The Complement System

Part 1

Definition

The **complement system**, also known as **complement cascade**, is a part of the immune system that *enhances (complements)* the ability of antibodies and phagocytic cells to clear microbes and damaged cells from an organism, promote inflammation, and attack the pathogen's cell membrane.

Introduction

-- The **complement system** is a **biochemical cascade**.

-- It is a **complex system of serum proteins.**

-- Many components are **serine proteases** which activate each other **sequentially**.

Cascade: A sequence of successive activation reactions involving enzymes (enzyme cascade) or hormones (hormone cascade) characterized by a series of amplifications of an initial stimulus.

-- The **complement system** belongs to the **innate immune system**.

-- However, it can be recruited and **brought into action by the adaptive immune system.**

Functions of complement

1. Lysis:

The components of complement cascade **attach directly to their receptors** on cell surface and **dissolve** the cell wall (e.g. invading bacteria) or the cell membrane (e.g. of dying cells)

2. Opsonization:

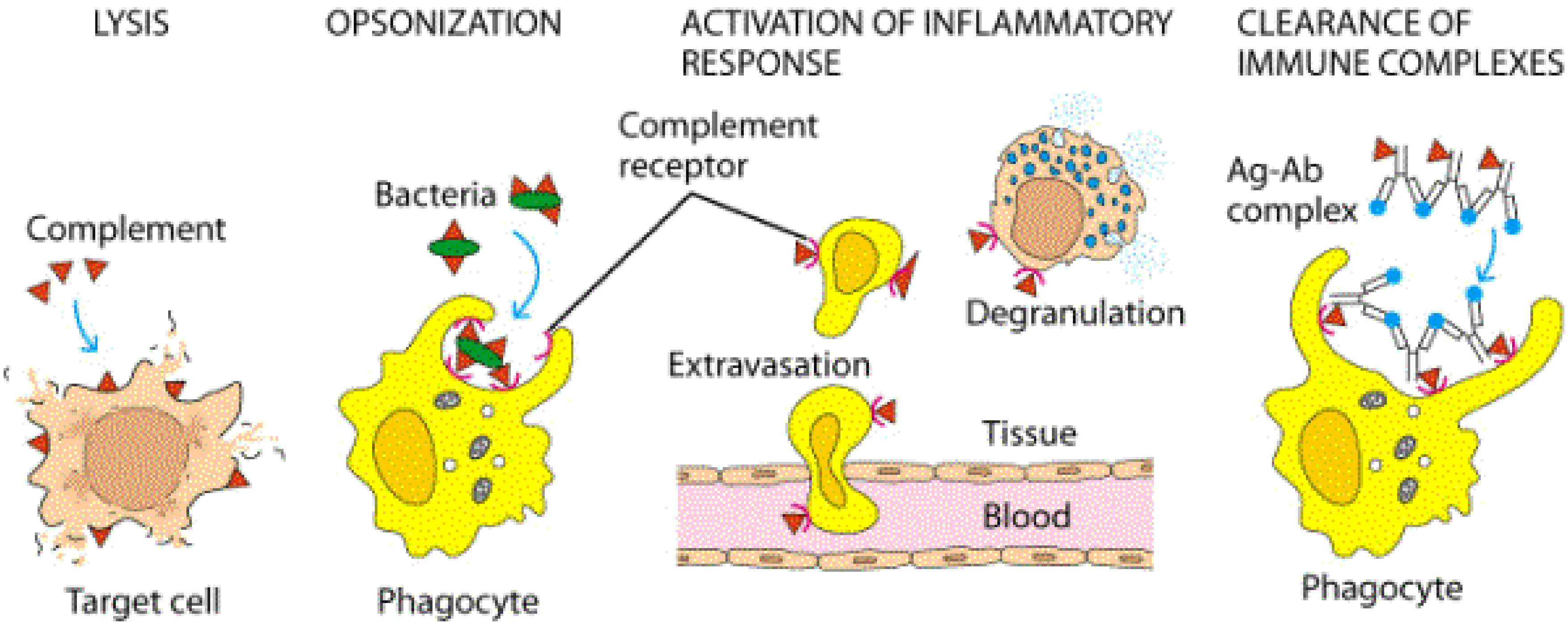
The complement components **cover** the surface of invading pathogen and this complex **gets attached** to the complement receptors on the surface of phagocytes, who engulf and destroy it.

