

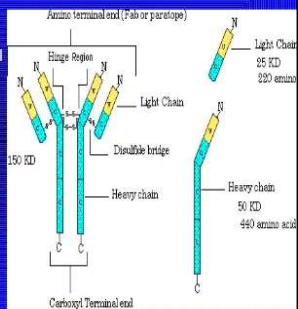
## Immunoglobulin

Immunoglobulin is a glycoprotein that is made in response to an antigen and can recognize and bind to the antigen that caused its production.

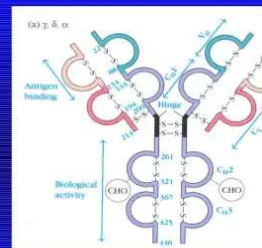
- Are gamma globulins
- Synthesized by plasma cells
- Constitute 25-30 % of total serum proteins
- Antibodies are present in serum, tissue fluids and mucosal surfaces.
- All antibodies are immunoglobulins, but all immunoglobulins may not be antibodies

## Basic structure

- Composed of 4 polypeptide chains.
- 2 identical light and 2 identical heavy chains
- Linked by disulphide bonds
- Light chains similar in all immunoglobulins
- Light chains occur in 2 varieties kappa and lambda
- Light and Heavy chains are subdivided into variable and constant region.
- Each heavy and light chain contains amino terminal in variable region carboxy terminal in constant region

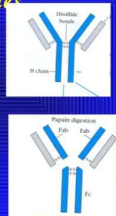


- Heavy chains are structurally and antigenically distinct for each class
- Each immunoglobulin peptide chain has intra chain disulphide bonds- form loops
- Each loop is compactly folded to form a globular structure-domain
- Light chain contains a single variable domain (VL) and a single constant domain (CL).
- Heavy chain contains one variable domain (VH) and 3 constant domains (CH1, CH2, CH3)
- Hinge region is the segment in heavy chain - between CH1, CH2



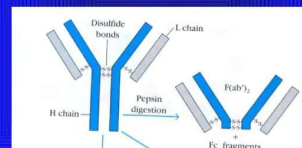
## Digestion with proteolytic enzymes

- Papain enzyme
- Peptide bonds in the hinge region are broken
- Produces 3 fragments
- 2 identical fragments called Fab fragments – antigen binding activity.
- Other fragment called Fc fragment (Fraction crystallizable)



## Pepsin digestion

- Produce a single fragment composed of two Fab like subunits F(ab)<sub>2</sub> binds antigen
- Fc fragment is not recovered- digested to small numerous peptides.

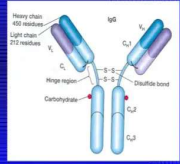


**Classification**

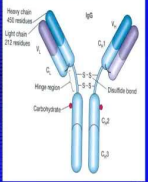
- Based on structure and antigenic nature of H chain the immunoglobulins are classified into 5 classes.
- Ig G- (gamma)
- Ig A- (alpha)
- Ig M- (mu)
- Ig D- (delta)
- Ig E- (epsilon)

**Immunoglobulin G (Ig G)**

- Most abundant class in serum
- Constitutes 80% total immunoglobulin
- Present in blood, plasma and tissue fluids
- Contains less carbohydrate than other immunoglobulins
- It has a half life of 23 days: the longest of all of the immunoglobulin isotypes

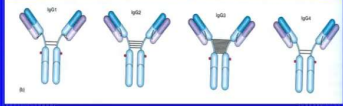


- Crosses placenta and provide natural immunity to foetus and neonate at birth
- Acts against bacteria and viruses by opsonizing
- Neutralize toxin
- Activate complement by classical pathway
- Catabolism of IgG is unique in that it varies with its serum concentration



**Sub classes of Ig G**

- Ig G1, Ig G2, Ig G3, Ig G4.

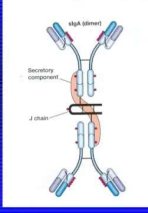


**Biological function of subclasses**

- IgG1, IgG3, IgG4 – cross placenta and protect foetus
- IgG3 activates complement
- IgG1 and IgG3 binds to Fc receptor on phagocytic cells, monocytes and macrophages and mediate opsonization.

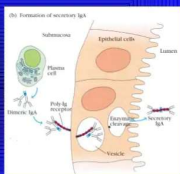
**Immunoglobulin A (Ig A)**

- Constitutes 10-15 % of total immunoglobulins
- Present in milk, saliva, tears, mucous of respiratory tract, digestive tract and genitourinary tract
- In serum exist as monomer
- In external secretions exist as dimer called secretory immunoglobulin.
- Has 'J' chain and secretory piece.
- Half life: 6-8 days



### Formation of secretory Ig A

- Dimeric Ig A binds to the receptor on the surface of the epithelial cells –endocytosed and transported across the cell to the luminal surface
- After reaching the surface, the poly-Ig receptor is cleaved
- The portion of the receptor that remains attached to the Ig A dimer – secretory component
- Secretory piece protects Ig A from digestive enzymes and denaturation by bacterial proteases

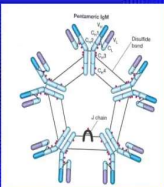


### Functions

- Provides local immunity.
- Secretory Ig A binds to surface antigens of microorganism and prevent its attachment and invasion of the mucosal surfaces of respiratory and digestive tract- immune elimination.
- Secretory IgA provides important line of defense against *salmonella*, *Vibrio cholerae*, *N. gonorrhoeae*, influenza virus and poliovirus.
- Secretory IgA present in breast milk protects newborn during first months of life.
- Activates complement by the alternative pathway
- Promotes phagocytosis and intracellular killing of microorganisms

