Immunoglobulins or Antibodies (Igs)

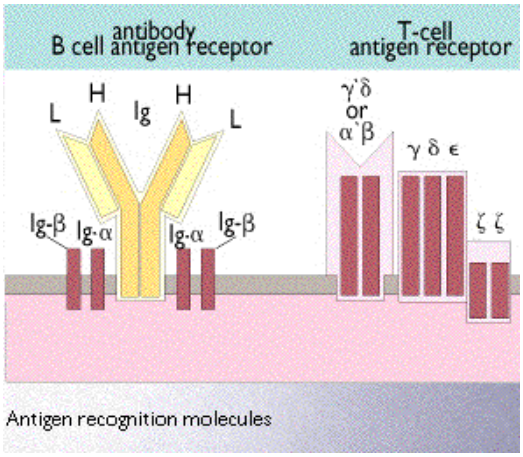
Immunoglobulins are glycoproteins in the immunoglobulin superfamily that function as antibodies. The terms *antibody* and *immunoglobulin* are often used interchangeably. They are found in the blood and tissue fluids, as well as many secretions. An antibody is used by the acquired immune system to identify and neutralize foreign objects like bacteria and viruses. Each antibody recognizes a specific antigen unique to its target. By binding their specific antigens, antibodies can cause agglutination and precipitation of antibody-antigen products, prime for phagocytosis by macrophages and other cells, block viral receptors, and stimulate other immune responses, such as the complement pathway.

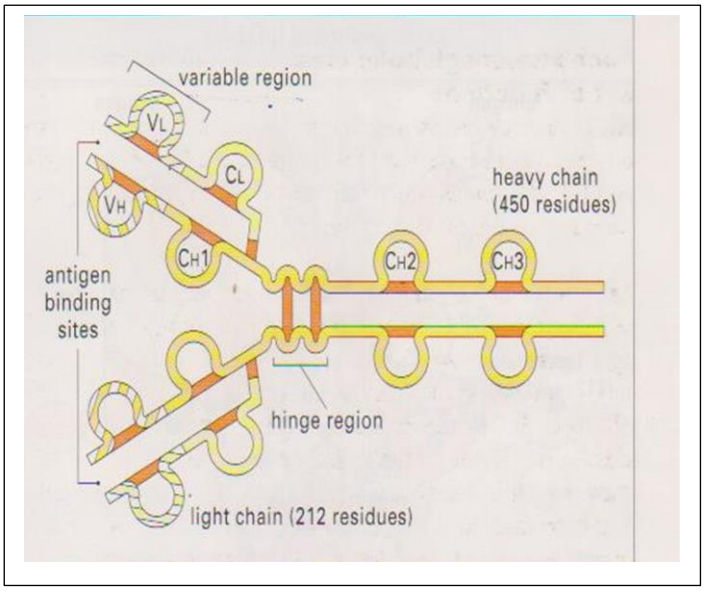
- They are glycoprotein constitute about 20% of serum proteins, they are secreted by plasma cells after B. cell activation .
- it's a soluble form of B-cells surface Ag-receptors. In general each Abs can bind specifically to just one Ag.
- Ig. Consists of at least one basic unit called monomer, the later also consists of two heavy chains which are identical.
- In addition to that two light chains either **Kappa or Lambda.**
- Nomenclature of Ig depends on the type of heavy chain, it might be either **Alpha , Beta, Gamma, Epsilon or Delta**.
- There are disulfide bonds (S-S bonds) bind between chains (inter-chain bonds)and intra-chains bonds .

The four chains show two ends NH2 terminal; end which is variable and superimposed in antigen binding and also it is known as **Fragment antigen binding region (Fab)region**. The other end is Carboxyl terminal end (COOH) end ,it is constant and is known as **Fragment crystalizable (FC)** region . Via this region antibody binds to the FC receptors on B .cells and macrophages.

The amino acid sequence either in heavy or light chains are not linear due to intrachain (S-S) bonds which make chain like the dome , so called **Domains**.

