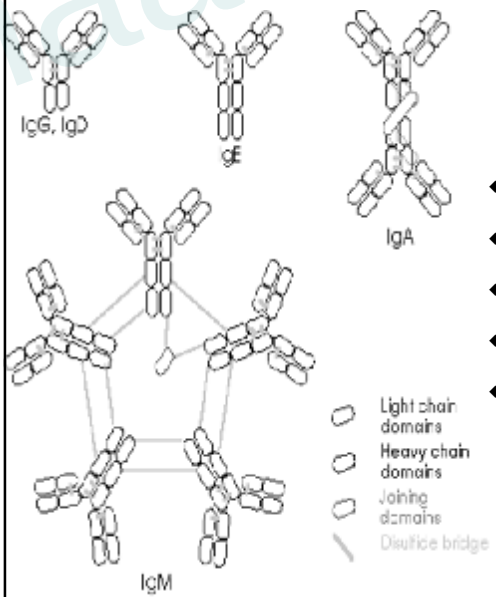
Learning objectives

- Discuss the general properties of Igs
- Describe the basic structure of Igs
- Define Igs hypervariable regions
- Define Igs classes and subclasses
- Understand the mecanisms of diversity

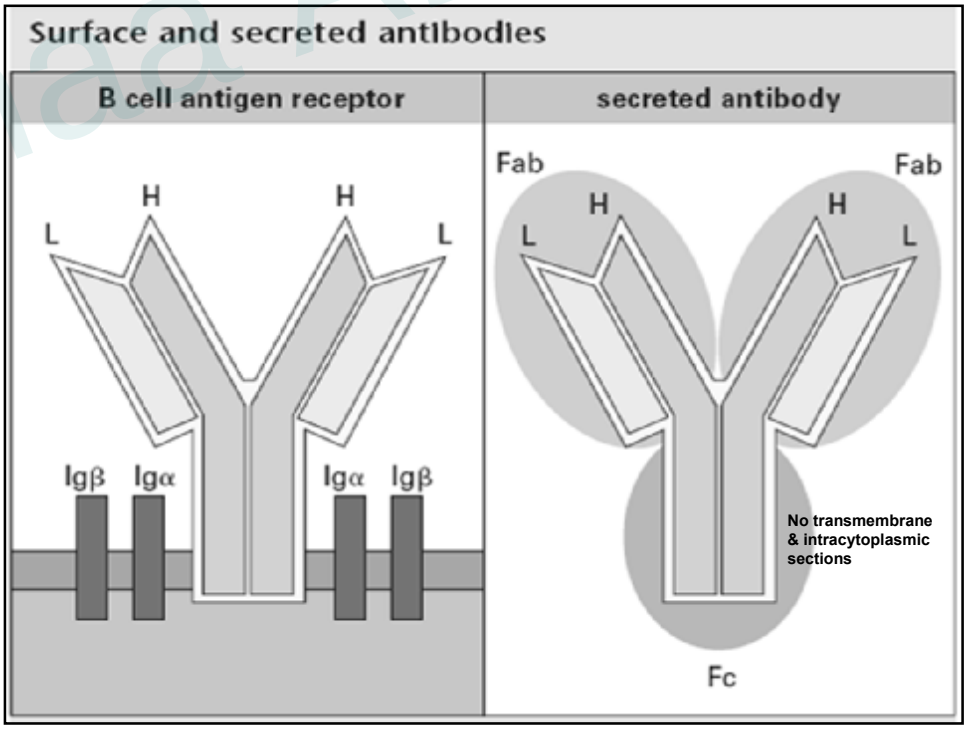
Immunoglobulins



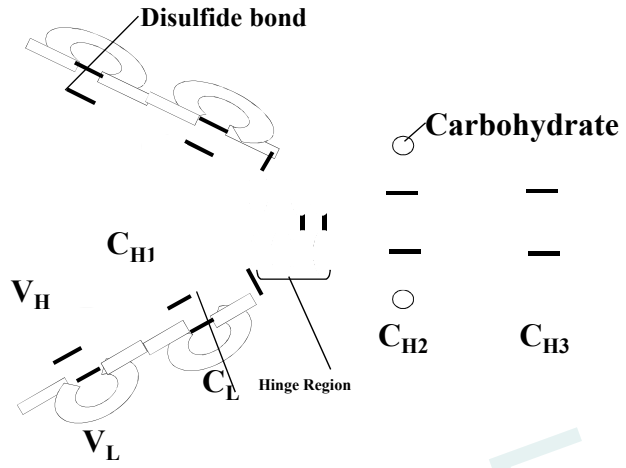
- **Definition**
- **Structure**
- **Types, charactristics**
- **Diversity**
- **Functions**

Immunoglobulins

- ✓ Glycoprotein molecules in serum and tissue fluid
- ✓ Produced by plasma cells in response to an immunogen
- ✓ React specifically with antigen
- ✓ B-cells display Ig molecules on surfaces
- ✓ Igs serve as **receptors for specific antigen**

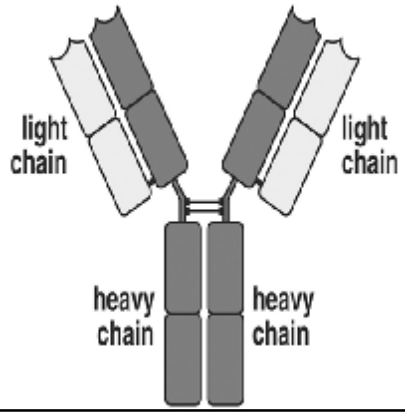


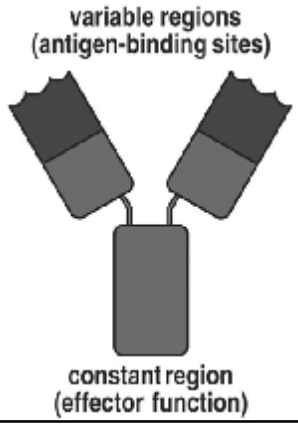
Immunoglobulin Structure



Antibody structure

Two identical Ig **heavy chains** (H)
Two identical **light chains** (L),
Variable region (V) & **constant region** (C).





