

# **HUMORAL IMMUNE RESPONSE**

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# ENTRY OF PATHOGEN



First line of defense - Innate Immunity



Second line of defense - Adaptive Immunity

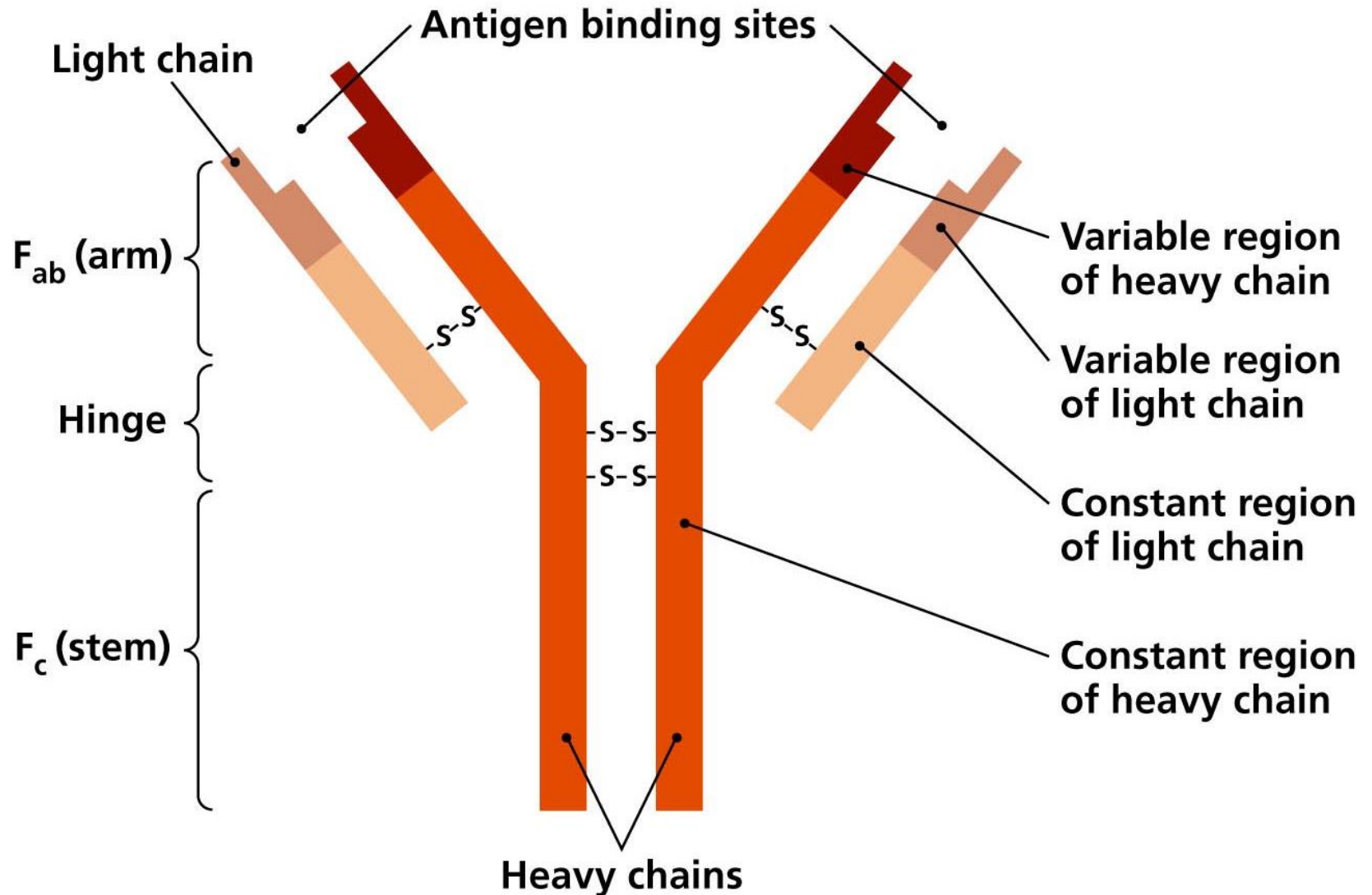
# TYPES OF ADAPTIVE IMMUNITY

Humoral	Cell Mediated
By antibodies produced by B lymphocytes	By Activated T lymphocytes
Against extracellular microbes / toxins	Against intracellular microbes

# Humoral immune response

- Mediated by antibodies
- Antibodies are produced by plasma cells derived from B lymphocytes
- Principal defense mechanism against extracellular microbes and their toxins

# Antibody Structure

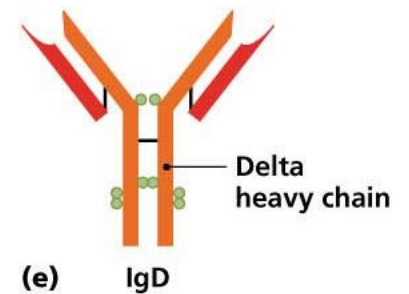
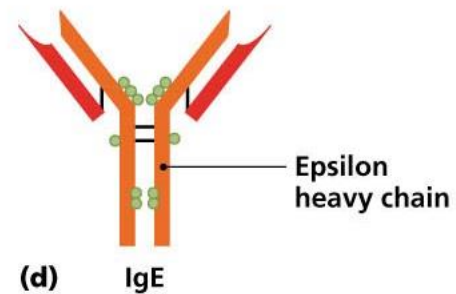
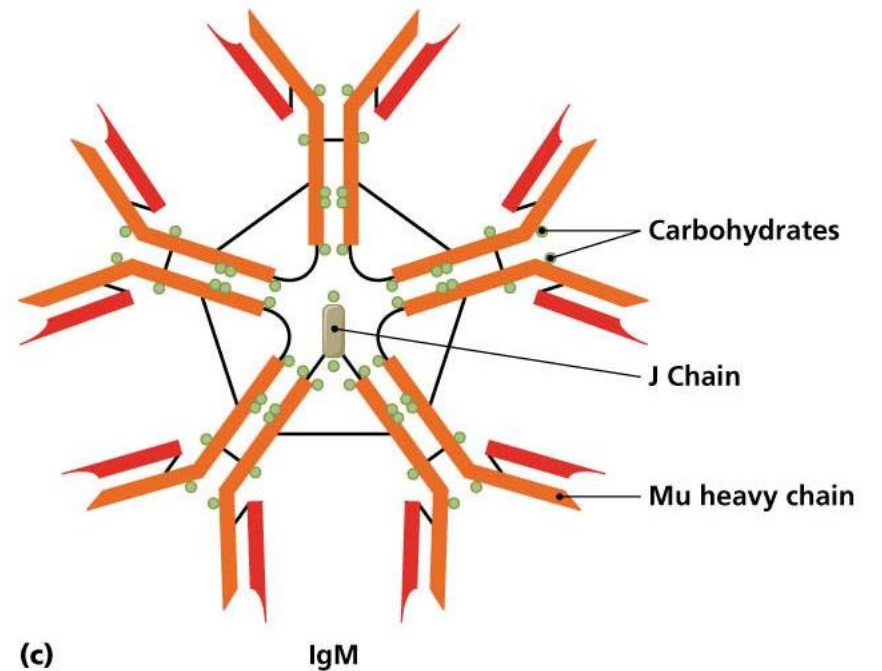
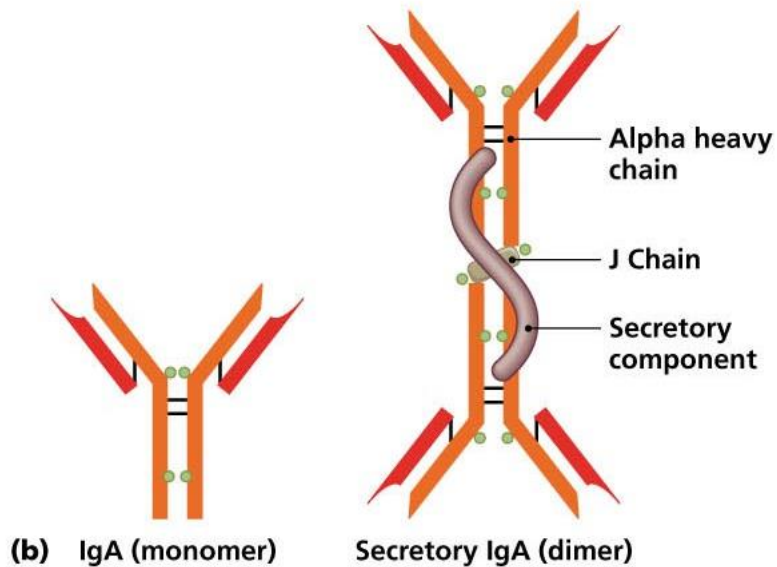
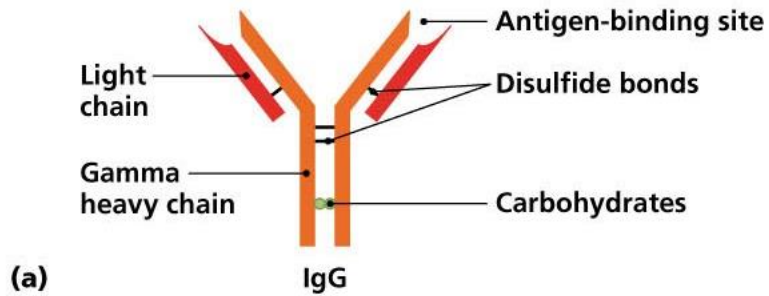


- Variable region binds to a different antigens
- Constant regions fall into five classes

