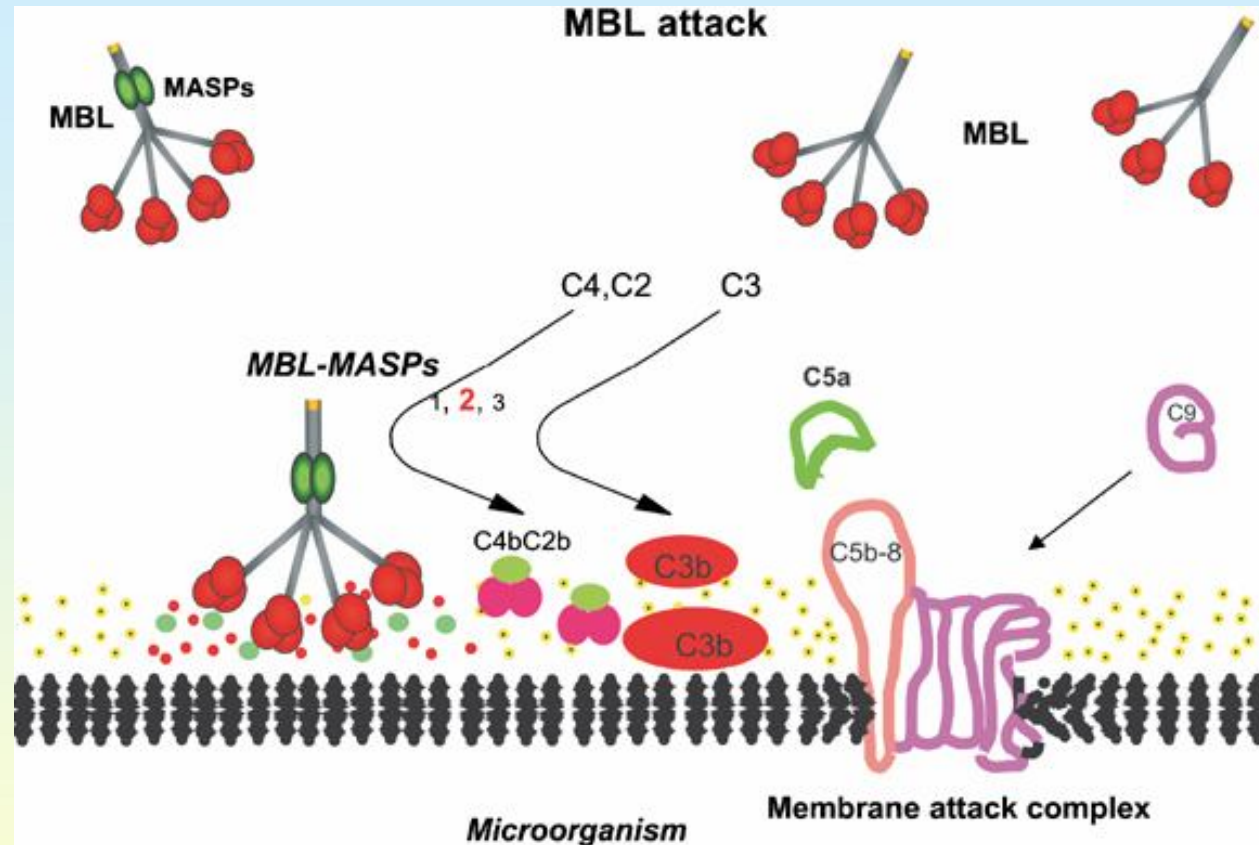


4. C4b2b3b is enzyme which cleavages **C5** (**C5 convertase**). **C5a** is chemotactic for polymorphonuclear leucocytes.
5. **C5b** binds **C6** and **C7**. **C5bC6C7** complex binds **C8**.
6. C5bC6C7C8 complex binds **C9** which generate cell membrane damage.