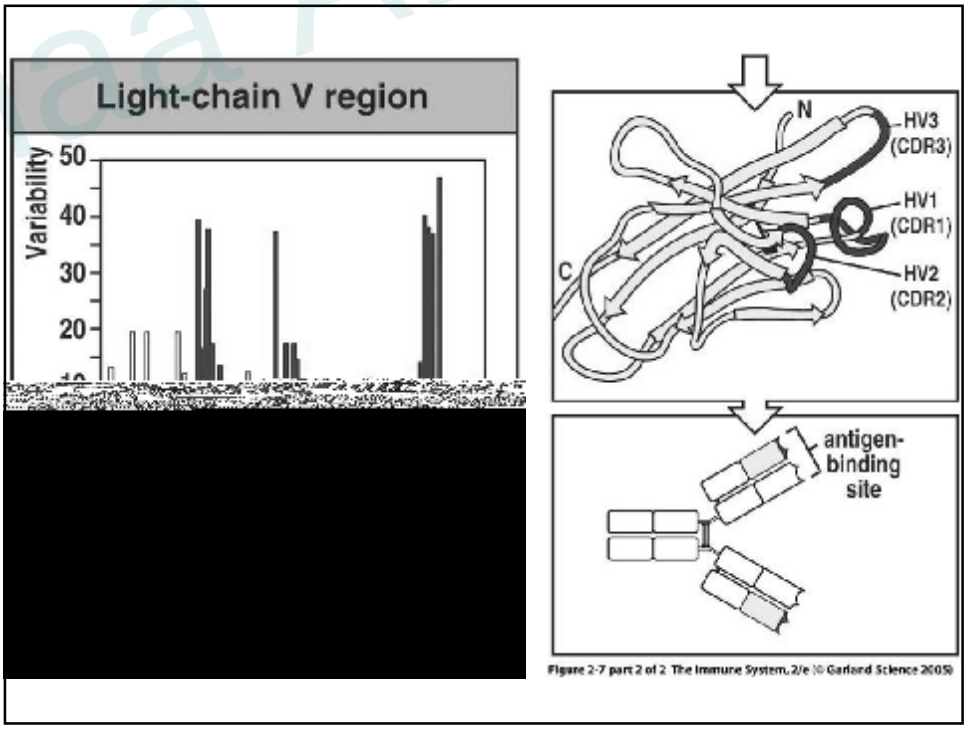
Variable(V) and Constant (C) Regions

- **V-region** **antigen binding**

lies in terminal portion of molecule
wide variation in amino a. sequences
Hypervariable regions of V domains
Complementarity-determining regions
(CDR1,CDR2,CDR3) *idiotype determinant*
Framework regions

- **C-region** **biologic functions**

lies in carboxyl or terminal portion of molecule
shows an unvarying amino acid sequence



- **Heavy chain types**

IgG	Gamma **(γ)**
IgM	Mu **(μ)**
IgA	Alpha **(α)**
IgD	Delta **(δ)**
IgE	Epsilon **(ε)**

- **Light chain types**

Kappa **(κ)**, Lambda **(λ)**

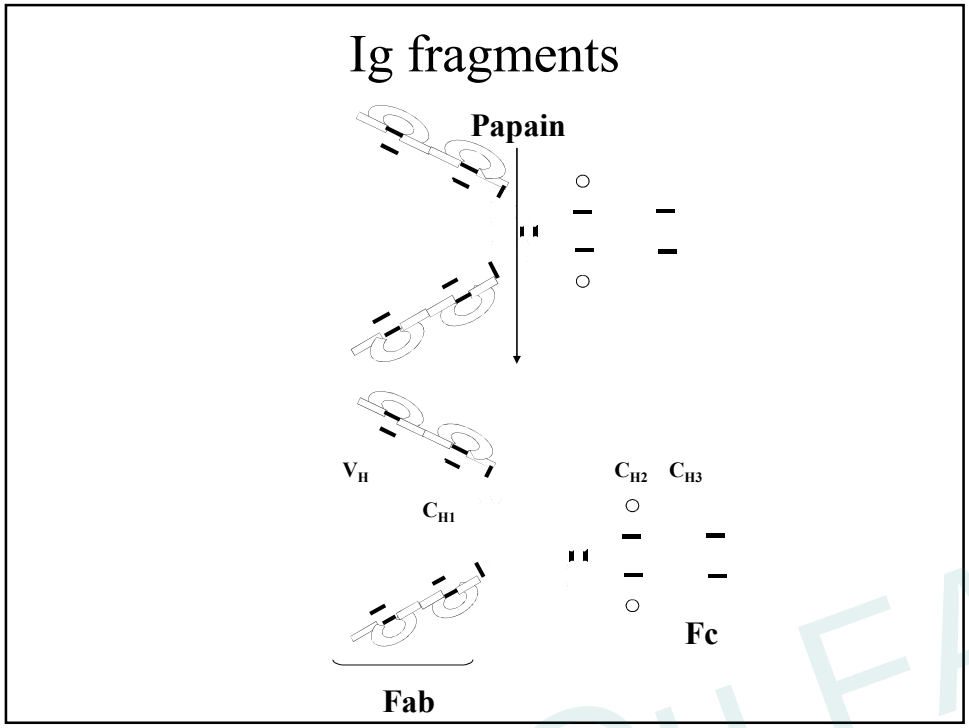
Ig subclasses

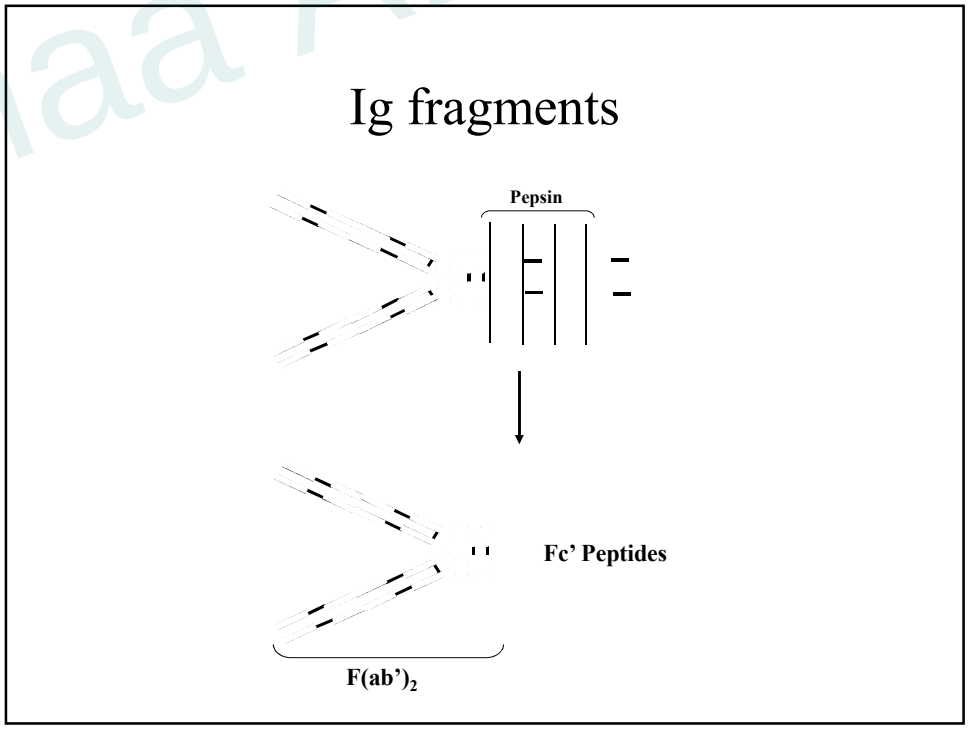
IgG

IgG1 - Gamma 1 (γ1)
IgG2 - Gamma 2 (γ2)
IgG3 - Gamma 3 (γ3)
IgG4 - Gamma 4 (γ4)

IgA

IgA1 - Alpha 1 (α1)
IgA2 - Alpha 2 (α2)