3. **Activation of inflammation**

   Complement components help activation of inflammation by attaching themselves to the surface of the **macrophages** and helping them to **travel between blood and tissue** through capillary walls (**extravasation**). Similarly they attach to the surface of granulocytes and release their toxic granules by dissolving the cell membrane.

4. **Clearance of immune (antigen- antibody) complexes:**

   It is similar to opsonization. Complement components **attach to circulating antigen- antibody complexes** and bring them to phagocytes for destruction.


LYSIS
OPSONIZATION
ACTIVATION OF INFLAMMATORY RESPONSE
CLEARANCE OF IMMUNE COMPLEXES
Complement
Target cell
Bacteria
Phagocyte
Complement receptor
Degranulation
Extravasation
Tissue
Blood
Ag-Ab complex
Phagocyte

Components of complement

-- There are **more than 30 components** of complement system.

-- These are **synthesized** primarily by **liver hepatocytes** and form nearly **5% of serum globulins**.

-- Most of these components circulate as inactive **proenzymes** (**zymogens)** until cleaved into active parts.

-- This **cleavage** of proenzymes **release cytokines** needed for **activation** of complement system.

C3

-- **C3** is the **key component** of complement.

-- It is an **abundant** serum protein (1.2 mg/ml).

-- It contains an unusual internal **thioester bond**.

thioester crosslink is usually formed between a cysteine side chain and the carboxamide group of an asparagine or glutamine side chain.

-- In **native C3**, thioester bond is **stable** but this bond can become **highly reactive** as a result of **conformational changes** in the structure of **C3**.

-- Generally the **activation** of **C3** comes about as a result of **proteolytic cleavage** of the **C3** molecule into **2** biologically active fragments, **C3a** and **C3b**.

  -- **C3a** is responsible for **immunological activity**.

  -- Main function of **C3b** is **opsonization.** It also has a role in immunological activity.

This is a small soluble fragment

It leads to increased vascular permeability
and recruitment and activation of phagocytes.
of the microorganisms by PMN and macrophages.

C3 ⟶ C3b +C3a

This is the large fragment and contains the now highly reactive thiolester.

It acts mainly by covalently tagging bacteria etc .

The C3b tag enhances the recognition, phagocytosis and killing
of the microorganisms by PMN and macrophages.

This tagging is called opsonisation.

Pathways of complement action

There are three pathways of complement action:

1. **Classical pathway**
2. **Alternative Pathway**
3. **Mannose-binding lectin pathway**

-- The components of the **classical pathway** are called **C1, C2, C3** etc.

Where components are **proteolytically cleaved**, the products are referred to as **C2a + C2b** etc.

-- **Alternative Pathway** specific components are given **letters** as names (**factor B** **etc.**).

-- **Mannose-binding lectin pathway** components are named by **abbreviations**, e.g., **MASP-1, MASP-2**, or **full names** such as **collectin-10**.

-- The **classical pathway** is activated by **antibody-antigen complexes.** So it is **antibody-dependent.**

-- The **alternative pathway** is initiated when a **previously activated** complement component binds to the **surface of a pathogen.** It activates complement in an **antibody-independent** **fashion.**

-- The **mannose-binding lectin pathway** also activates complement in an **antibody-independent** **fashion.** It involves binding of mannose-binding lectin in serum to mannose residues on the surface of the pathogen.