# Classes of antibodies

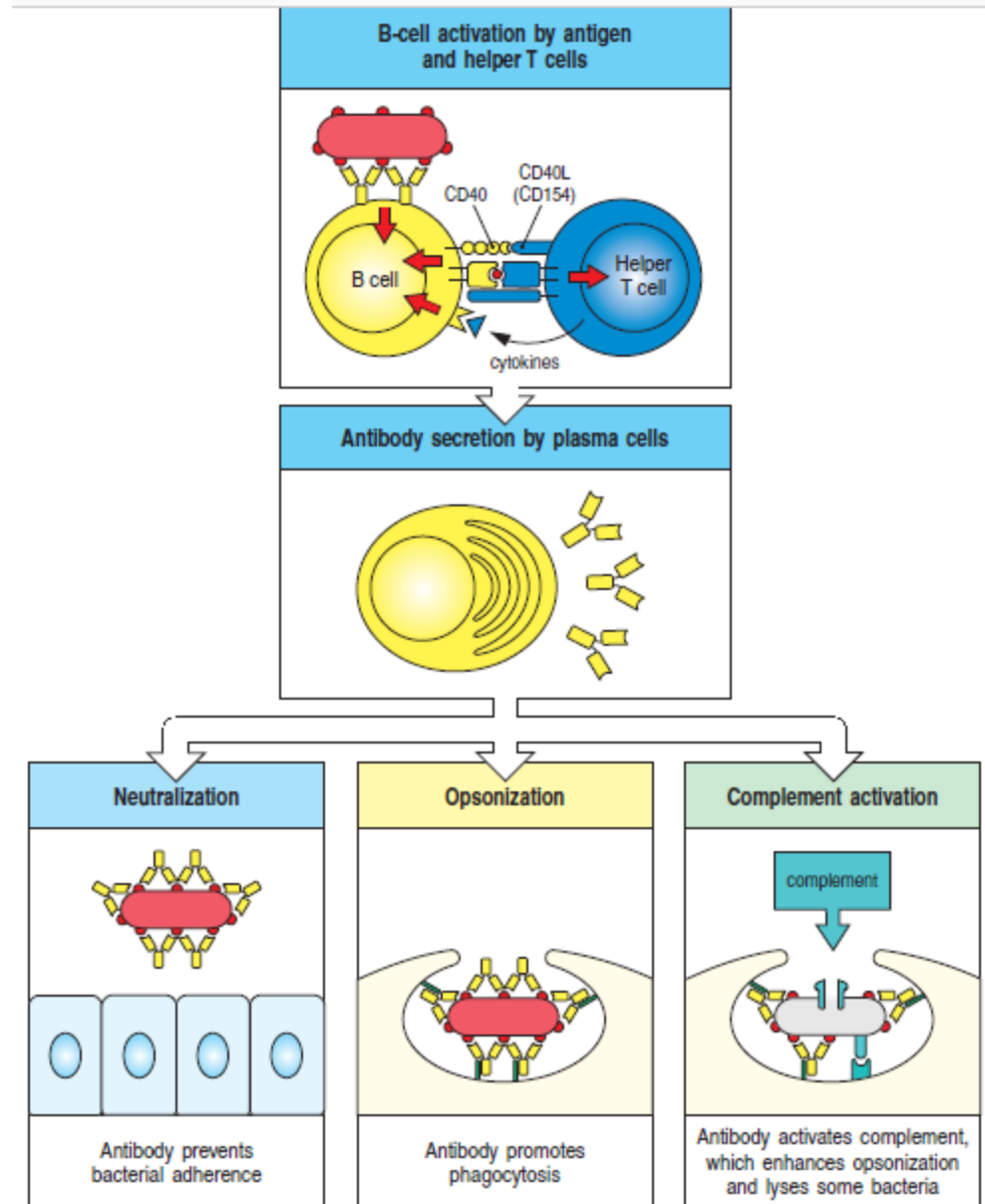
- Class depends on
  - type of antigen
  - portal of entry
  - antibody function needed
- Five different classes of antibodies present

# Classes of Antibodies





# Importance of Antibodies

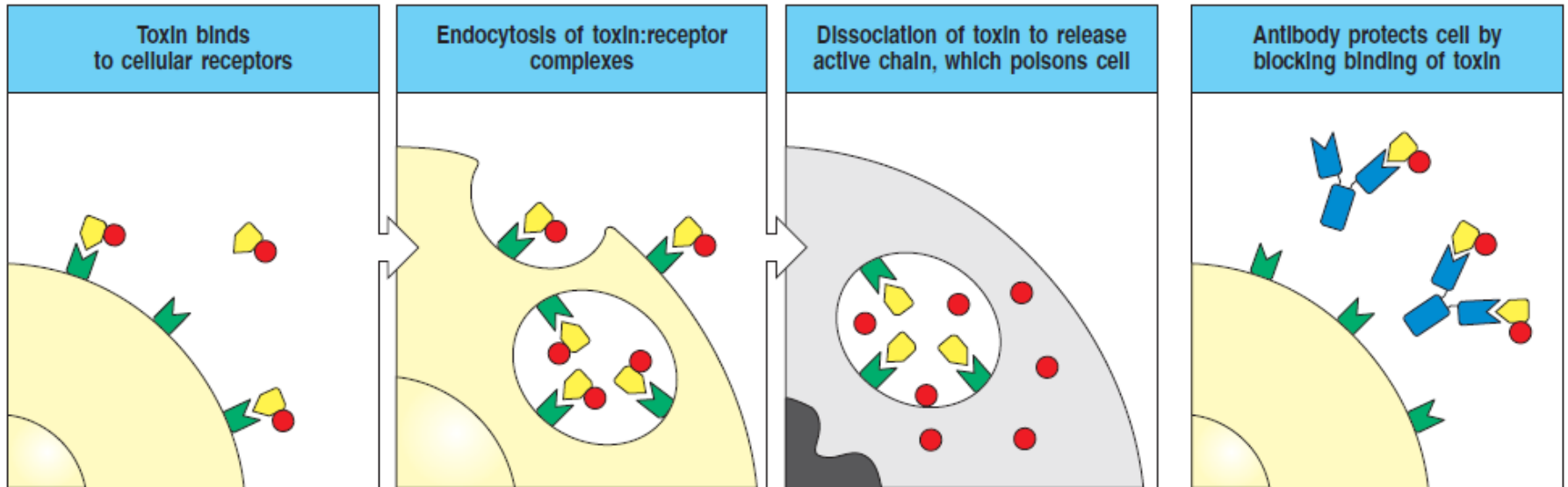


# Importance of Antibodies.....

## Neutralization

- To enter cells, viruses and intracellular bacteria bind to specific molecules on the target cell surface
- Antibodies that bind to the pathogen can prevent this and are said to neutralize the pathogen
- Neutralization by antibodies is also important in preventing bacterial toxins from entering cells.

# Neutralization



# Importance of Antibodies.....

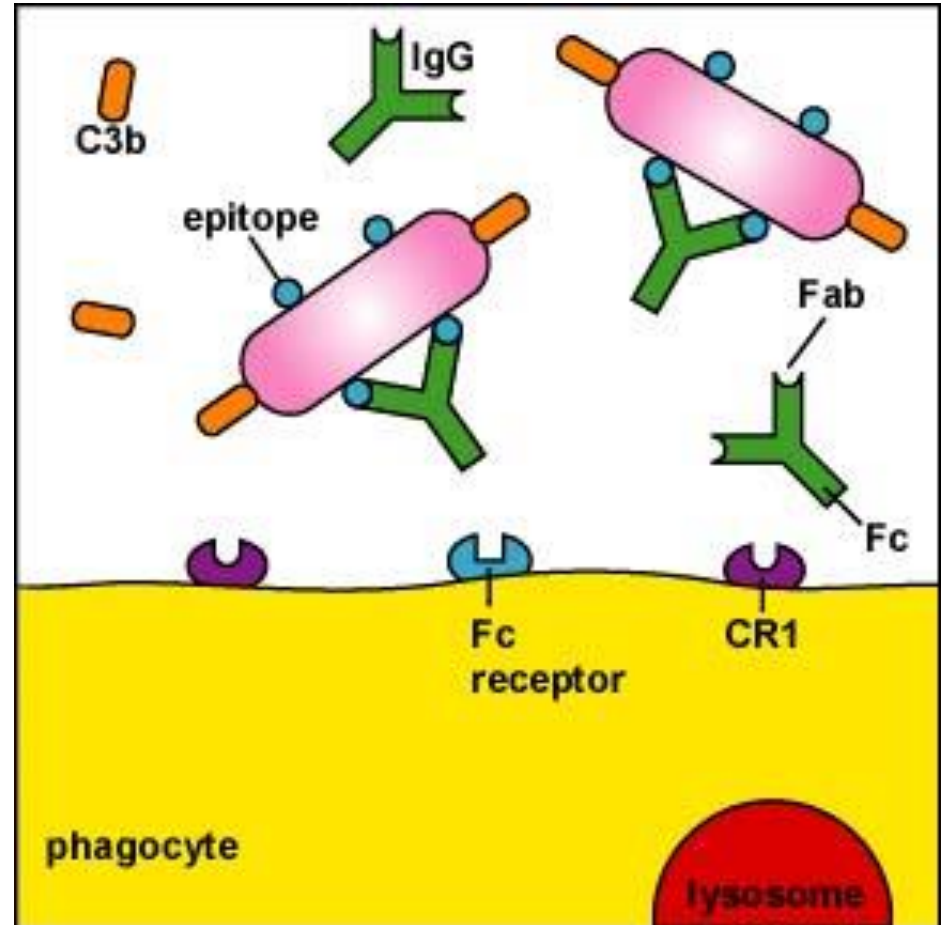
## Opsonization

- ▣ Coating the surface of a pathogen to enhance phagocytosis is called opsonization
- ▣ Antibodies protect against bacteria that multiply outside cells, by facilitating uptake of the pathogen by phagocytes.

# Importance of Antibodies.....

## Opsonization

- Antibodies bound to the pathogen are recognized by phagocytic cells by **Fc receptors** that bind to the antibody constant region (C region).