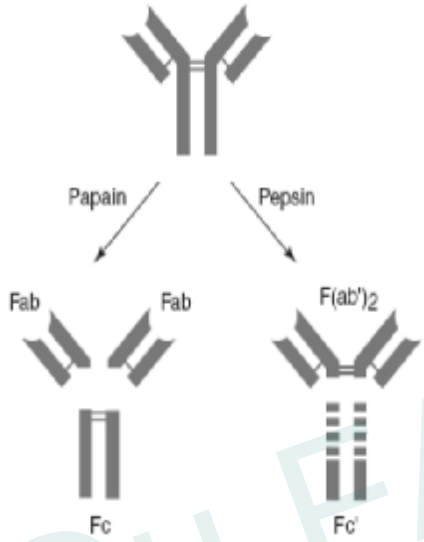


Ab Fragments Produced by Enzymatic Digestion

Fab fragment: antigen binding site

Fc (crystallizable fragment):

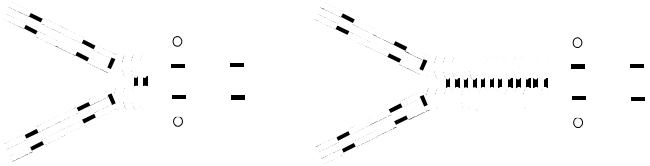
Complement fixation (IgM and IgG)
Opsonization (IgG)
Placental attachment (IgG)
Mucosal attachment (IgA)
Binding to mast cells (IgE)



Igs
Classes, charactristics

IgG

- Monomer (7S)
- Major serum Ig (systemic immunity)
- Major Ig in extravascular spaces
- Placental transfer (FcRn (neonatal Fc receptor),
- Fixes complement
- Binds to Fc receptors
  - Phagocytes - opsonization
  - NK cells - ADCC

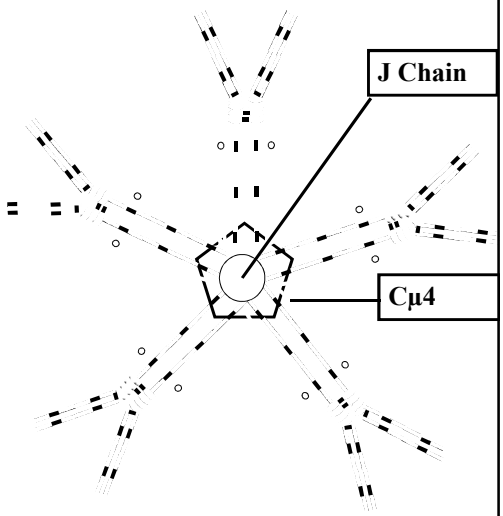


IgG1, IgG2 and IgG4 | IgG3

IgM

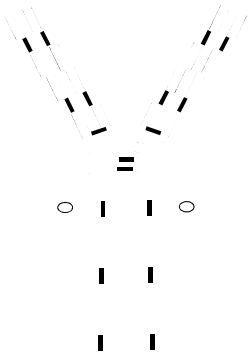
Pentamer (19S)

- J chain



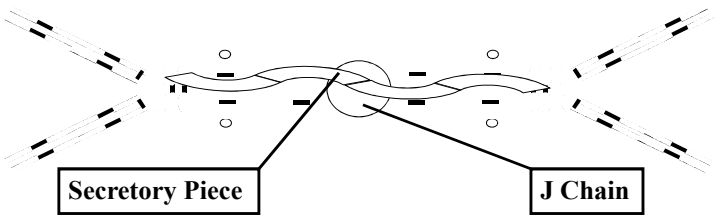
IgM

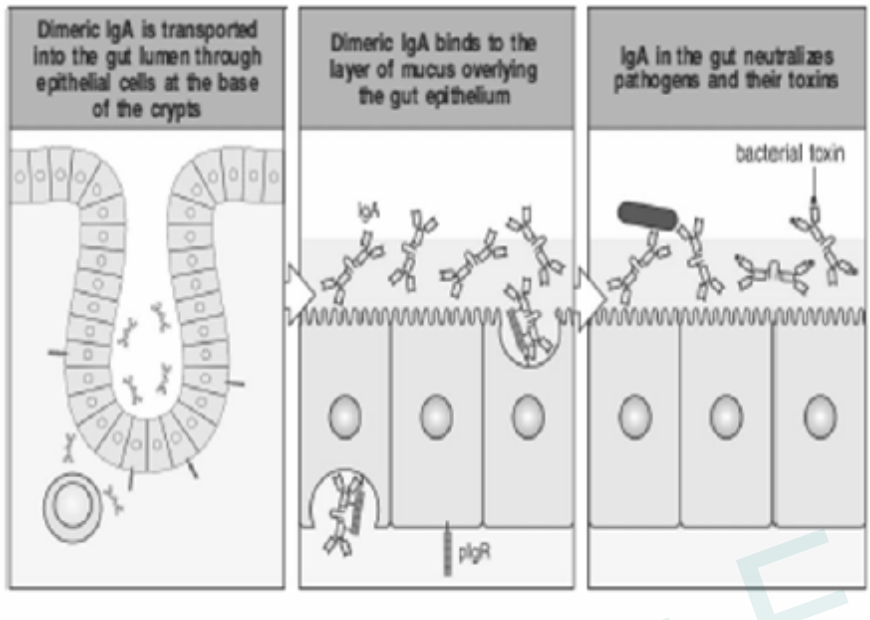
- 3rd highest serum Ig
- First Ig made by fetus and B cells
- Fixes complement
- Agglutinating Ig
- Binds to Fc receptors



IgA

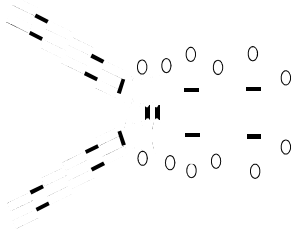
- **Serum - monomer**
- **Secretions (sIgA)**
  - **Dimer (11S)**
  - **J chain**
  - **Secretory component**
- **2nd highest serum Ig**
- **major secretory Ig**, Tears, saliva, gastric and pulmonary secretions
- **Does not fix complement**





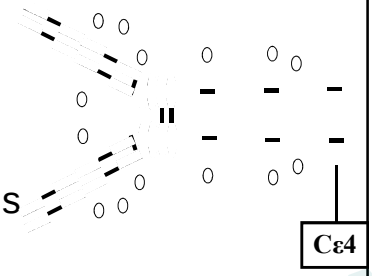
IgD

- Monomer
- 4th highest serum Ig
- B cell surface Ig
- Does not bind complement



IgE

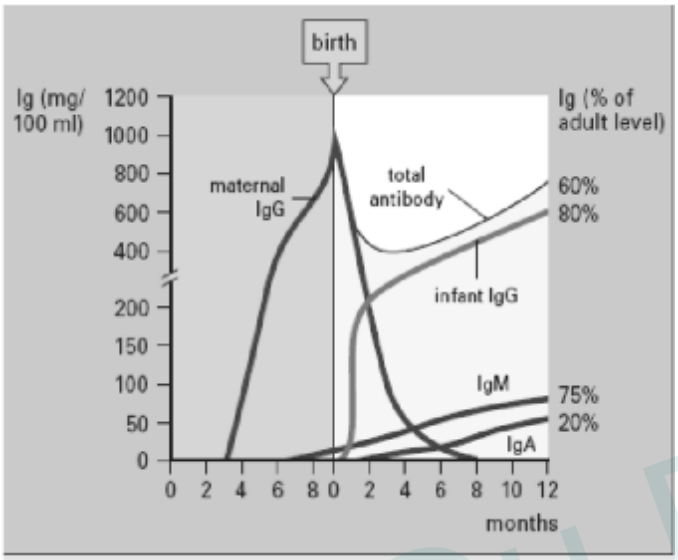
– monomer
– least common serum Ig
– binds to basophils and mast cells
– sensitizes cells on mucosal surfaces such as the conjunctival, nasal, and bronchial mucosae
– parasitic infections
– binds to Fc receptor on eosinophils (high-affinity FcεRI)
– does not fix complement