### Immunoglobulin M (Ig M)

- Accounts for 5-10% of total serum proteins
- Polymer of five monomeric units (pentamer)
- Held together by disulfide bonds and 'J' chain
- Mol. Wt. of 900,000-10,00,000 (millionaire molecule)
- Half life: 5 days



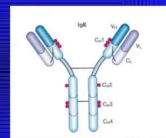
- Most of IgM (80%) present intravascularly
- Present in low concentration in intercellular tissue fluids
- Cannot cross placenta
- Presence of IgM antibody in serum of newborn indicate congenital infection.
- Earliest immunoglobulin to be synthesized by foetus (20 weeks)
- First immunoglobulin to be produced in primary response to antigen
- Relatively short-lived hence it's demonstration in the serum indicates recent infection
- Monomeric IgM appears on the surface of unstimulated B lymphocytes and act as receptors for antigens

### Functions

- It agglutinates bacteria
- Activates complement by classical pathway
- Causes opsonization and immune hemolysis
- Believed to be responsible for protection against blood invasion by microorganisms

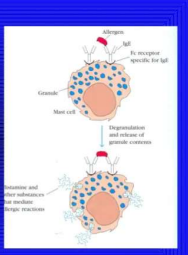
### Immunoglobulin E (Ig E)

- Structure is similar to Ig G
- Has 4 constant region domains.
- Mol. Wt. 1,90,000
- Half life: 2 days
- Heat labile (inactivated at 56°C in 1 hour)
- Normal serum concentration 0.3 ug/ml
- Mostly present extra cellularly
- Does not cross placenta



- Produced in the lining of respiratory and intestinal tract
- Known as reagin antibody
- Does not activate complement nor agglutinate antigens
- Binds to the Fc receptors on the membranes of blood basophils and tissue mast cells
- Mediates immediate hypersensitivity reaction and P.K. reaction
- Responsible for symptoms of anaphylactic shock, hay fever and asthma.
- Play a role in immunity against helminthic parasites

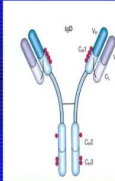
- IgE binds to Fc receptors on the membrane of blood basophils and tissue mast cells.
- When two IgE molecules on the surface of these cells are cross linked by binding of the same antigen- cells degranulates.
- Release histamine and pharmacological mediators of anaphylaxis from cell.
- The physiological role of IgE appears to be protection against pathogens by mast cell degranulation and release of inflammatory mediators



- Mediates P.K. reaction (PRAUSNITZ & KUSTNER)
- The presence of a serum component responsible for allergic reaction was first demonstrated by Prausnitz and Kustner in 1921.
- Kustner was suffering from atopic hypersensitivity to certain species of fish
- Kustner's serum was injected intracutaneously in Prausnitz
- After 24 hrs small quantity of cooked fish antigen was injected at the same site
- A wheal and flare reaction occurred within minutes.

**Immunoglobulin D (Ig D)**

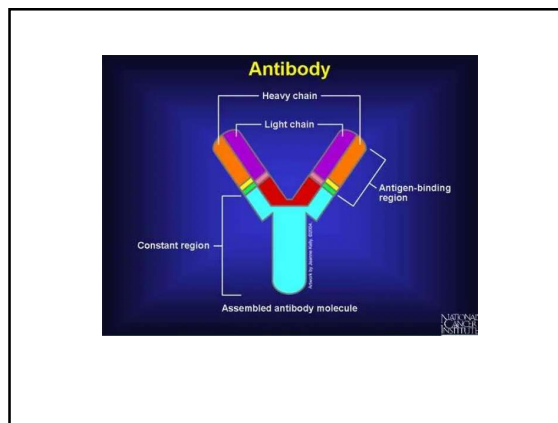
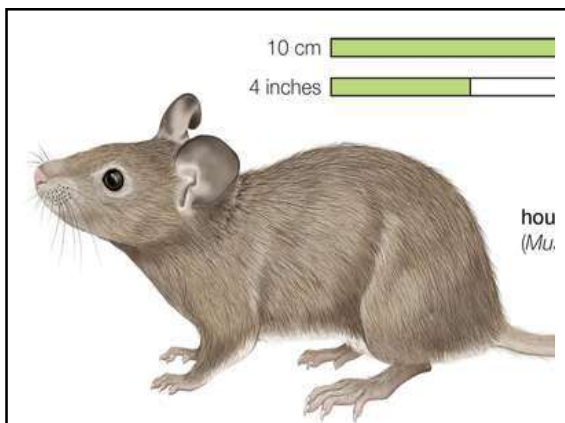
- Structure is similar to IgG
- Serum concentration 30 micrograms per ml
- Constitutes 0.2% of total immunoglobulins
- Half life: 3 days
- IgD together with IgM is major membrane bound immunoglobulin on unstimulated B lymphocytes-acts as recognition receptors for antigens



**Take home message**

**Role of different immunoglobulin classes**

- IgG: Protects the body fluids
- IgA: Protects the body surfaces
- IgM: Protects the blood stream
- IgE: Mediates type I hypersensitivity
- IgD: Role not known



### Isotypes

- Antigenic (amino acid) differences in constant regions of heavy chains
- IgG and IgM are different isotypes; constant region of their H chains ( $\gamma$  and  $\mu$ ) is different antigenically

### Immunoglobulin Isotypes

- Definition
- Location
- Occurrence
- Importance
  - Ig levels
  - B cell tumors
  - Immunodeficiencies

IgG ( $\gamma$ ), IgA ( $\alpha$ ), IgM ( $\mu$ )



### Idiotype

- Antigenic determinants formed by specific amino acids in hypervariable region
- Each idiotype is unique for immunoglobulin produced by a specific clone of antibody-producing cells
- Anti-idiotype antibody reacts only with hypervariable region of specific immunoglobulin molecule that induced it

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