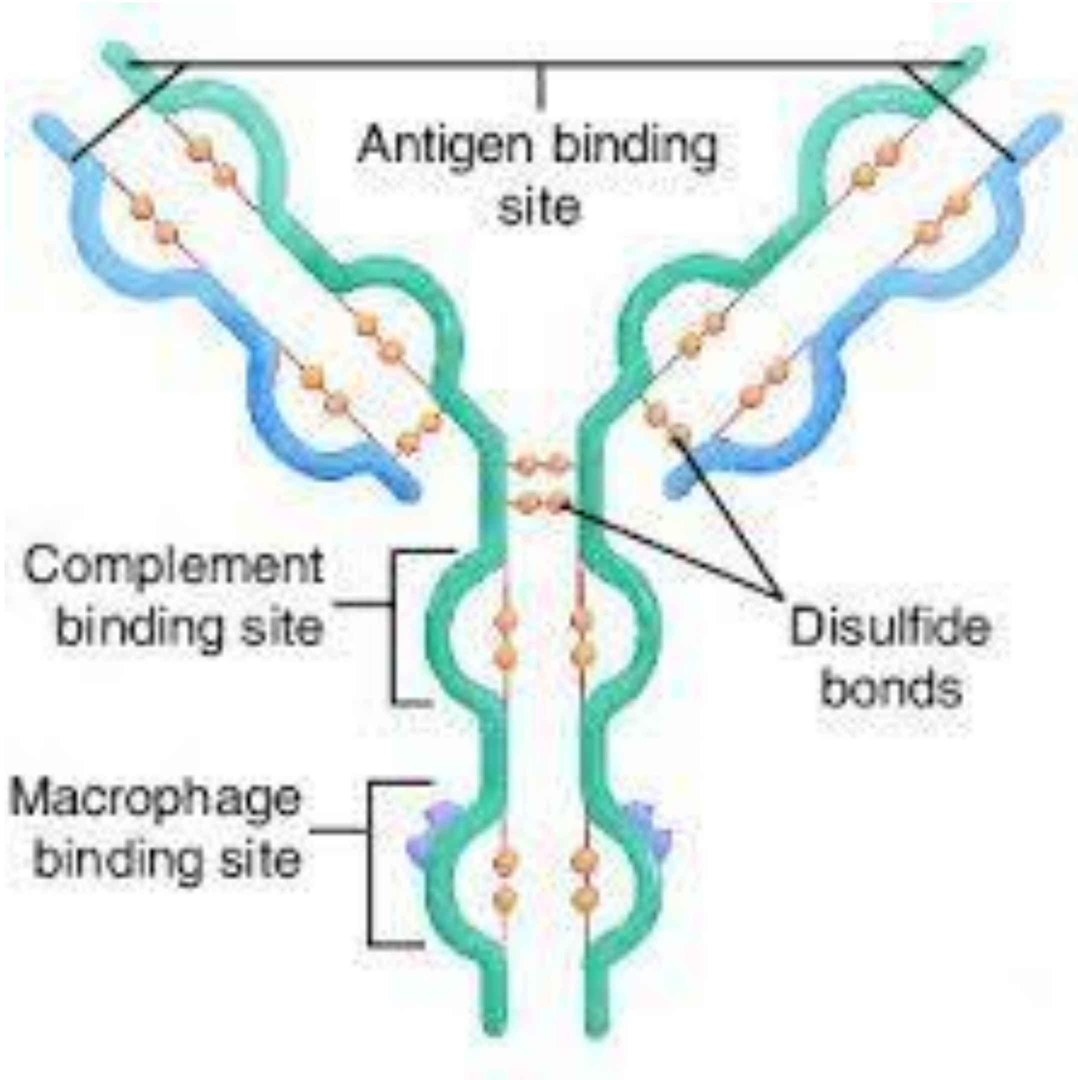
Classical pathway of complement activation

-- **Complement** is **activated** either by the formation of:

-- **soluble Ag-Ab complexes**

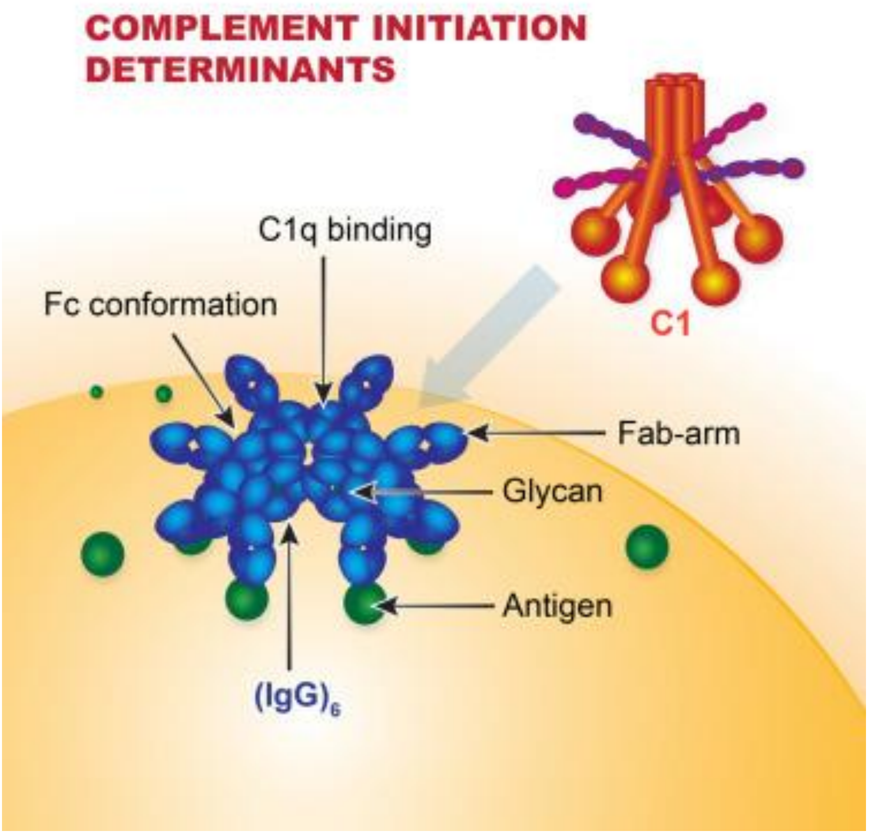
-- or by binding of **Ab** (IgM or IgG1,2,3) to **Ag on a target cell.**

-- This activation of complement happens because **Ag-Ab complexes** induce conformational change in **Ab** exposing binding sites for **C1** components.


Antigen binding site
Complement binding site
Disulfide bonds
Macrophage binding site

For example:

IgM/IgG attachment to antigen exposes **3 binding sites** for**C1q**.