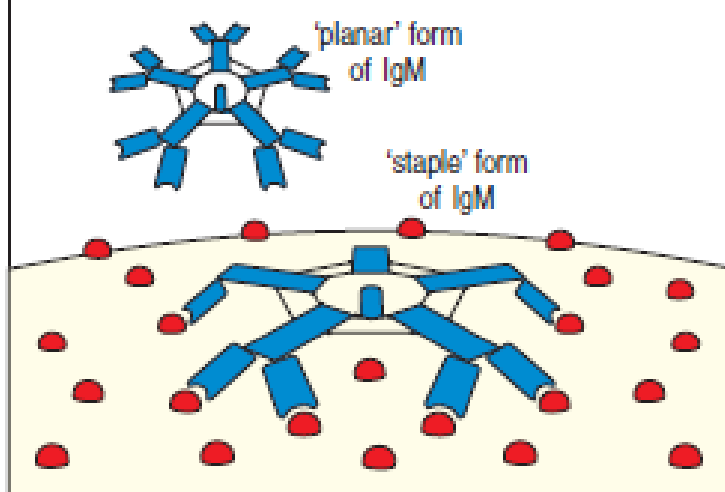


# Importance of Antibodies.....

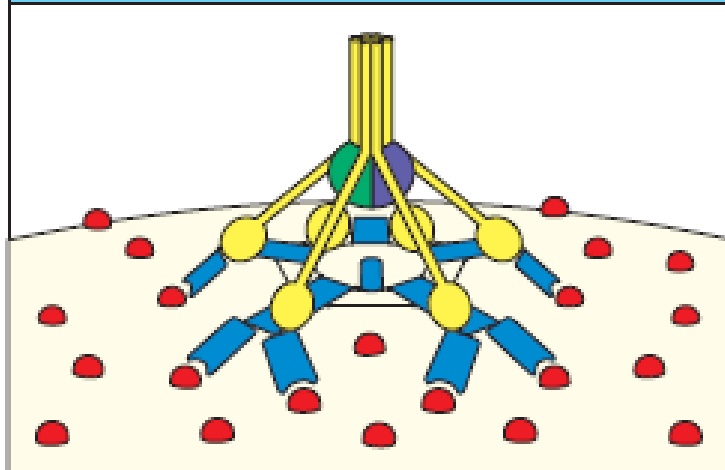
## Activate the complement system

- ▣ By the **classical** pathway
- ▣ Complement components **opsonize** the pathogen by binding complement receptors on phagocytes.
- ▣ Other complement components **recruit phagocytic** cells to the site of infection
- ▣ Terminal components of complement **lyse** microorganisms directly by forming pores in their membranes

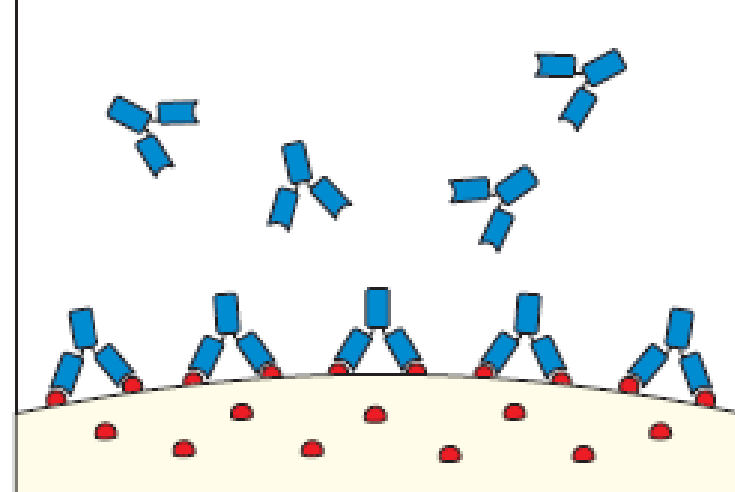
Pentameric IgM molecules bind to antigens on the bacterial surface and adopt the 'staple' form



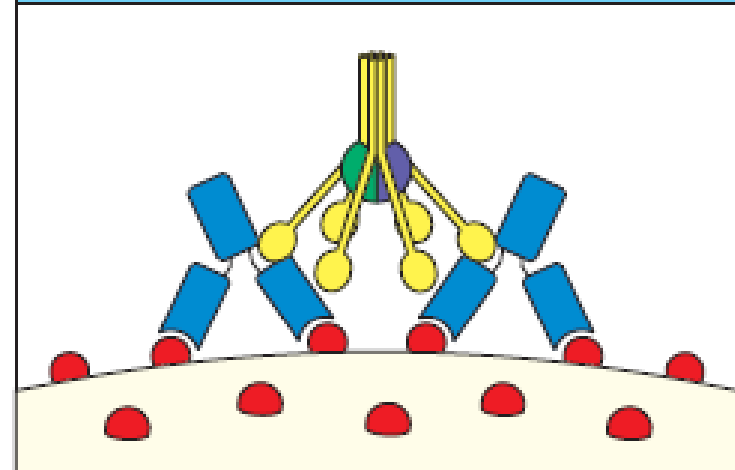
C1q binds to one bound IgM molecule



IgG molecules bind to antigens on the bacterial surface



C1q binds to at least two IgG molecules



Binding of C1q to Ig activates C1r, which cleaves and activates the serine protease C1s

# Phases of humoral immune response

- Antigen recognition
- Activation of B lymphocytes
- Communication
- Battle (effector functions)
- Memory

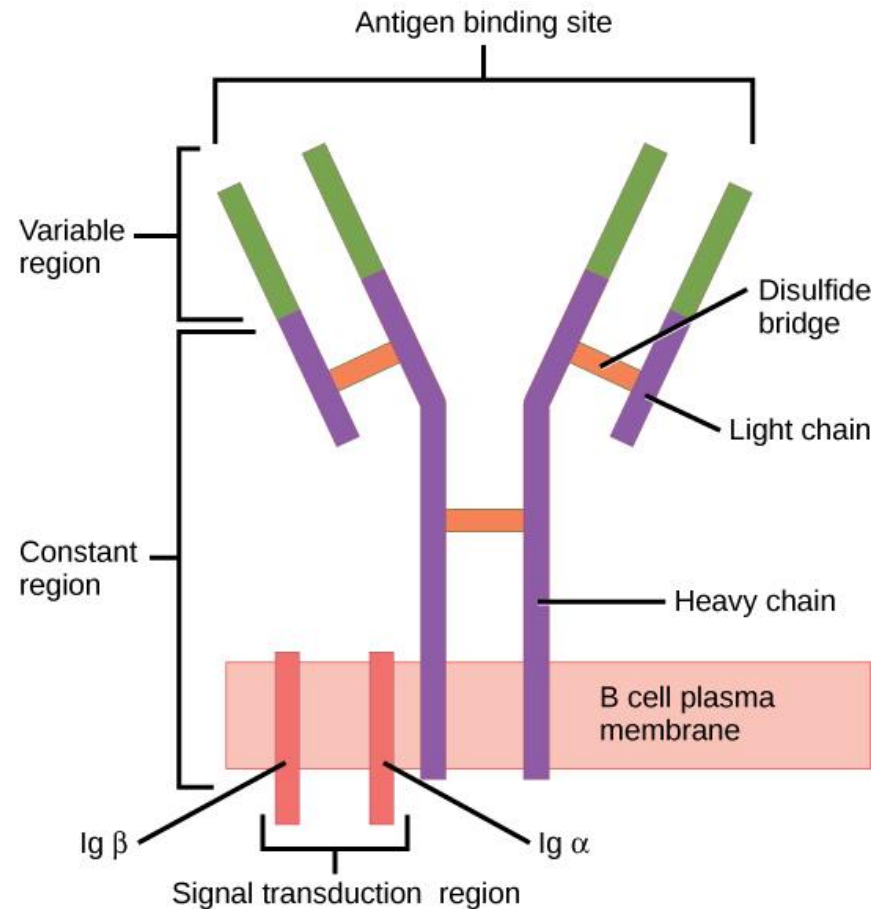


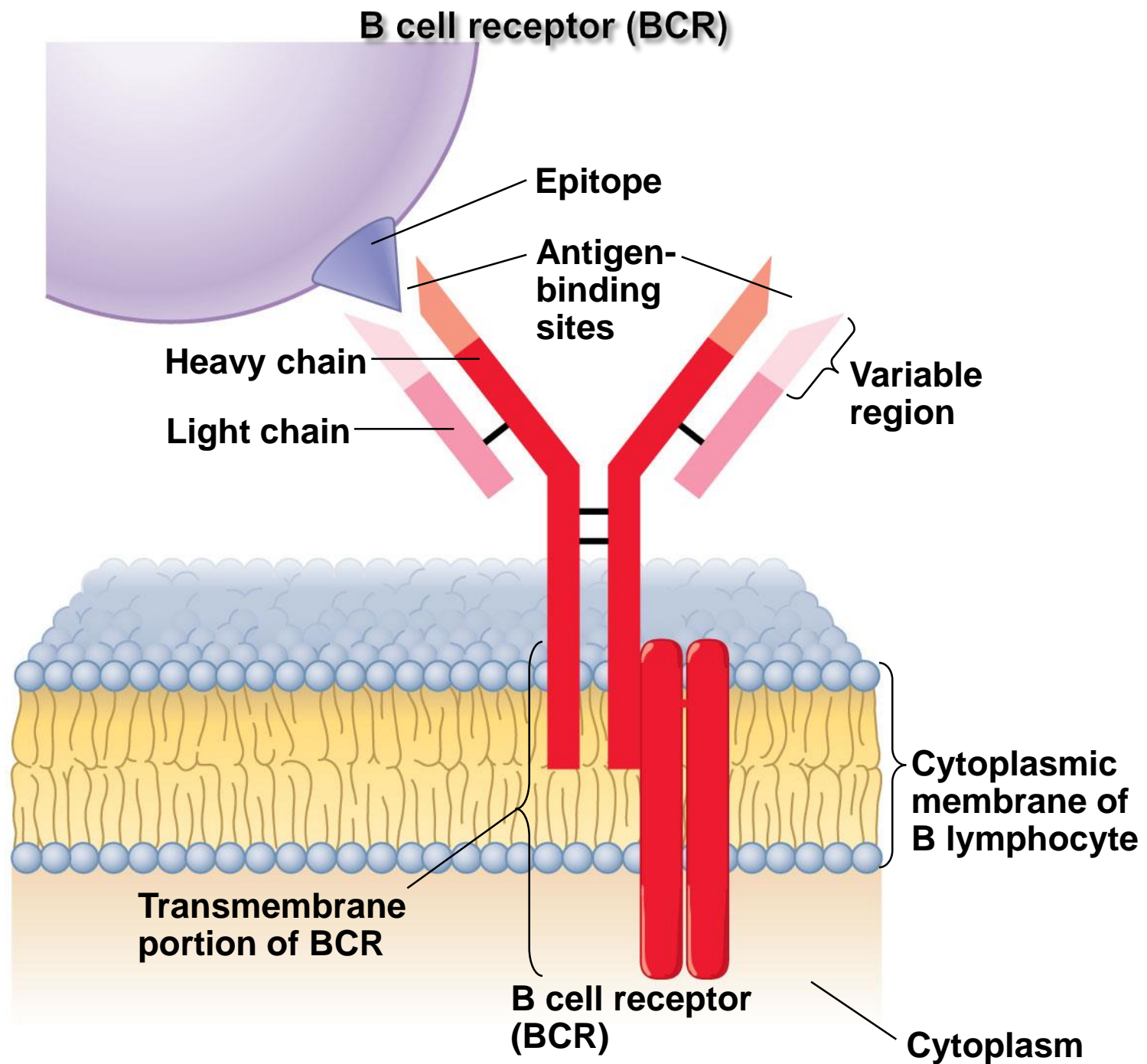
# Antigen recognition

- B cells express two classes of antibodies, IgM and IgD that function as the receptor for antigens (B cell Receptor / BCR)

# B cell receptor (BCR)

- One B cell possesses multiple copies of same BCR
- Variable region - antigen-binding site