# Structure and the binding domains of C1q



# Mannose-binding lectin pathway



1. MBL in the blood complexes with a serine protease called MASPs (MBL-associated serine proteases).
2. When MBL binds to mannose on the surface of a bacterium the MASP protein functions like a convertase cut C3 into C3a and C3b.
3. The C3b fragments can then bind to the surface of the bacterium can cause the complement cascade.



# Structure of mannose binding lectin

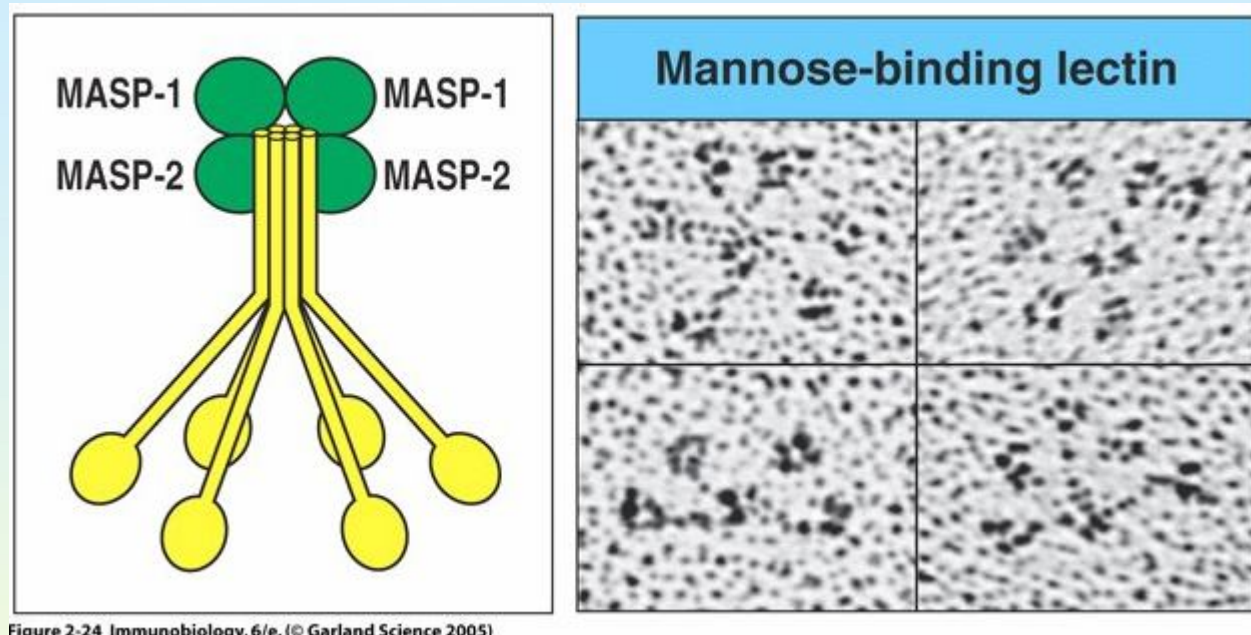
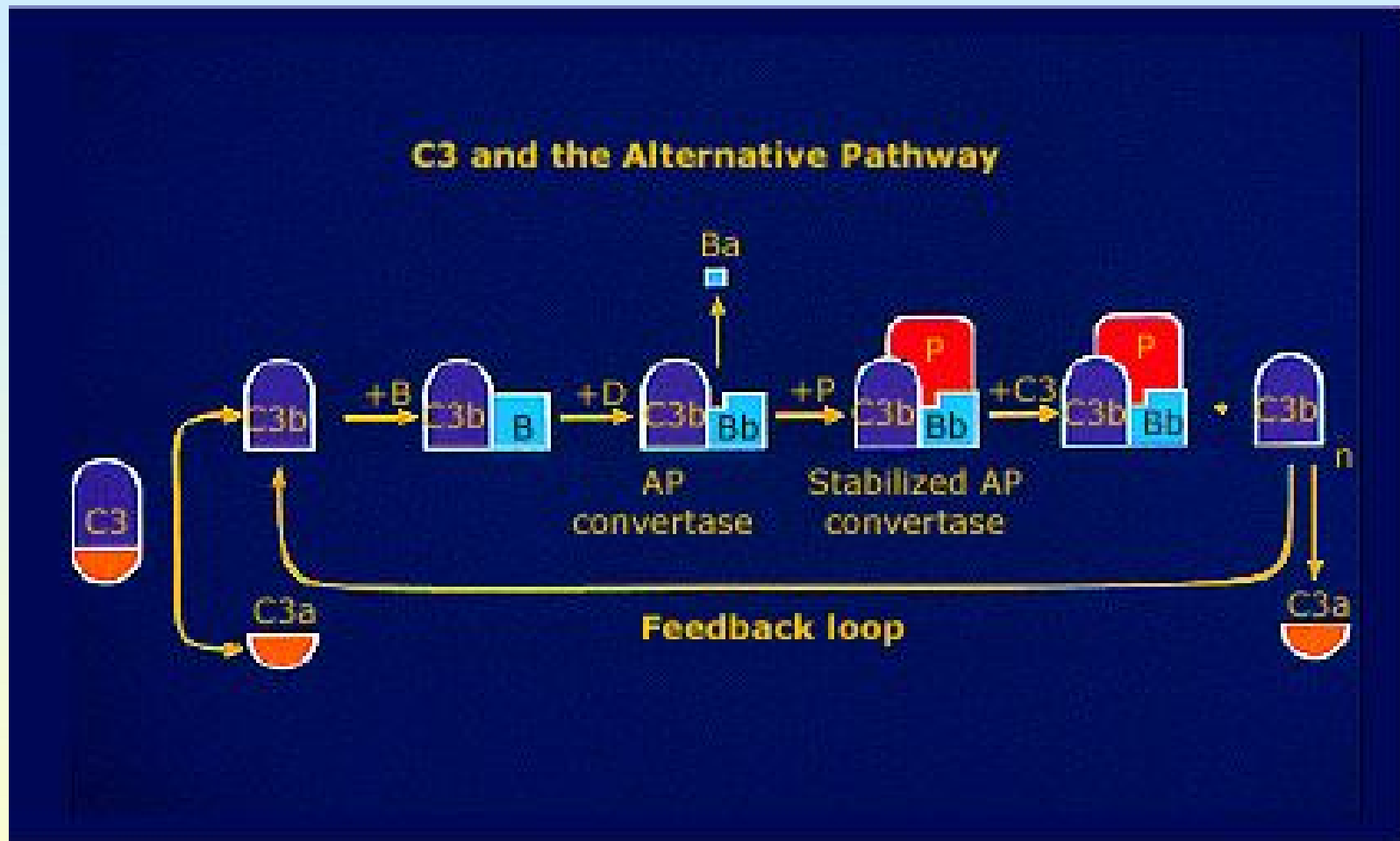