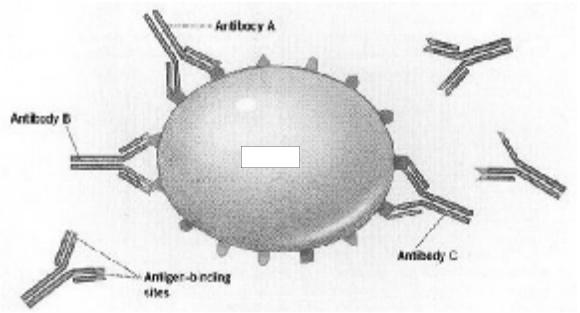
Physicochemical properties of human immunoglobulin classes

property	immunoglobulin type									
	IgG1	IgG2	IgG3	IgG4	IgM	IgA1	IgA2	sIgA	IgD	IgE
heavy chain	γ_1	γ_2	γ_3	γ_4	μ	α_1	α_2	α_1/α_2	δ	ϵ
mean serum conc. (mg/ml)	9	3	1	0.5	1.5	3.0	0.5	0.05	0.03	0.00005
sedimentation constant	7s	7s	7s	7s	19s	7s	7s	11s	7s	8s
mol. wt (kDa)	146	146	170	146	970	160	160	385	184	188
half-life (days)	21	20	7	21	10	6	6	?	3	2
% intravascular distribution	45	45	45	45	80	42	42	trace	75	50
carbohydrate (%)	2–3	2–3	2–3	2–3	12	7–11	7–11	7–11	9–14	12

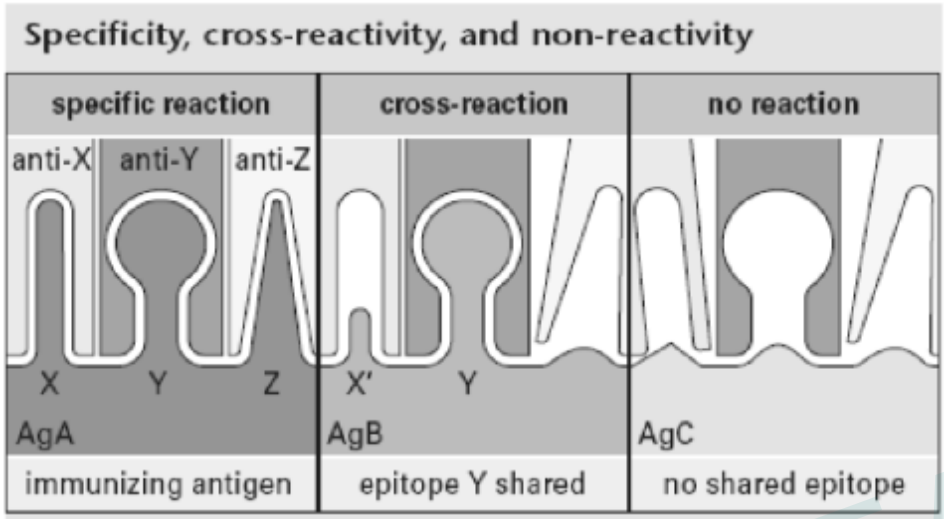
Igs in the serum of the fetus and newborn child



antibodies combine with their specific antigen (like a lock and key)



- this renders the pathogen harmles

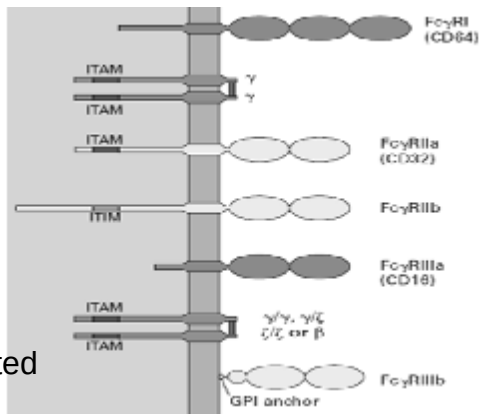


Fcγ receptors

Immunoreceptor tyrosine-based activation (ITAM)

immunoreceptor tyrosine-based inhibitory (ITIM)

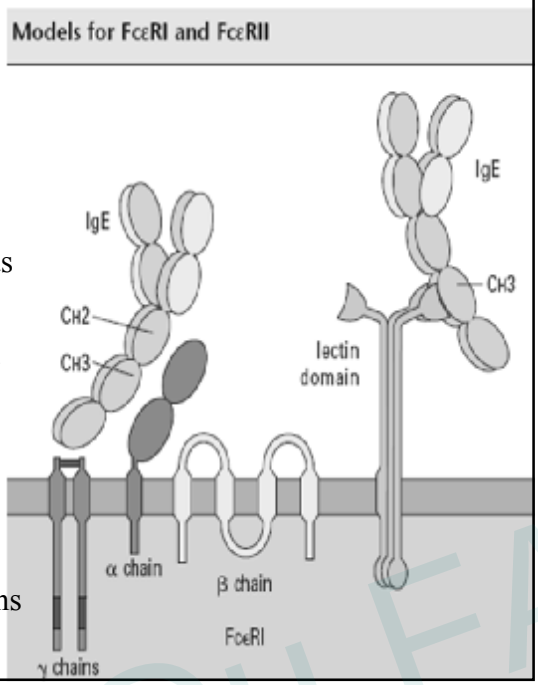
Phosphorylation of the ITAM :
- phagocytosis
- antibody-dependent cell-mediated cytotoxicity (ADCC)
- mediator release
- enhancement of Ag presentation



high-affinity FcεRI
mast cells and basophils
'classical' IgE receptor;

α chain is a glycoprotein and has two extracellular domains homologous to Ig domains;
a member of the Ig superfamily.