# B cell receptor (BCR)

## BCR has two crucial functions

1. **Signal transduction**, involving changes in receptor oligomerization.
2. Mediate **internalization of antigen** for subsequent processing of the antigen **and presentation of peptides** to helper T cells

# Activation of humoral Immune Response

- HIR is initiated when B cells that bind antigen are **signaled by helper T cells** or by certain **microbial antigens alone**.
- Two types
  - T-dependent humoral immunity
  - T-independent humoral immunity

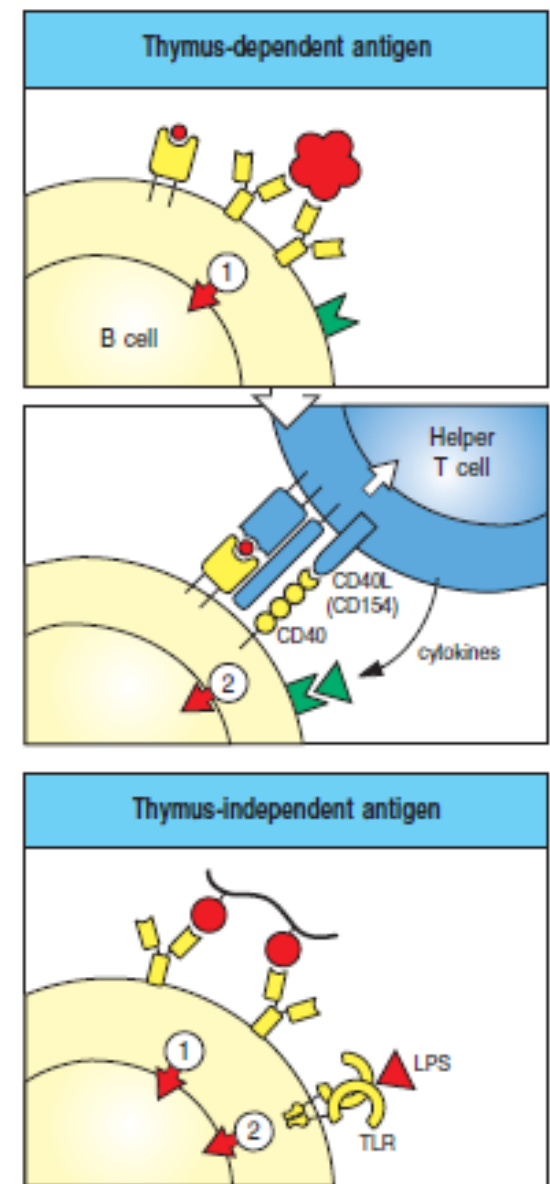


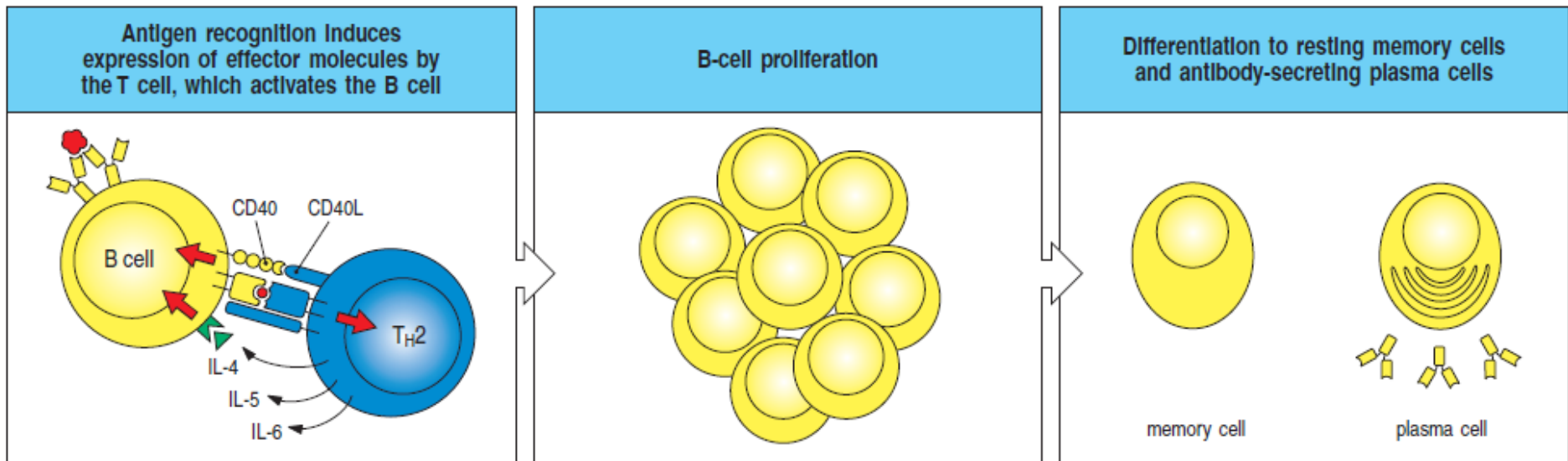
Fig. 10.2 A second signal is required for B-cell activation by either thymus-dependent or thymus-independent antigens. The first signal (indicated as 1

# T-dependent humoral immunity

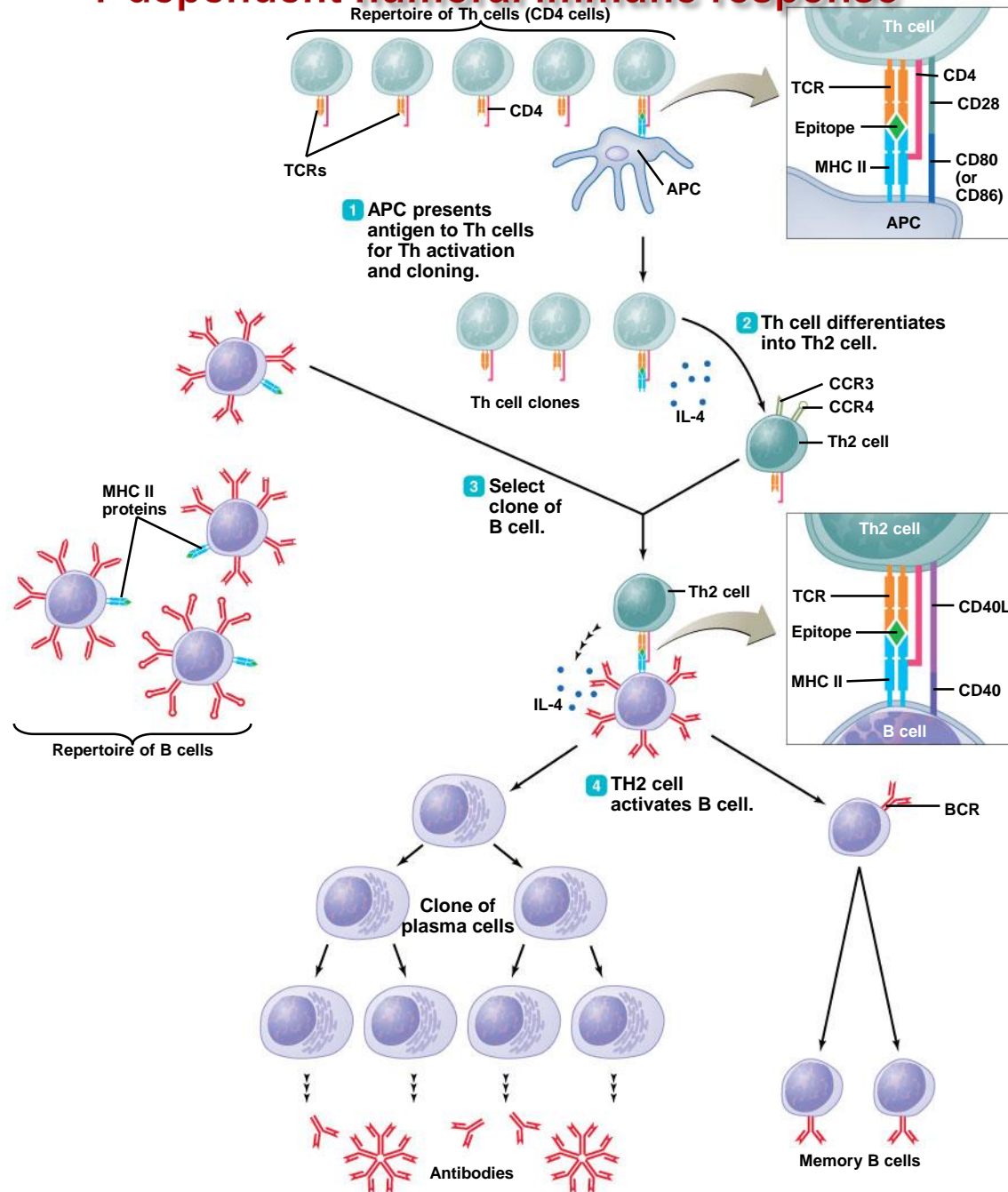
- ▣ Antibody responses to **protein antigens** require antigen-specific **T-cell help**.
- ▣ To receive T-cell help, the **B cell** must **be displaying** **antigen** on its surface in a form a T cell can recognize.
- ▣ Helper T cells that recognize the **peptide: MHC II** complex

# T-dependent humoral immunity

- ▣ The effector **T cells make cytokines** that cause the **B cell to proliferate** and its progeny to differentiate into **antibody-secreting cells** and into **memory B cells**