The Ag recognition of foreign Ag is the hallmark of the specific adaptive immune response. Two distinct types of the molecules are involved in these processes. The immunoglobulins and the T-cell Ag-receptor (TCR).





They have an important functions :

1- Domains in variable regions of light and heavy chains have binding activity to antigen .

2- Domains at constant regions have biological activities like :

a- Complement binding .

b- Cytophilic activity.

Antibody Structure

Repeating Domains of ~110 a/a

Intrachain disulfide bonds within each domain

- Heavy chains: 1 VH and either 3 or 4 CH (CH1, CH2, CH3, CH4)
- Light chains: 1 VL and 1 CL

Hinge Region: Rich in proline residues (flexible)

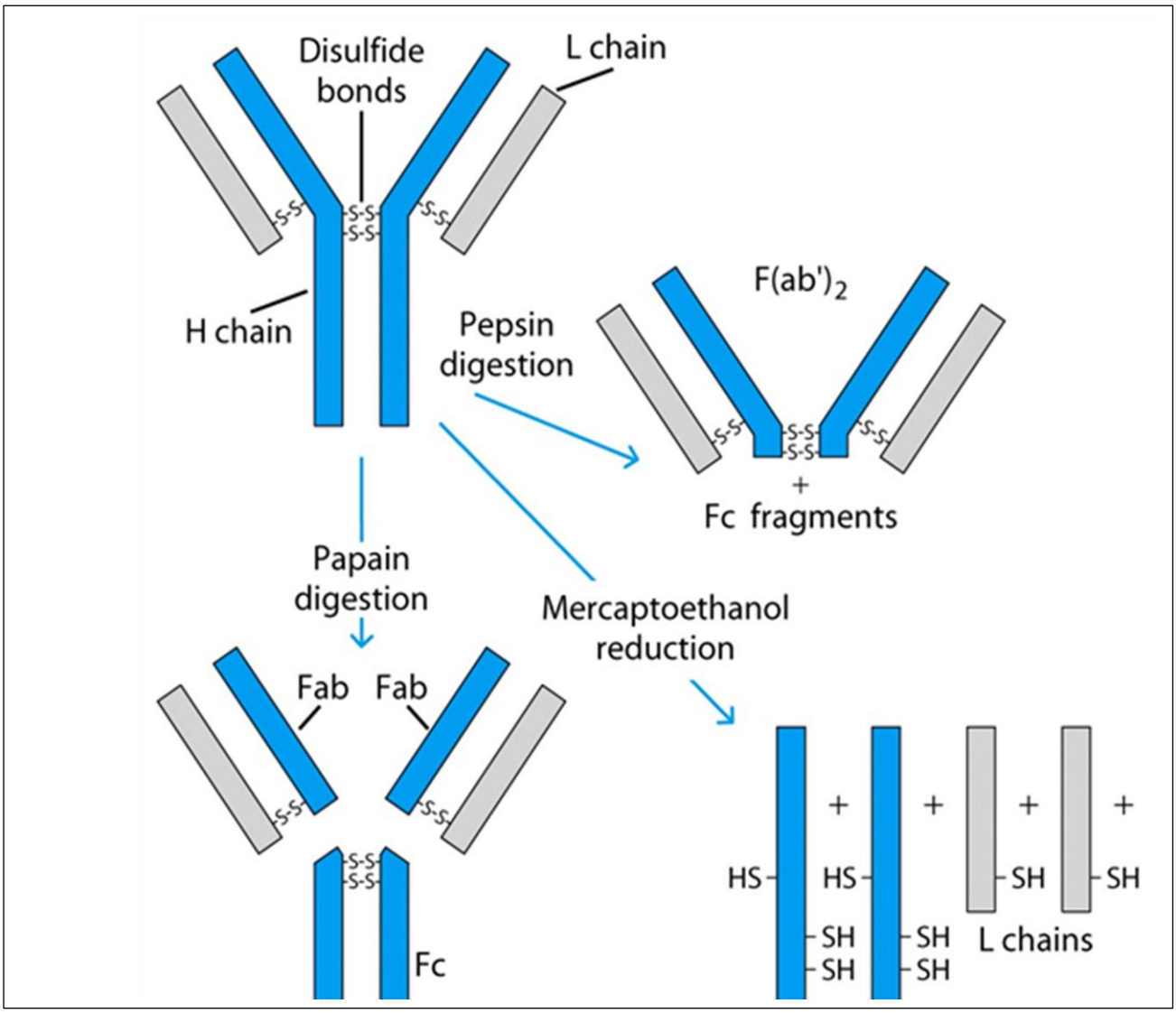
Hinge found in IgG, IgA and IgD

Proline residues are target for proteolytic digestion (papain and pepsin)

Rich in cysteine residues (disulfide bonds)

IgM and IgE lack hinge region

They instead have extra CH4 Domain



Interaction of Antibodies with Antigens

The binding of Ag to Ab involves the formation of multiple non covalent bounds between the Ag and amino acids of the binding site including:- hydrogen and electrostatic bounds, Van der Waals and hydrophobic forces) are weak by comparison with covalent bounds. However the large number of interaction results in a large total binding energy.