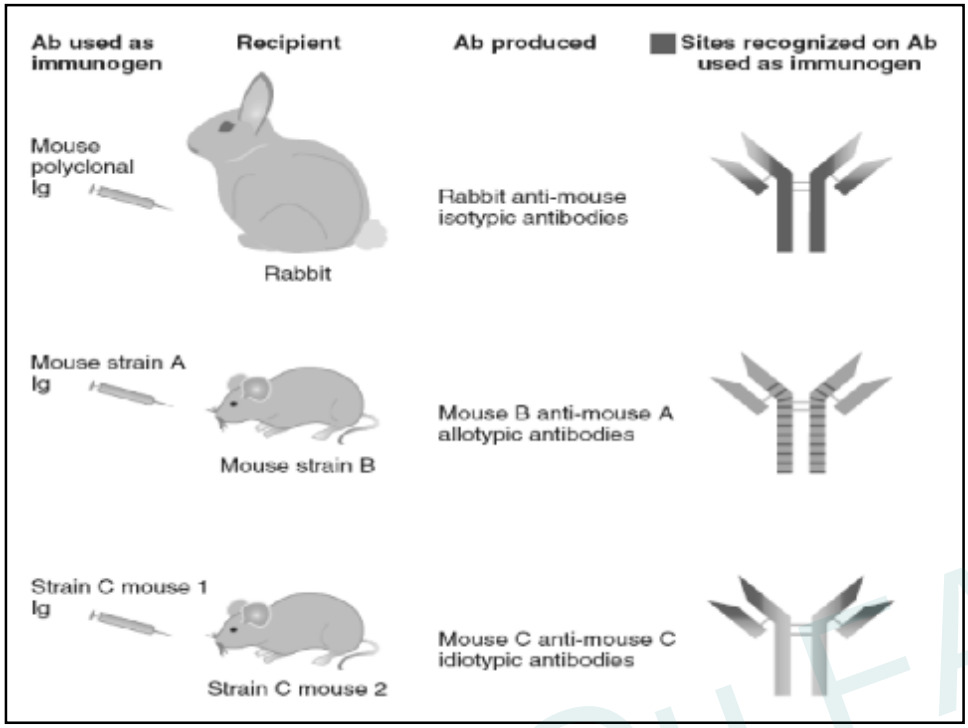
low-affinity FcεRII
leukocytes and lymphocytes.
not a member of the Ig superfamily,
substantial structural homology with several animal C-type lectins (e.g. mannose-binding lectin [MBL]).



Individual's *antibody repertoire*

The total collection of antibody specificities produced in an individual's lifetime,

Diversity" its hallmark



Immunoglobulin (Ig) gene Rearrangement

(No antigen)

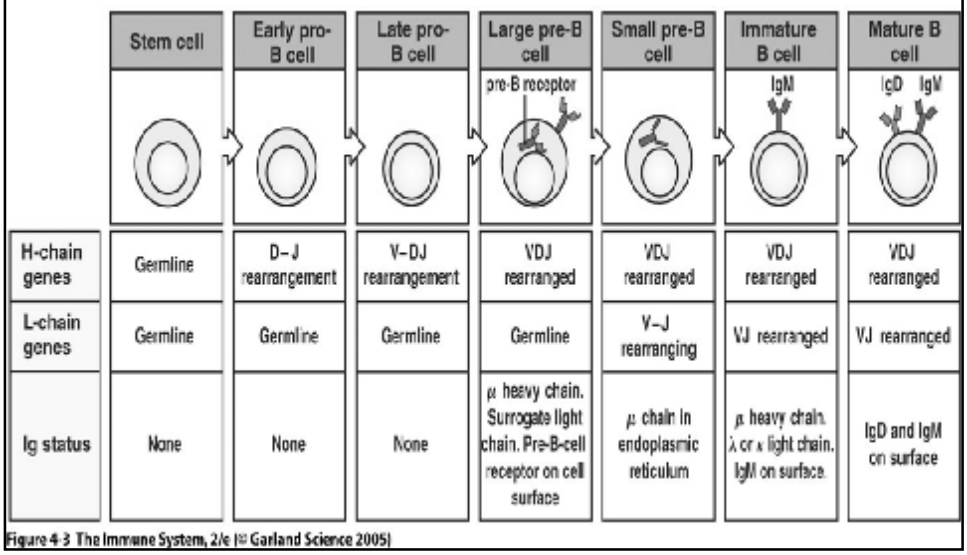
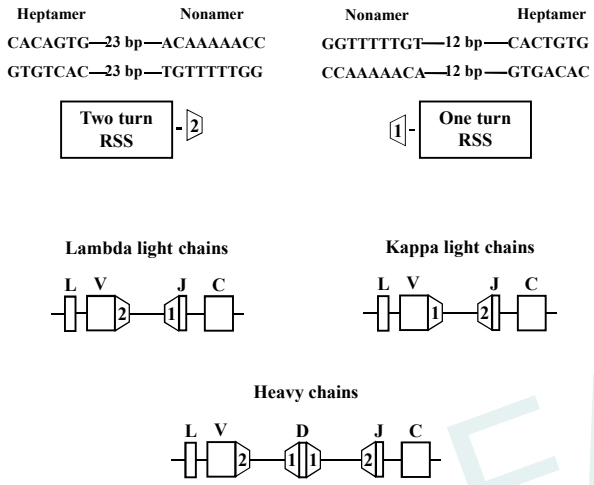


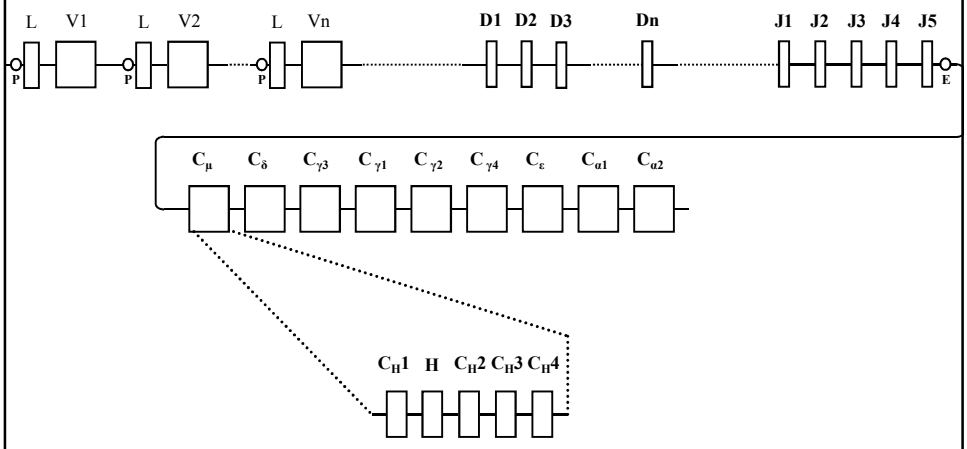
Figure 4-3 The Immune System, 2/e (© Garland Science 2005)