# T-dependent humoral immune response





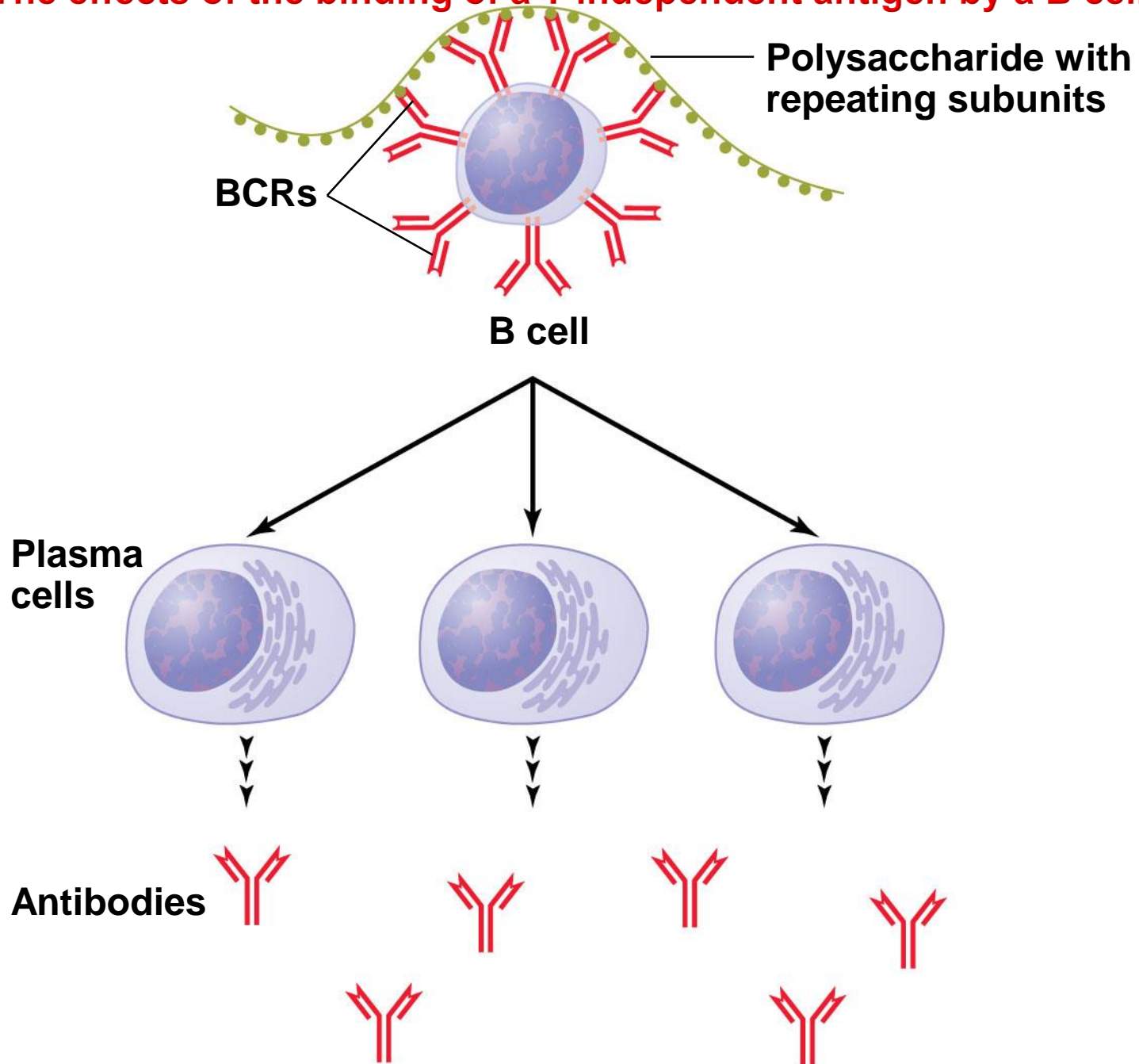
# Activation of B lymphocytes

- Activation of B lymphocytes - proliferation of antigen-specific cells (**Clonal expansion**)
- B cells differentiate into effector cells (plasma cells) that actively **secrete antibodies**
- Some B cells undergo **class switching** or **affinity maturation**
- Some B cells become **memory cells**

# T-independent humoral immunity

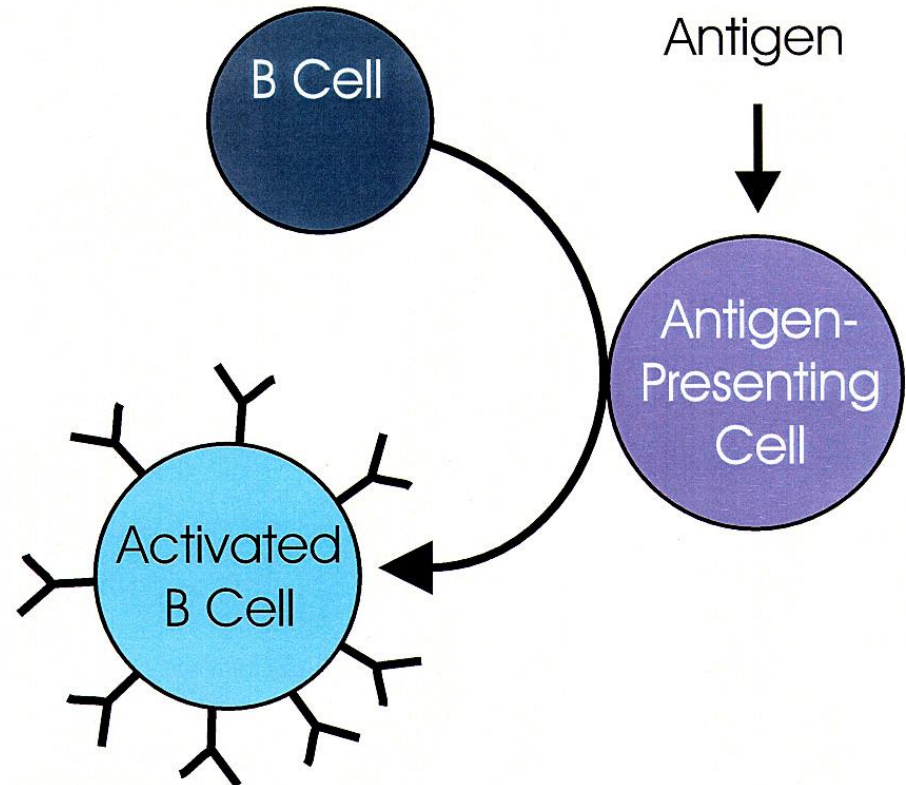
- Some microbial antigens (eg: polysaccharides, LPS) can **activate B cells** directly in the **absence of T-cell** help
- Ability of B cells to respond directly to these antigens **provides a rapid response** to many important pathogens.
- Response is **not strong**, especially in young children

# The effects of the binding of a T-independent antigen by a B cell



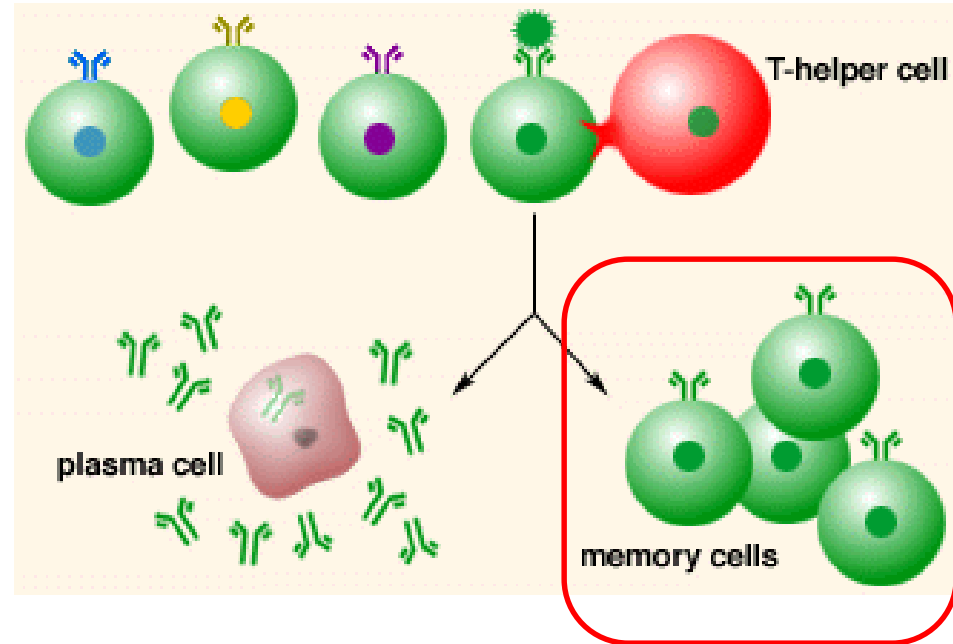
# Plasma Cells

- ▣ Secretes only antibody molecules  
**complementary** to the specific antigenic determinant
- ▣ Short-lived
- ▣ Die within a few days of activation



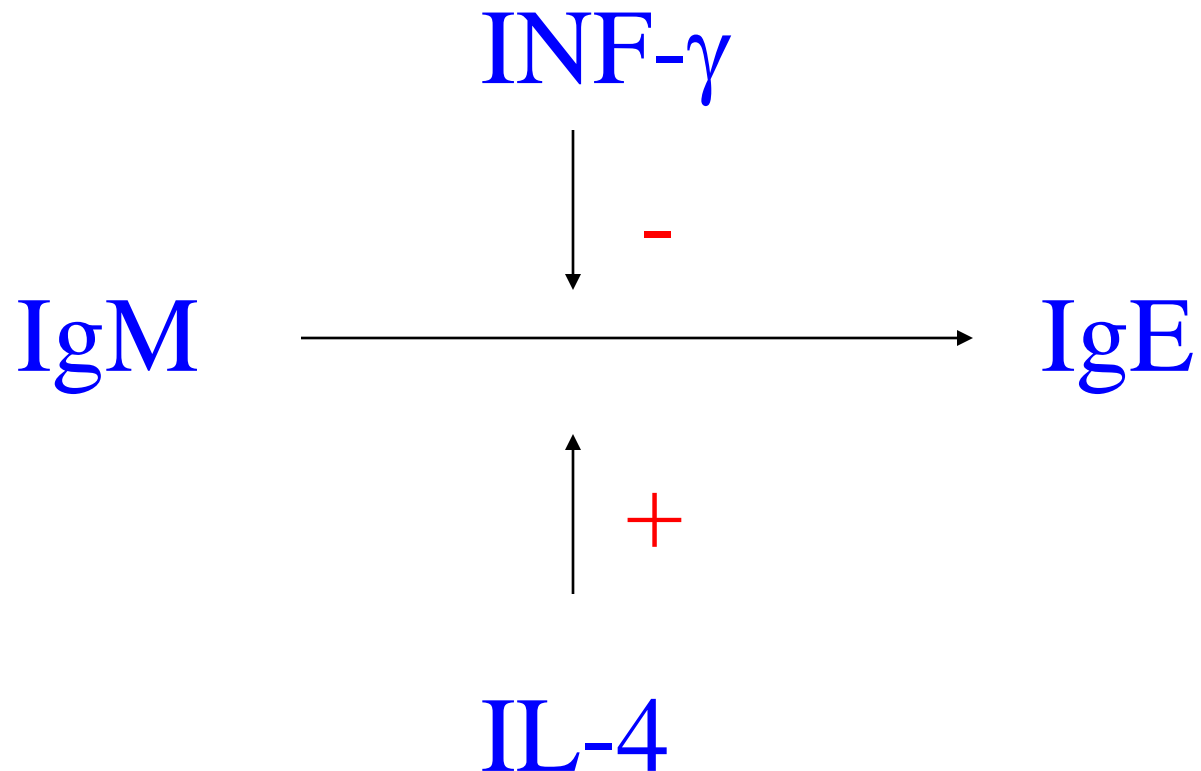
# Memory B Cells

- Produced by B cell proliferation
- Long-lived cells
- Divide only a few times and then persist in lymphoid tissue
- Do not secrete antibodies
- Have BCRs complementary to the antigenic determinant
- Initiate antibody production if antigen is encountered again



# Class switching

The process of making B cells to produce different heavy chain class.