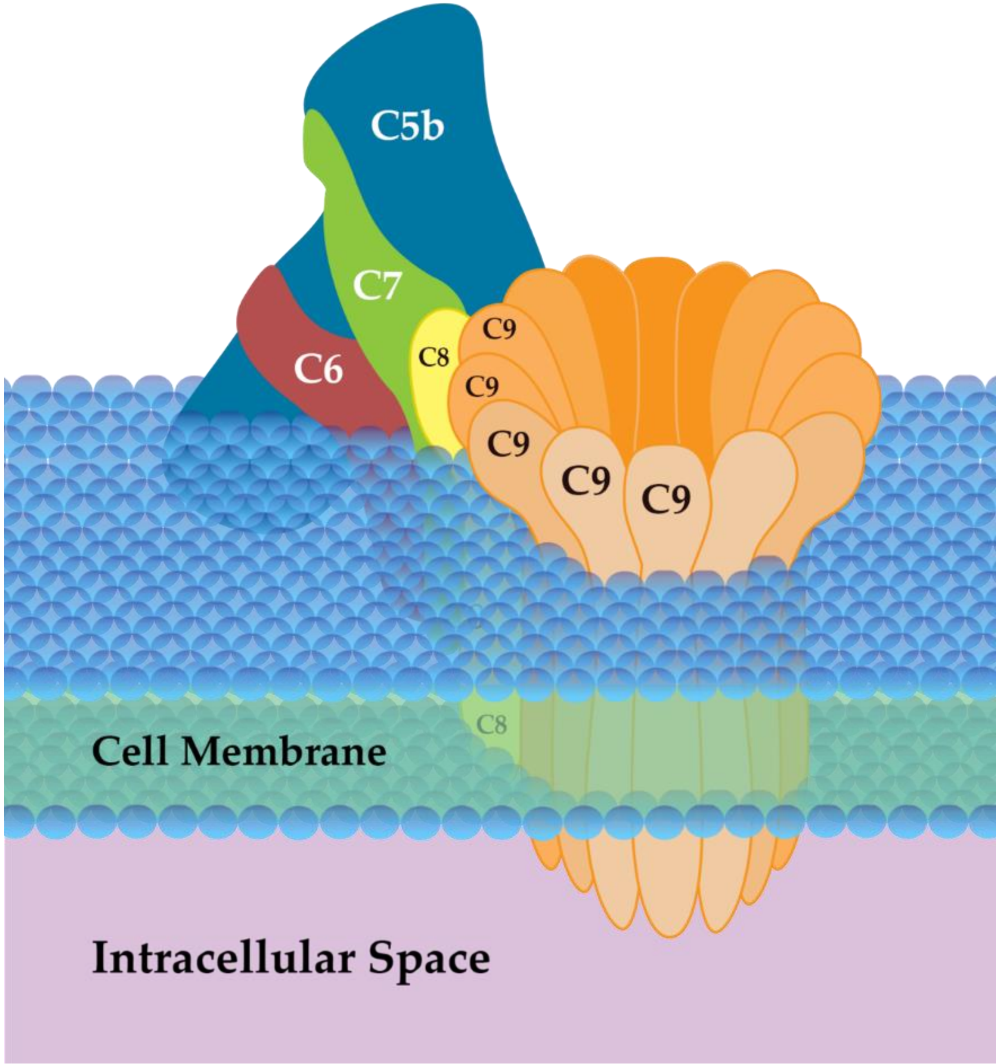


-- Due to attachment of **C1q** to antibody (which is attached to antigen on the cell surface), **C5 convertase** is produced by the cell, which **cleaves C5** to **C5a** and **C5b**.

-- **C5a** is an **anaphylatoxin** and a **chemotactic factor**.

-- **C5b** binds to **C6** and **C7** to form a complex that interacts with **C8** and **C9** to produce **membrane attack complex** which causes **cytolysis**.

Membrane Attack Complex



Classic Pathway

Components of the Classical Pathway

Native component	Active component(s)	Function(s)
C1(q,r,s)	C1q	Binds to antibody that has bound antigen, activates C1r.
	C1r	Cleaves C1s to activate protease function.
	C1s	Cleaves C2 and C4.
C2	C2a	Unknown.
	C2b	Active enzyme of classical pathway; cleaves C3 and C5.
C3	C3a	Mediates inflammation; anaphylatoxin.
	C3b	Binds C5 for cleavage by C2b. Binds cell surfaces for opsonization and activation of alternate pathway.
C4	C4a	Mediates inflammation.
	C4b	Binds C2 for cleavage by C1s. Binds cell surfaces for opsonization.

Alternative Pathway of Complement activation

-- It **does not** require Ag-Ab complex formation.

-- It is initiated by **foreign cell surface proteins** such as bacterial polysaccharides, fungal cell walls and viral envelopes.

-- These foreign proteins induce the formation of a complex between ***preformed*** **C3** and **factor B** (already present in serum).

-- This complex is cleaved by protease **factor D** (which is also present in the serum) to produce **C3b,** and **Bb**.

-- These fragments act as **C3 convertase** to generate more **C3b** which is needed for opsonization of invading pathogens.

Mannose-binding lectin pathway

-- It is also an **antibody-independent pathway.**

-- It is activated by attachment of **mannose-binding lectin** in our body to **mannose** residues found on surface of invading microbes.

-- This binding activates **MASP-1** and **MASP-2** (Mannan-binding lectin serine protease 1 and 2) that cleave and activate **C2** and **C4.**

-- These components in turn activate the **classical pathway.**

-- This process **bypasses** the **antibody-requiring step** and so it is protective **early** in infection before antibody is formed.