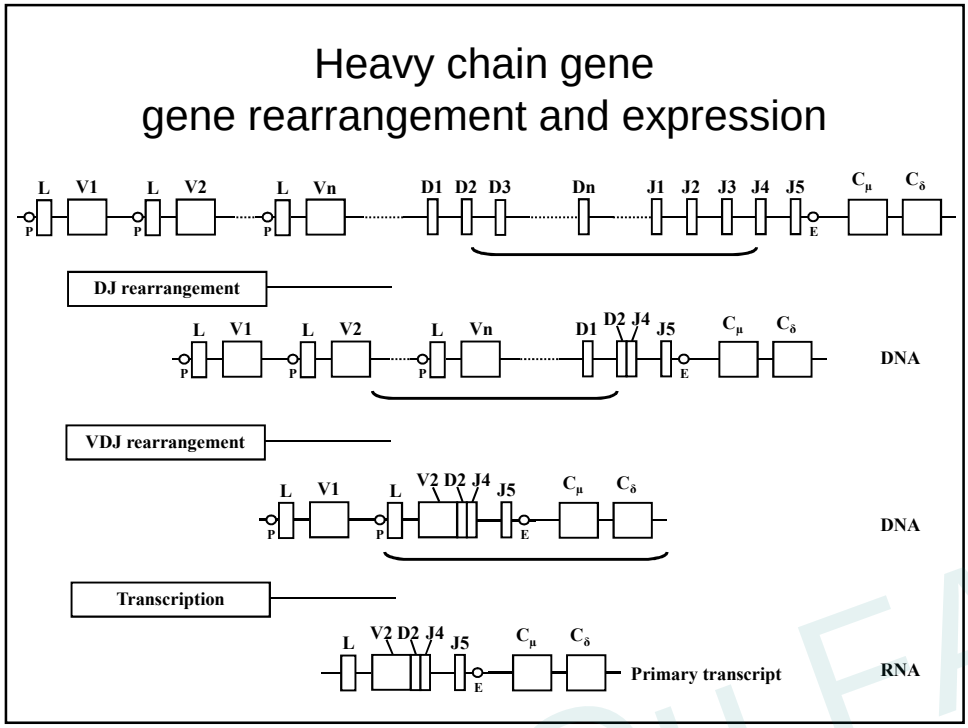
Mechanism of DNA Rearrangements

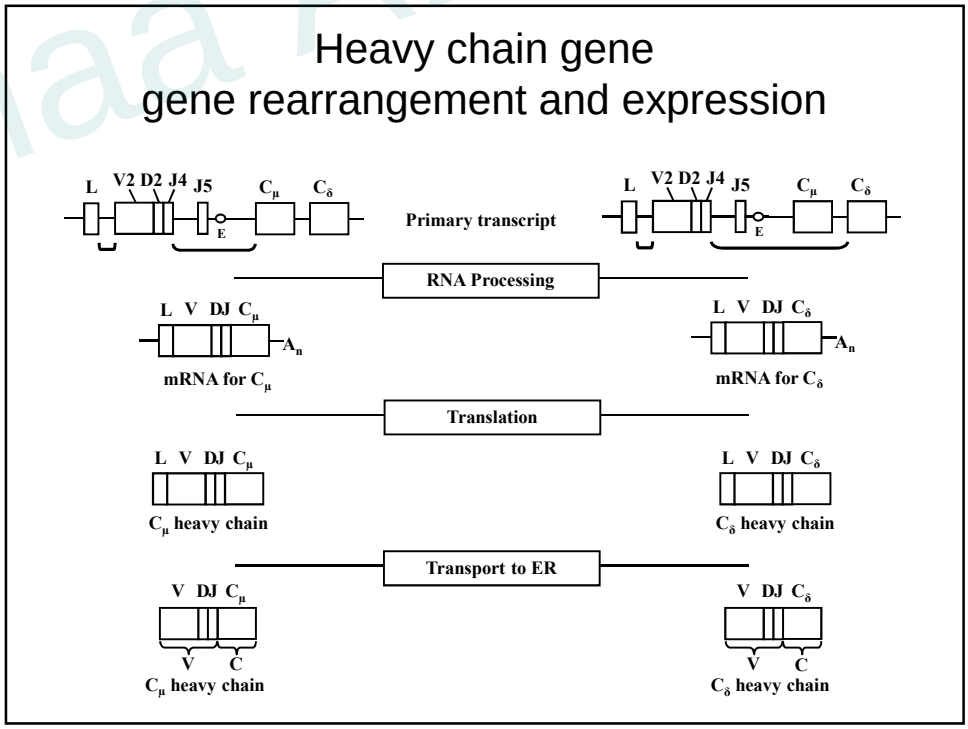
Recombination signal sequences (RSS)
- Nonamer (9)
- Heptamer (7)



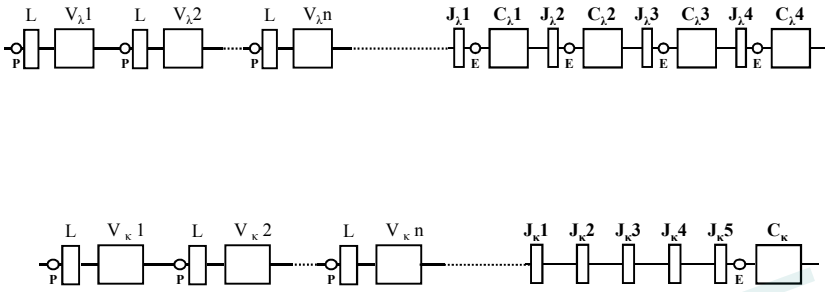
Heavy chain gene family germline gene organization