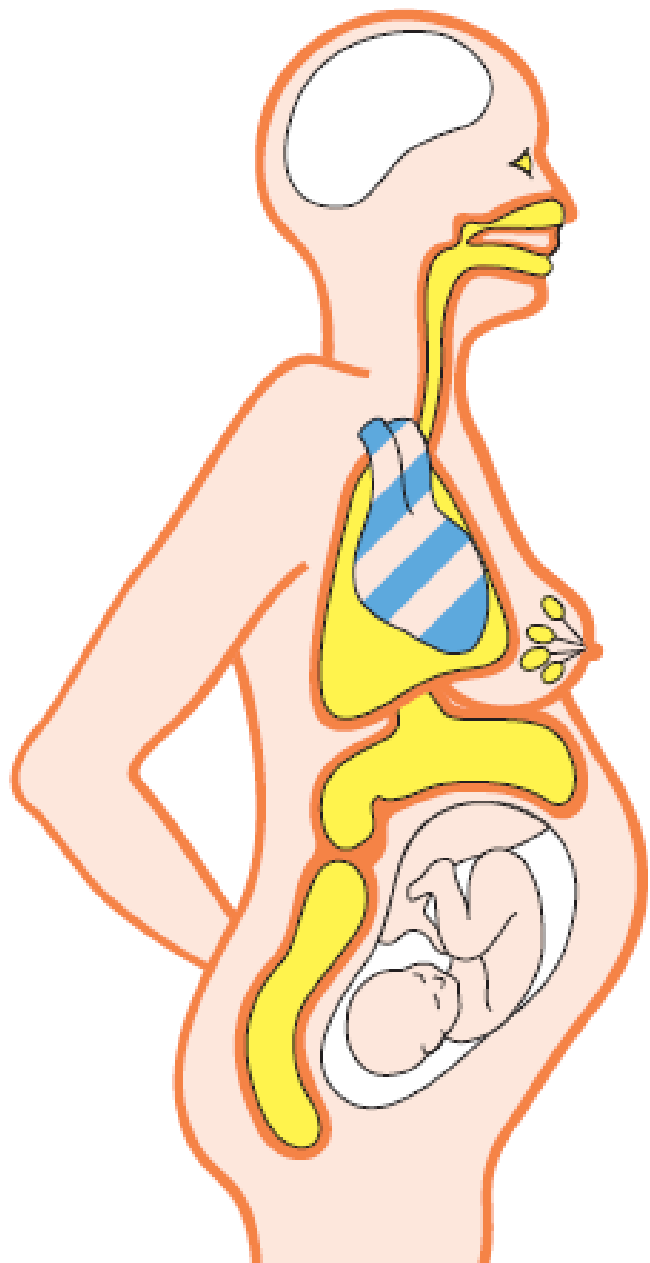
## Role of cytokines in regulating expression of antibody classes

Cytokines	IgM	IgG3	IgG1	IgG2b	IgG2a	IgE	IgA
IL-4	Inhibits	Inhibits	Induces		Inhibits	Induces	
IL-5							Augments production
IFN- $\gamma$	Inhibits	Induces	Inhibits		Induces	Inhibits	
TGF- $\beta$	Inhibits	Inhibits		Induces			Induces

# **Different classes of antibodies**



Distribution	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Transport across epithelium	+	-	-	-	-	-	+++ (dimer)	-
Transport across placenta	-	-	+++	+	++	+/-	-	-
Diffusion into extravascular sites	+/-	-	+++	+++	+++	+++	++ (monomer)	+
Mean serum level (mg ml <sup>-1</sup> )	1.5	0.04	9	3	1	0.5	2.1	$3 \times 10^{-5}$



## **Immunoglobulin classes are selectively distributed in the body.**

IgG and IgM predominate in blood

IgG and monomeric IgA are the major antibodies in extracellular fluid within the body.

Dimeric IgA predominates in secretions across epithelia, including breast milk.

The fetus receives IgG from the mother by transplacental transport. IgE is found mainly associated with mast cells just beneath epithelial surfaces

The brain is normally devoid of immunoglobulin.

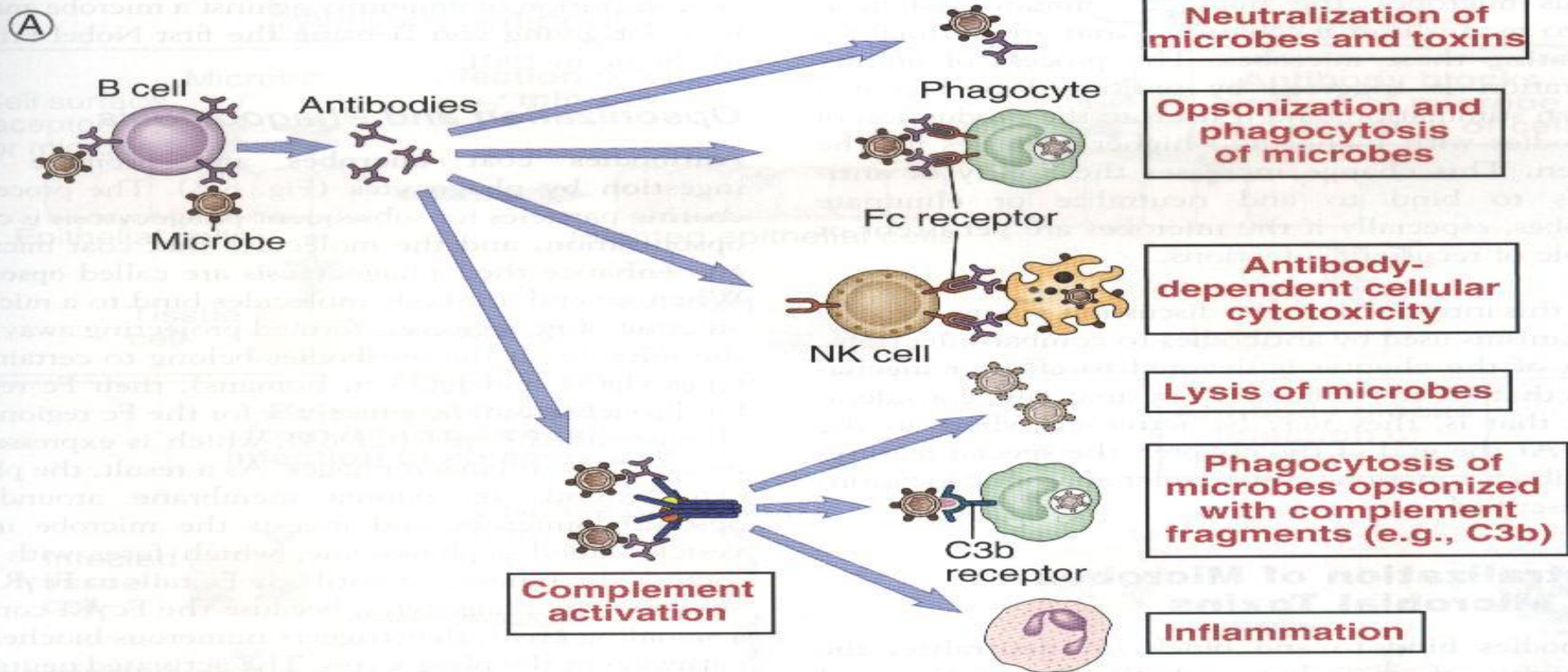
IgG

IgM

Dimeric  
IgA

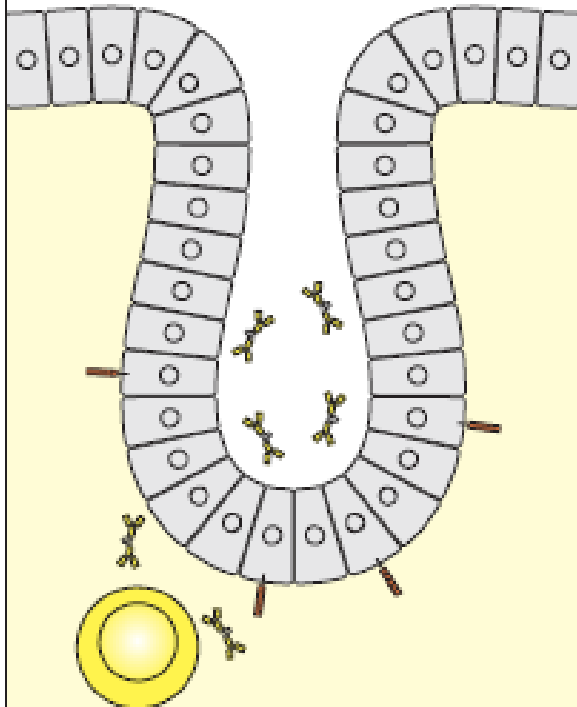
IgE

Functional activity	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Neutralization	+	-	++	++	++	++	++	-
Opsonization	+	-	+++	*	++	+	+	-
Sensitization for killing by NK cells	-	-	++	-	++	-	-	-
Sensitization of mast cells	-	-	+	-	+	-	-	+++
Activates complement system	+++	-	++	+	+++	-	+	-

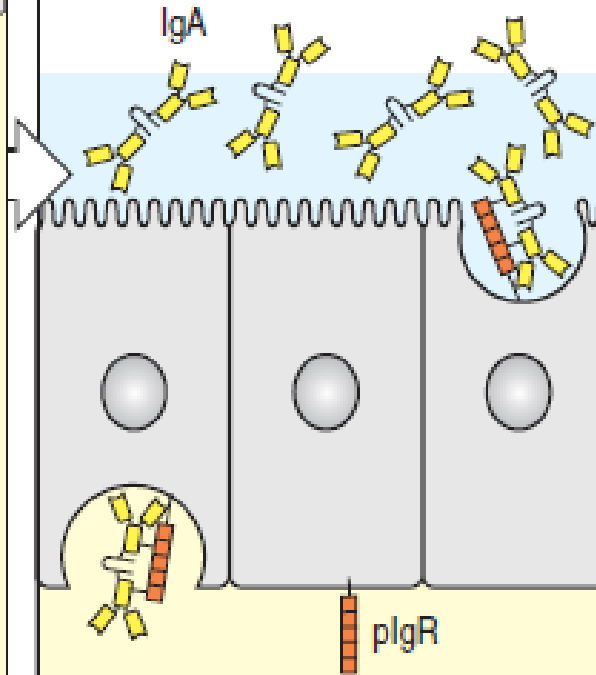


B Antibody isotype	Isotype specific effector functions
IgG	Neutralization of microbes and toxins Opsonization of antigens for phagocytosis by macrophages and neutrophils Activation of the classical pathway of complement Antibody-dependent cellular cytotoxicity mediated by NK cells Neonatal immunity: transfer of maternal antibody across placenta and gut Feedback inhibition of B cell activation
IgM	Activation of the classical pathway of complement
IgA	Mucosal immunity: secretion of IgA into lumens of gastrointestinal and respiratory tracts, neutralization of microbes and toxins
IgE	Antibody-dependent cellular cytotoxicity mediated by eosinophils Mast cell degranulation (immediate hypersensitivity reactions)