Types of Immunoglobulins

According to the constant region , the immunoglobulines are classified into:

IgG, the heavy chain there is **Gamma** type .

IgM. , ==========Muta.

IgE.,= = = = = = = = ========Epsilon .

IgD. ,==========Delta .

IgA., ==========Alpha.

IgG: It is predominant Ig and constitute about 75% of total serum Igs. it is predominant in secondary immune response ,so its yield is late. There are four subclasses, IgG1 is the predominant and constitute about 65% of the total IgG . IgG2 is about 23-25% while IgG3 is 6% and IgG4 IS 4%. IgG is 7S sedimentation rate, MW is 15000 Daltons and 19-23 half life.

- **It is the only Ig that can pass through placenta and give defense to the baby in the first six months of life .**
- It has the ability to fix complement.
- it plays a role in **Antibody Dependent Cell Cytotoxicity (ADCC),** through this mechanism IgG binds to the FC receptor present on cells like polymorphnuclear cells , killer cells B.cells and macrophages, while the antigen will bind to these molecules (Igs.) via FC regions , killing action will occur.
- It is good opsonin , opsonization means that the antibody will coat the foreign antigen to make it susceptible to phagocytosis,

(Recognized easily by the phagocyte after binding with antibody

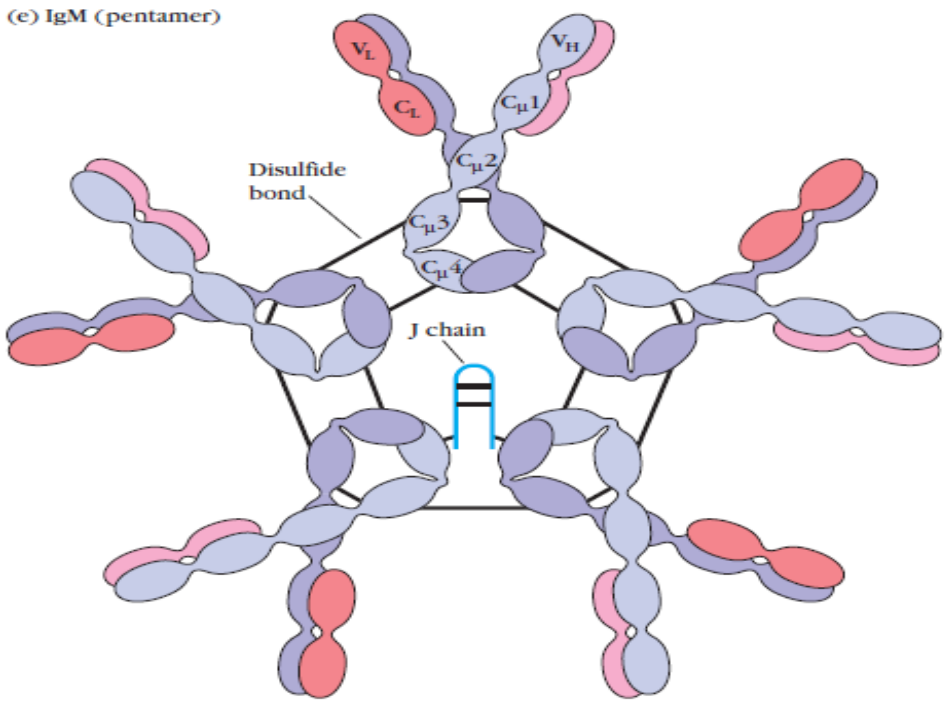
IgG.