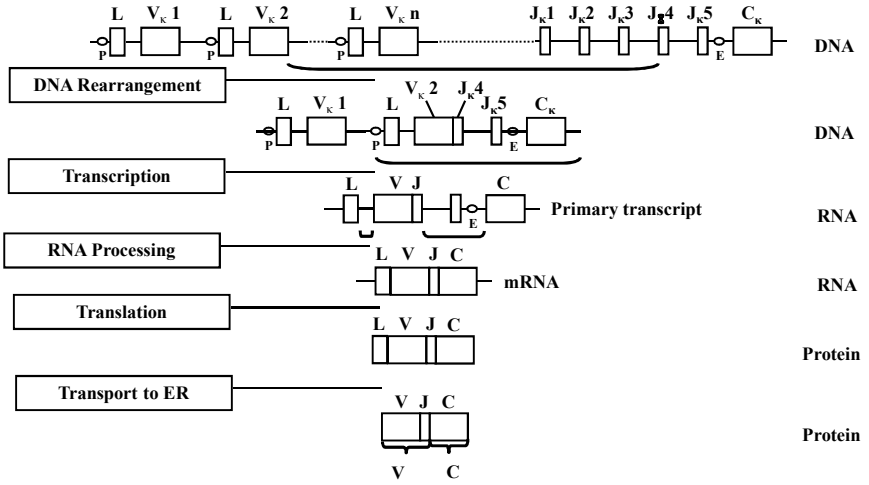


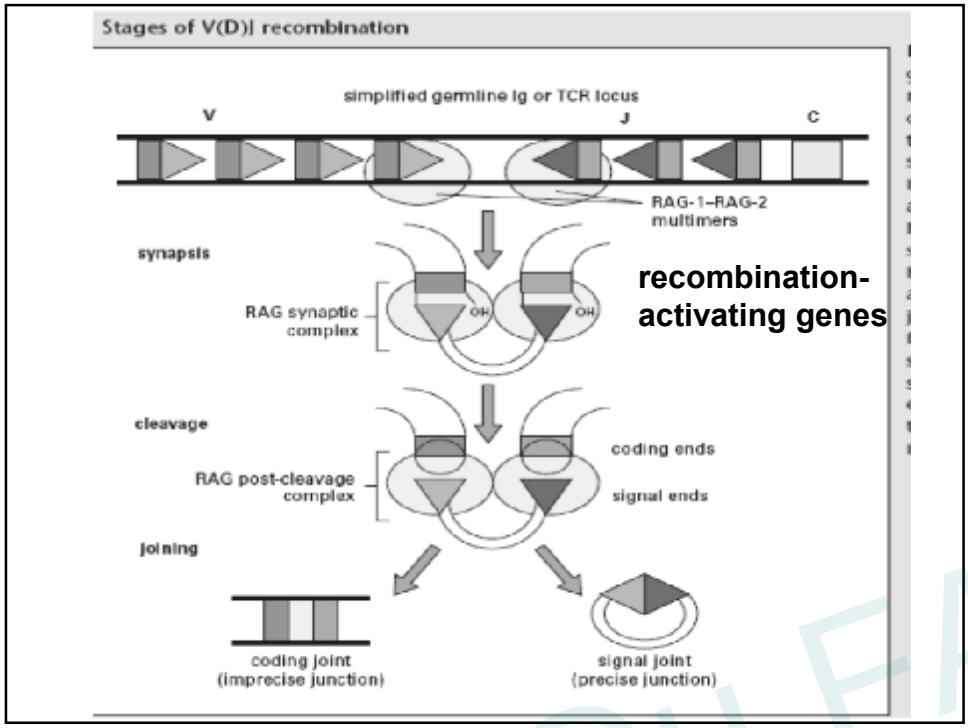


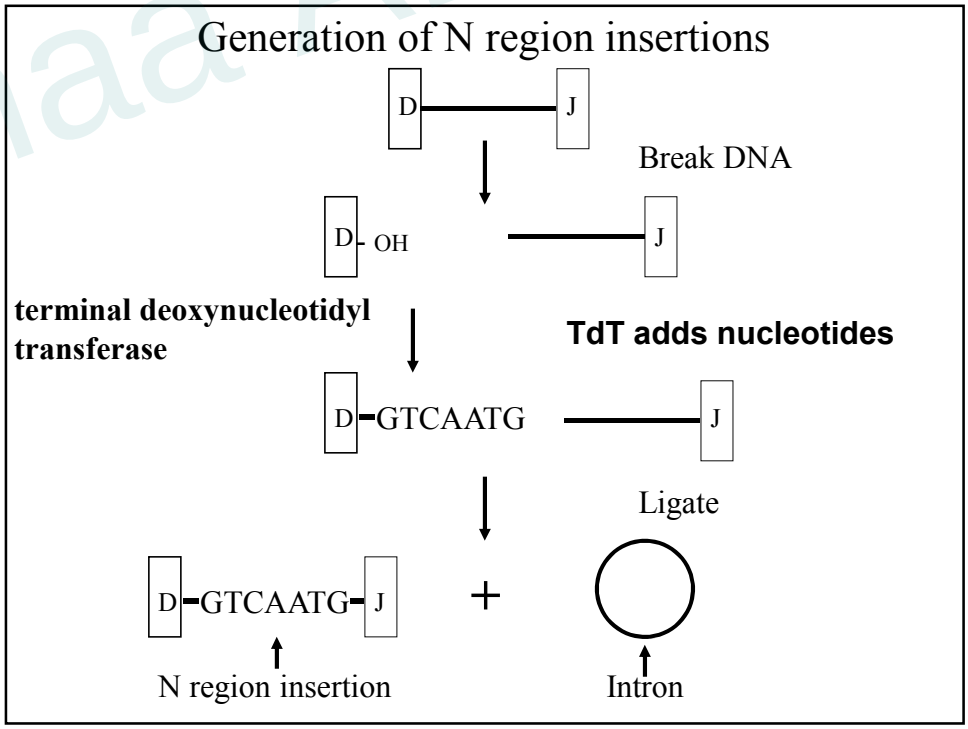
Light chain gene
germ line gene organization



Light chain gene
gene rearrangement and expression



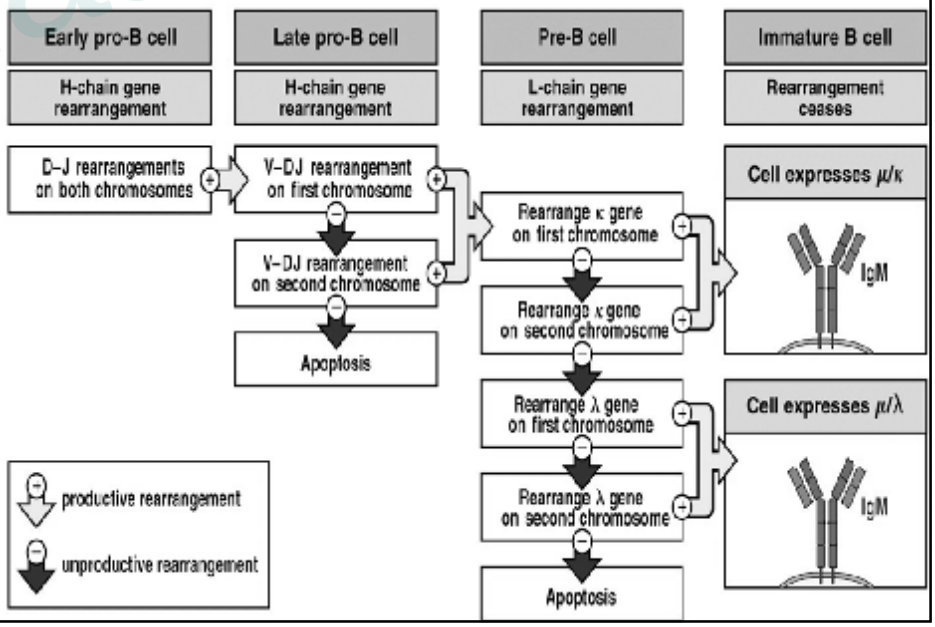




Origin of Antibody Diversity
Current concepts

- Multiple V genes
- V-J and V-D-J joining
- Junctional diversity
- N region insertions
  – Amino acid sequences not encoded in the germline

Productive Gene Rearrangement ----> Survival



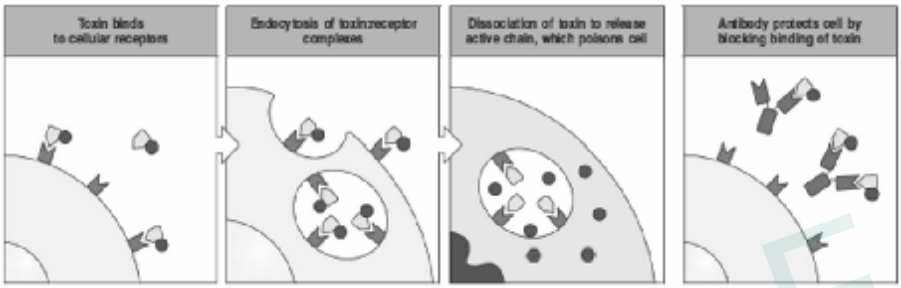
Functions of Immunoglobulins

- **Recognize and bind Ag**
- **Effector functions**
  - promote the killing
  - removal of the immune complex
    - Fixation of complement
    - Binding to various cells