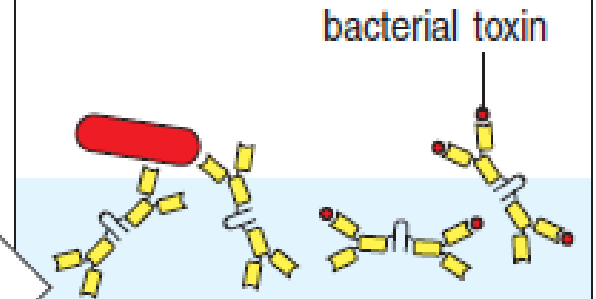
Dimeric IgA is transported into the gut lumen through epithelial cells at the base of the crypts

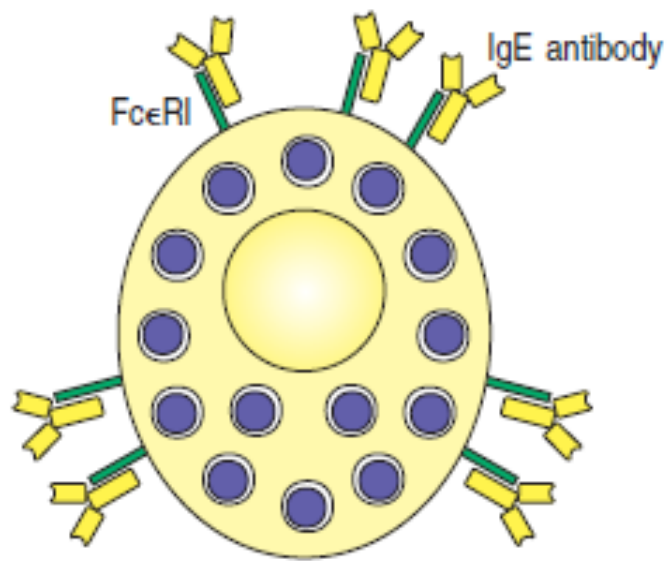


Dimeric IgA binds to the layer of mucus overlying the gut epithellum

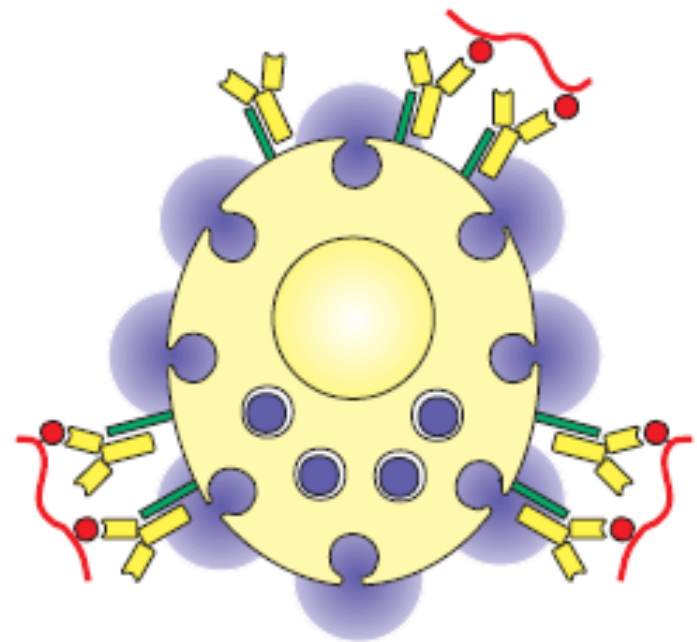


IgA in the gut neutralizes pathogens and their toxins





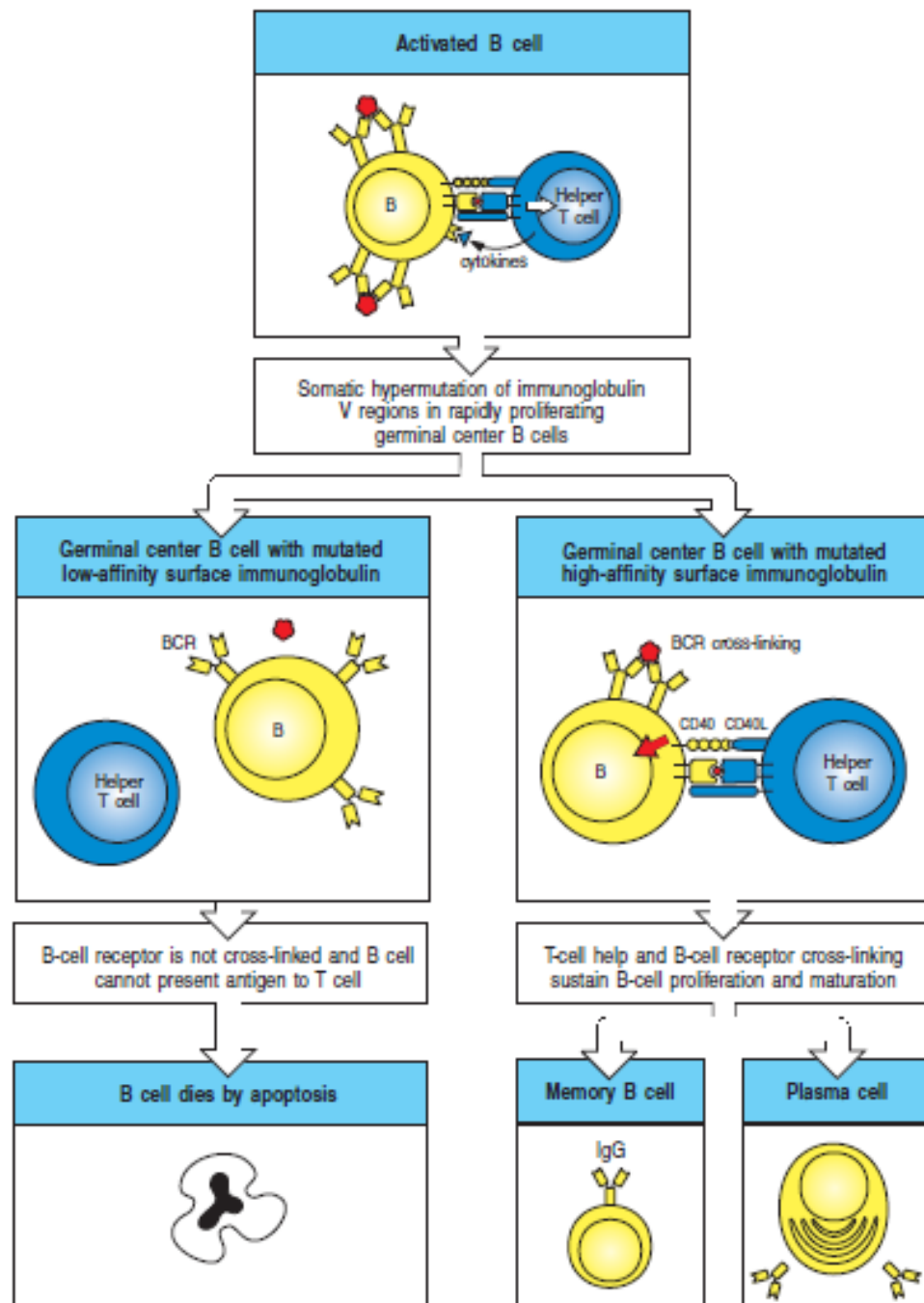
Resting mast cell contains granules containing histamine and other inflammatory mediators



Multivalent antigen cross-links bound IgE antibody, causing release of granule contents

# Affinity maturation

- **Affinity** : **strength** with which the **epitope** binds to an individual **paratope** (antigen-binding site) on the antibody.
- **Affinity maturation**: The process that leads to increased affinity of antibodies for a protein antigen during the course of an immune response