Figure 2-24 Immunobiology, 6/e. (© Garland Science 2005)

- MBL forms clusters of two to six carbohydrate-binding heads around a central collagen-like stalk.
- MBL complexes with MBL-associated serine proteases 1 (MASP-1) and 2 (MASP-2).
- On binding of MBL to bacterial surfaces, these serine proteases become activated and can then activate the complement system by cleaving and activating C4 and C2.

# Alternative pathway



After **C3b** is generated, it can bind to factor **B**. Factor **D** can then cleave factor **B** to form the **C3 convertase** (**C3bBb**). The attachment of **properdin** (**P**) stabilizes the complex and allows it to generate more **C3b**. The end result is the deposition of large amounts of **C3b** on the pathogen. Adapted from Liszewski, MK, Atkinson, JP. The complement system. In: Immunology Scope Monograph, Schwartz, BD (Ed), Upjohn, Kalamazoo, 1992.

# The function of major proteins of complement system

- 1. *Opsonisation*:** C3b and, to a lesser degree, C4b molecules are opsonins. They coat foreign organisms, enhancing their phagocytosis because phagocytes have receptors that recognize complement proteins bound to pathogen.
- 2. *Inflammation*:** The C5a and, less potently, the C4a and C3a fragments are important inflammatory activators inducing vascular permeability, recruitment and activation of phagocytes.

**3. *Lysis:*** C5b binds and recruits C6 and C7 to the target surface. C7 and subsequently C8 change conformation to expose hydrophobic domains which insert in the lipid bilayer. The C5b678 complex catalyses the polymerisation of the final component C9 which forms a transmembrane pore of ~ 10nm diameter causing lysis of the cell. This macromolecular assembly is known as the Membrane Attack Complex (MAC).

**4. *Immune complex clearance:*** Complement has a very important role in solubilising and causing removal from the circulation of immune complexes. It does this by the binding of C4b and C3b, covalently bound to the immune complex, to CR1 complement receptors on red blood cells which transport the complexes to the liver and spleen where they give the complexes up to phagocytes for destruction.



# Main function of component cleavages:

## *1. Complement-mediated chemotaxis*

**C5a** is chemotactic for all types of phagocytic cells

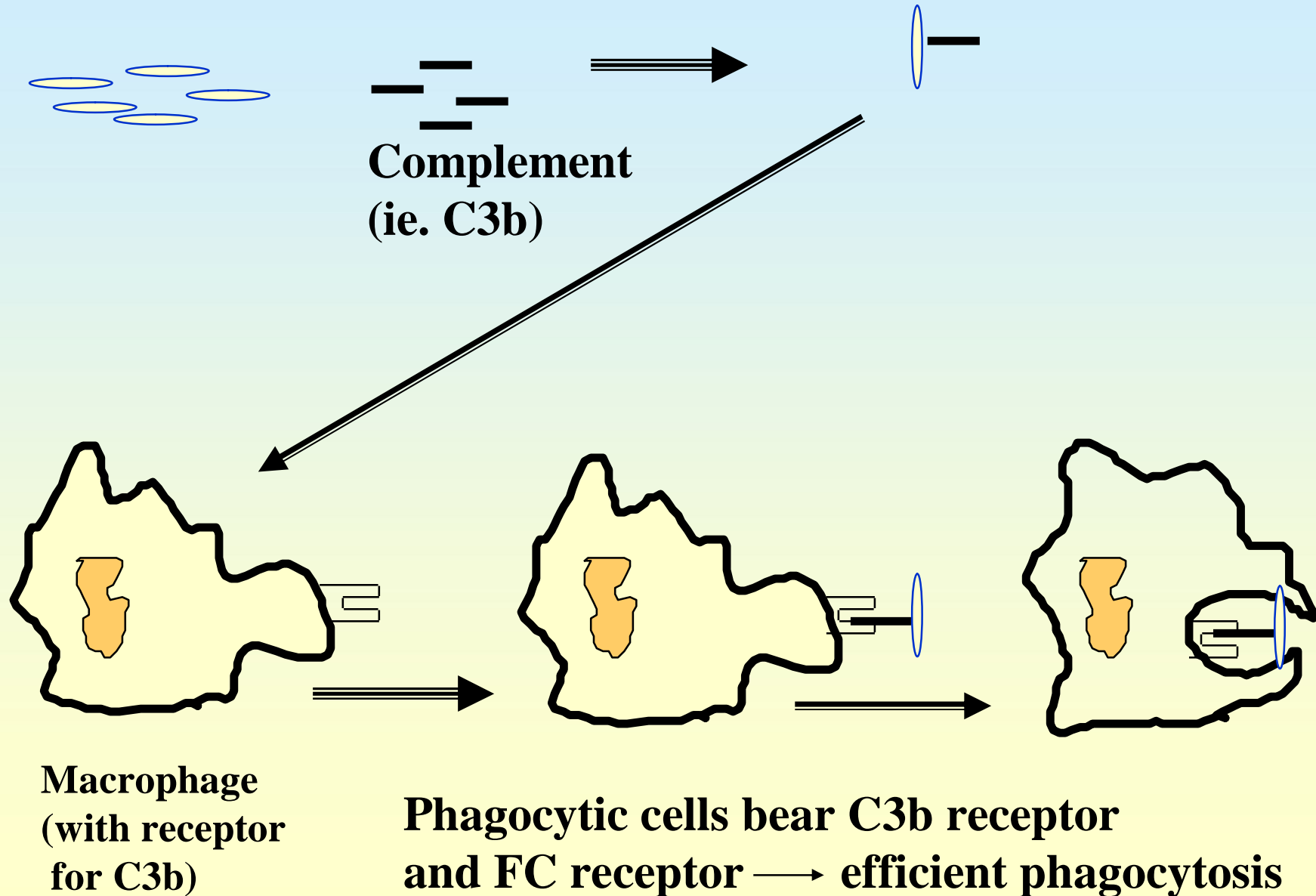
- (neutrophils, eosinophils, macrophages, basophils)
- stimulates “respiratory burst” of neutrophils