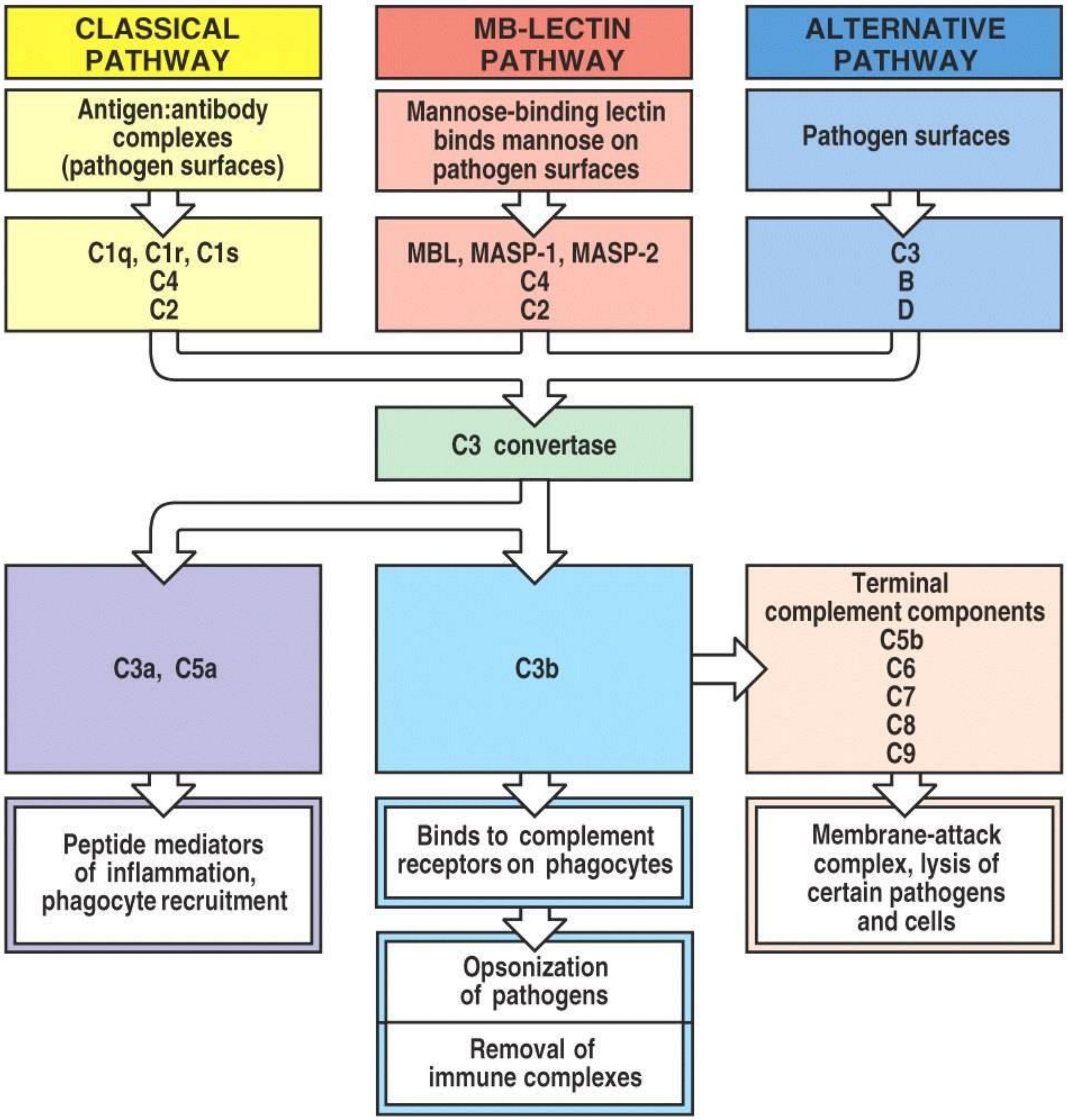
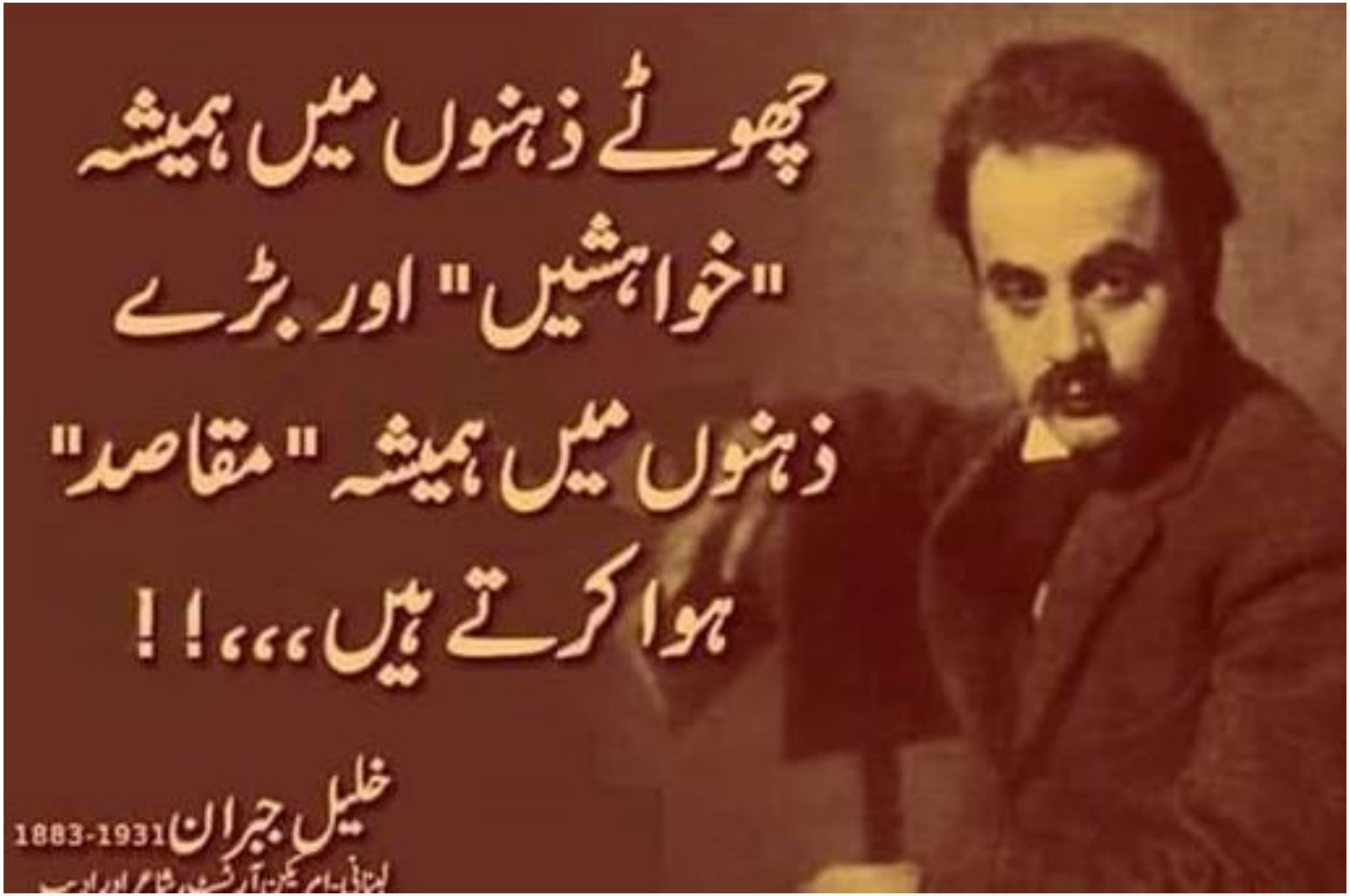


Figure 2-19 Immunobiology, 6/e. (© Garland Science 2005)



چھوٹے ذہنوں میں ہمیشہ
"خواہشیں" اور بڑے
ذہنوں میں ہمیشہ "مقاصد"
ہوا کرتے ہیں،،، !!
خلیل جبران
1883-1931


Thank You!