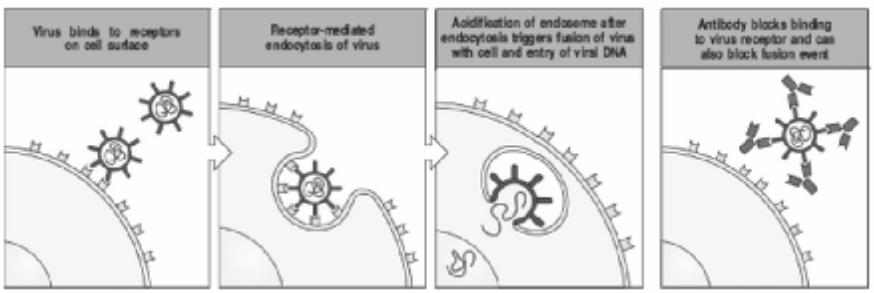
Actions of antibodies

- **Neutralize** bacterial toxins
- **Agglutinate** bacteria, preventing their spread and facilitating phagocytosis
- **Activation the complement** leading to bacterial lysis
- **Attraction** of phagocytes
- attach to the surface of bacteria and act as opsonins, enhance phagocytosis (Opsonization)
- **Stimulation** of inflammation
- Prevent adhesion of bacteria to their target cells
  - e.g. IgA on mucosal surfaces

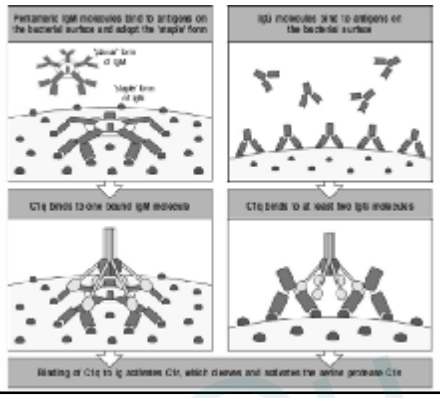
Neutralization of toxins by IgG antibodies their damaging action



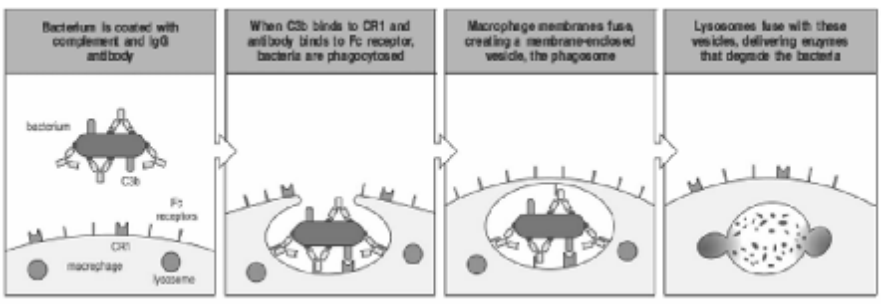
Viral infection of cells can be blocked by neutralizing antibodies



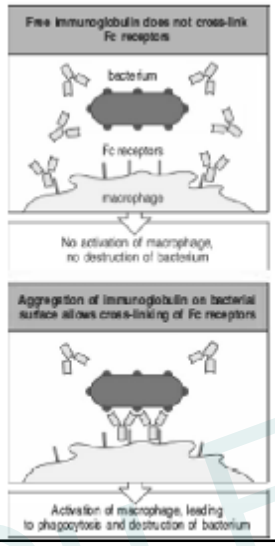
The classical pathway of complement activation is initiated by the binding of C1q to antibody on a pathogen surface.



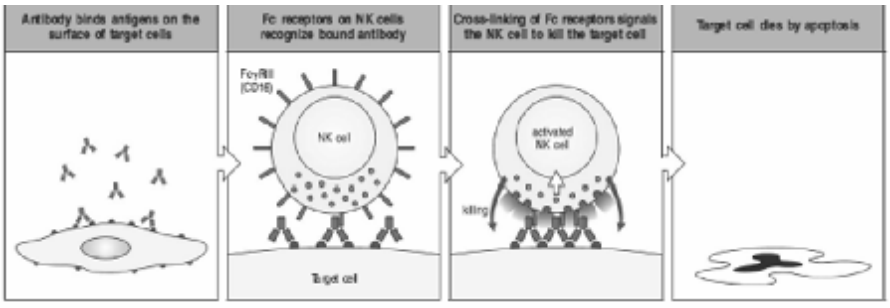
Fc and complement receptors on phagocytes trigger the uptake and degradation of antibody coated bacteria.



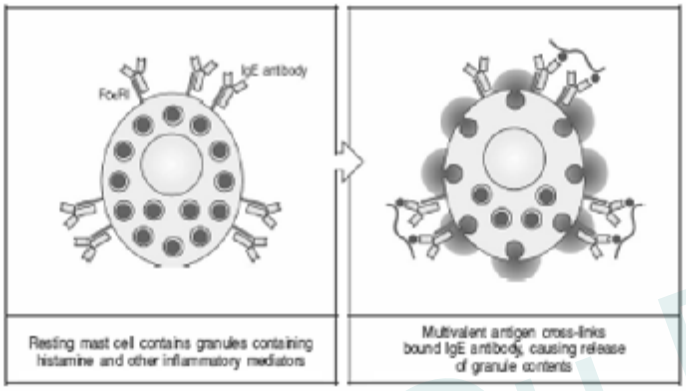
Bound antibody is distinguishable from free immunoglobulin by its state of aggregation.



antibody dependent cell-mediated cytotoxicity (ADCC)



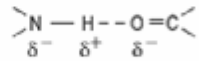
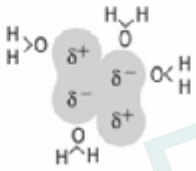
IgE crosslinking on mast-cell surfaces leads to a rapid release of inflammatory mediators.



Antibodies act as adapter molecules for immune effector systems

1 immune complex	2 immune complex/ pathogen	3 target cell/ pathogen	4 antigen
C1q → complement classical pathway	FcR → opsonization phagocytosis	FcR → recognition killing	FcR → sensitization cell activation

The noncovalent forces that hold together the antigen:antibody complex

Noncovalent forces	Origin	
Electrostatic forces	Attraction between opposite charges	
Hydrogen bonds	Hydrogen shared between electronegative atoms (N, O)	
Van der Waals forces	Fluctuations in electron clouds around molecules polarize neighboring atoms oppositely	
Hydrophobic forces	Hydrophobic groups interact unfavorably with water and tend to pack together to exclude water molecules. The attraction also involves van der Waals forces	

Acquired immunity

تصنف المناعة المكتسبة بحسب دور المضيف إلى:

- **مناعة فاعلة active immunity**
- **مناعة منفعلة passive immunity**
- **مناعة متبناة adoptive immunity**