**C3a, C4a and C5a** are **anaphylatoxins**

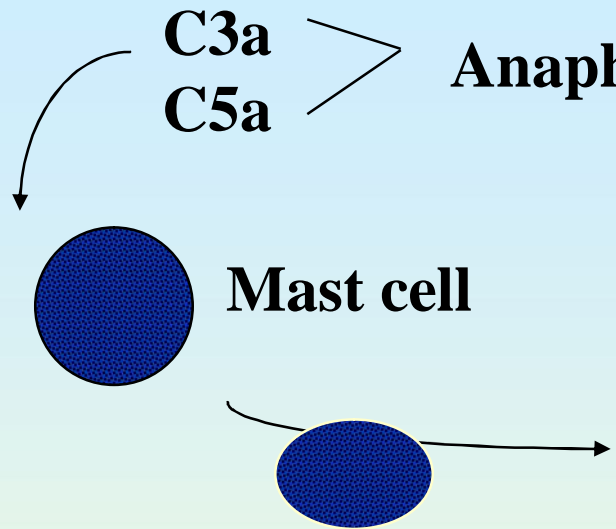
hormone like peptides cause smooth muscle contraction, vascular permeability, release of histamin from mast cells and basophils and lysosomal enzymes release from granulocytes.

## 2. Complement-mediated opsonization

Phagocytosis: phagocytic cells have C' receptors



### 3. Complement-mediated inflammation



- Cause smooth muscle ( lung and intestinal wall) to contract.

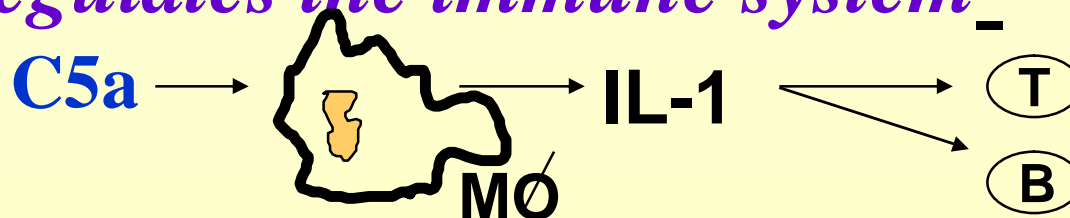
- Mast cells degranulate releasing vasoactive amines.

- Vascular permeability resulting in EDEMA.

### 4. Removal of immune complexes

↑ Phagocytosis

### 5. Regulates the immune system



# Anaphylatoxins and disease

## Target

Smooth muscle

Mast cells

Blood capillary wall

Vascular endothelium

Leukocytes

Platelets

Immune response

## Effect

Contraction

Histamine release

Increase in vascular permeability

Increased adhesiveness for leukocytes

Adhesion, aggregation, chemotaxis,  
release of lysosomal enzymes,  
generation of oxygen radicals

Aggregation, release of serotonin

**C3a**:suppression

**C5a**:enhancement