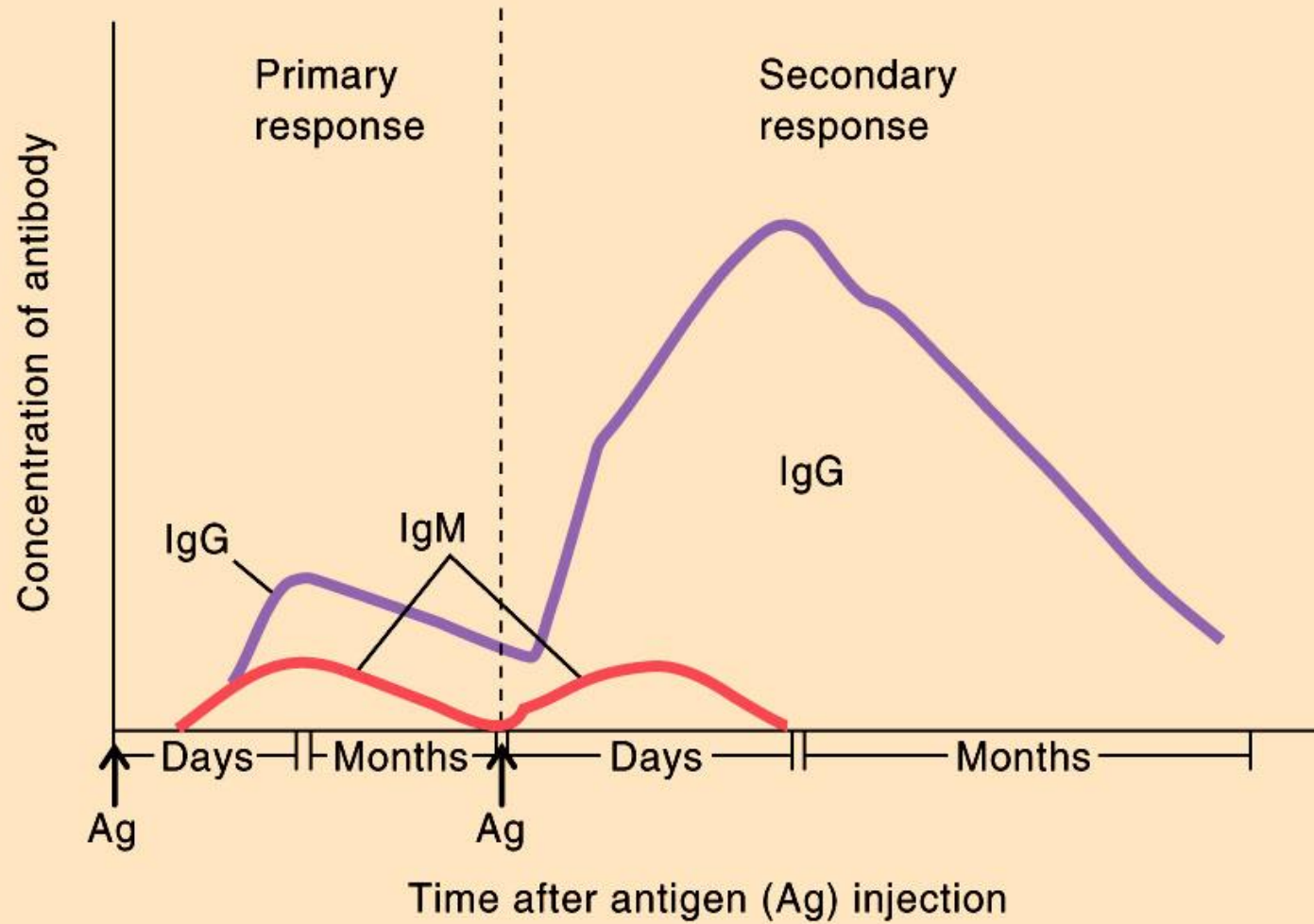


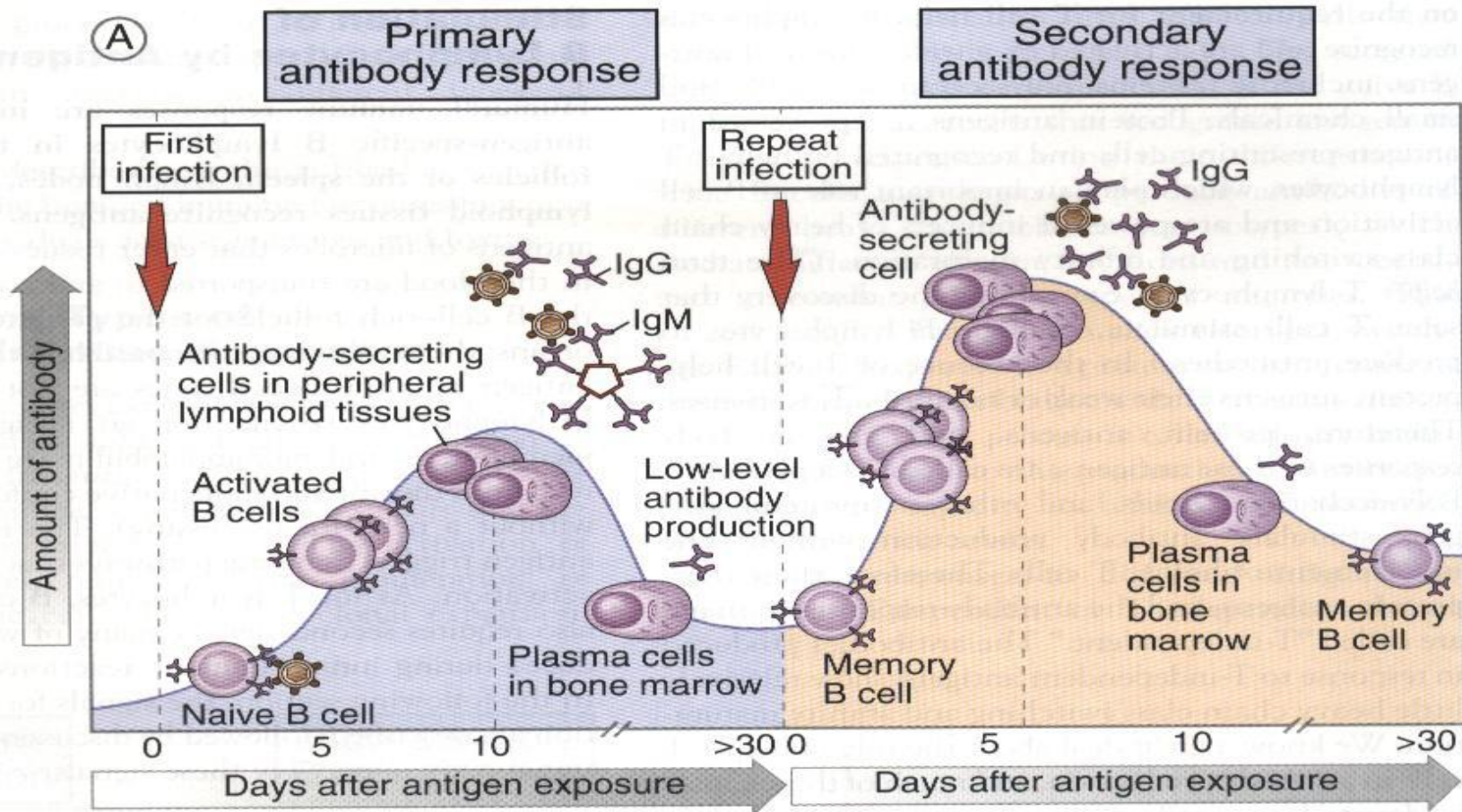
# Affinity maturation

- The fine tuning of antibody responses to **increase the affinity** of the antibody for the antigen and the **switching to most immunoglobulin classes** other than IgM depend on the interaction of antigen-stimulated B cells with **helper T cells** and other cells in the peripheral lymphoid organs.
- Thus, antibodies induced by **microbial antigens alone** tend to have **lower affinity** and to be **less functionally versatile** than those induced with T-cell help.

# Types of immune response

- Primary (first exposure)
  - Mainly IgM
  - IgG is present
- Secondary (subsequent exposure)
  - Mainly IgG





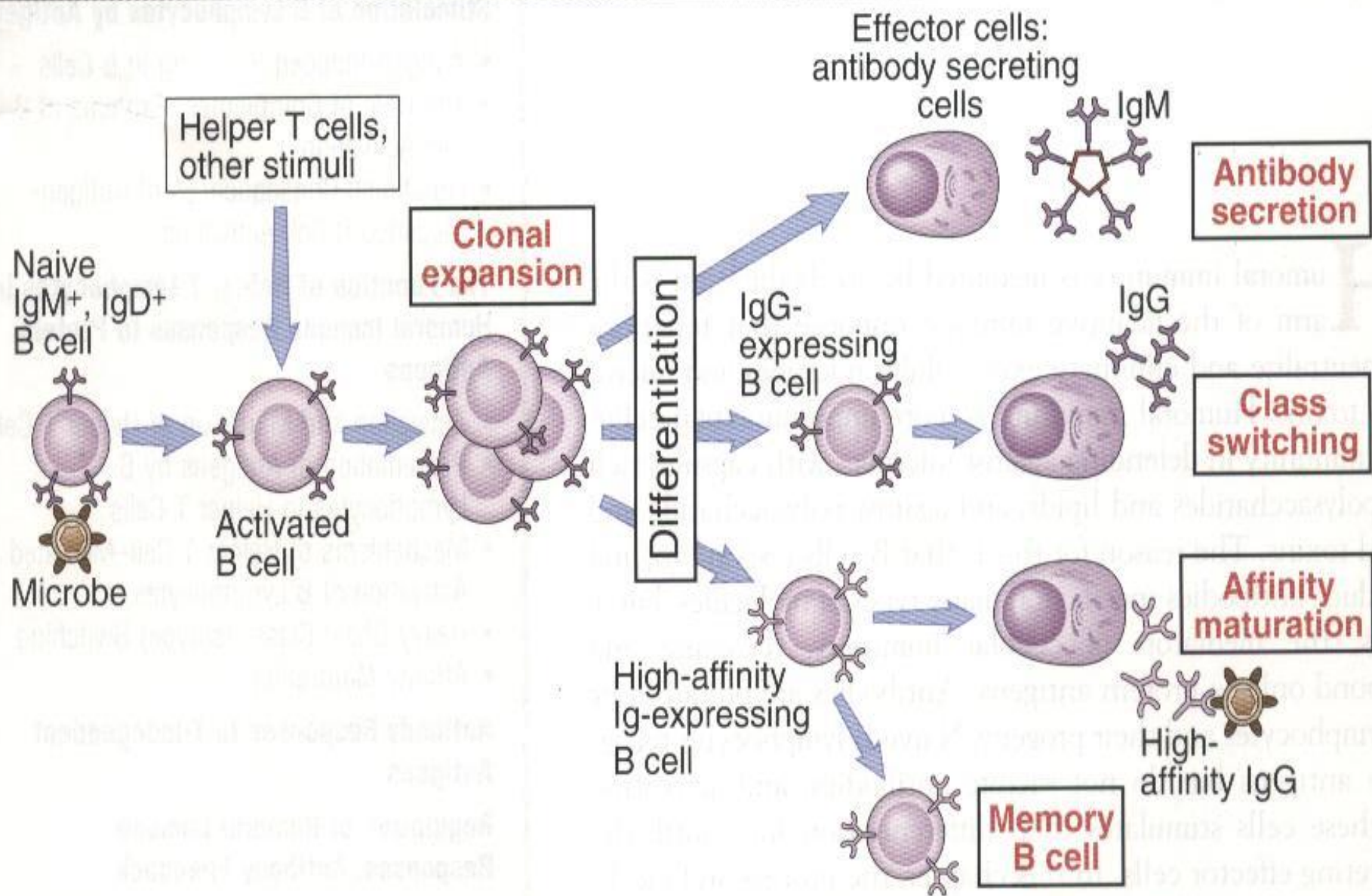
**(B)**

	Primary response	Secondary response
Lag after immunization	Usually 5-10 days	Usually 1-3 days
Peak response	Smaller	Larger
Antibody isotype	Usually IgM>IgG	Relative increase in IgG and, under certain situations, in IgA or IgE (heavy chain class switching)
Antibody affinity	Lower average affinity, more variable	Higher average affinity (affinity maturation)



## Antigen recognition

## Activation of B lymphocytes



# **HUMORAL IMMUNE RESPONSE**

## Activation Phase