- ❖ is blocking antibody , it means that this antibody can blocks certain reactions of antigens and antibodies through binding to a certain sites on antigens.
- ❖ It is neutralizing antibody , IgG can neutralize toxins suitable for its bindings.

IgM. : It is predominant in primary immune response so it arise early, it constitute about 105 of the total serum Igs. Its MW. Is 900kDs.and 19 S sedimentation rate as well as 2-3 days half life. There are two forms of IgM, monomeric and pentameric forms , this typing is according to the number of basic units that found.

IgM . is present on the surface of B. lymphocyte as part of antigenic receptor of these cells.

It is good complement fixing antibody ,because of its pentameric form which enable it to bind many antigen complex molecules at the same time,



Biological activities of IgM:

1-Because it is pentameric , so it possess 10 Fab regions so it is good agglutinin . Agglutination is the reaction between antibody

wit suitable particulate antigen.

2- IgM Is opsonizing antibody

3- IgM can fix complement by classical way .

IgA:

It is the main immunoglobulin present in body secretions , tears , saliva, mucous, genital fluids. It is present into two forms ;

1- Monomeric type IgA1 and it has one basic unit. , serum IgA is monomeric .

2- Dimeric form IgA2, it is secretory IgA consists of two basic units bound to each via secretory piece, this form shows most of IgA

biological activities. is six times more than IgA1.

Its MW is 18 kD. and of 19s sedimentation rate. half life is 2-5 days .

Synthesis of IgA:

IgA undergo synthesis in the lamina propria of the mucous membranes in plasma cells . It is synthesized as monomer IgA,

Other polypeptide chain synthesized by joining chain(other plasma cell) will combine other IgA molecule to form the dimeric form. The dimeric IgA cross the mucous membrane to the lumen of the tract then the basal layer cells secrete special component which will combine to the dimeric IgA to give rise to the secretory form into the lumen. The importance of secretory piece is to :

a- Help IgA to pass quickly to the lumen

b- Prevent IgA from lytic enzymes.

functions of IgA :

Secretory IgA has the following functions :

1- neutralizing antibody .

2- Opsonization

3- Binds to polymorphnuclear cells

4- Blocking Ab.

5- Complement fixing . Serum IgA has unknown functions .

IgE:

Its heavy chain is epsilon type , its MW is 16kDs. and of 17S sedimentation rate, its half life is 2-3 days.

It is cytophilic antibody , It binds on mast cell s and basophils and predominates in allergy (Reagen) and parasitic infections.

IgE release:

If an individual exposed to a foreign substance like penicillin , pollen,(Allergen) , this stimulate plasma cells to secrete IgE , this IgE will bind to FC receptors on mast cells . on second exposure to the same allergen B bound IgE on mast cell will react with it soon.

This reaction will lead to the release of mediators of mast cells like histamine (Allergy mediators). Mediator release leads to anaphylaxis.

IgD: It is present on B.cells and its biological activity is not known though it shares in B. cell receptor.

It is MW. is 170kDS. with 7S sedimentation rate and it is half life is 2-8 days.

Biological Activities of Antibodies

1-Opsonization: Ab. acts as starter for the macrophages and makes antigen more recognizable by macrophages.

2- Complement fixation .

3- Toxin neutralization .

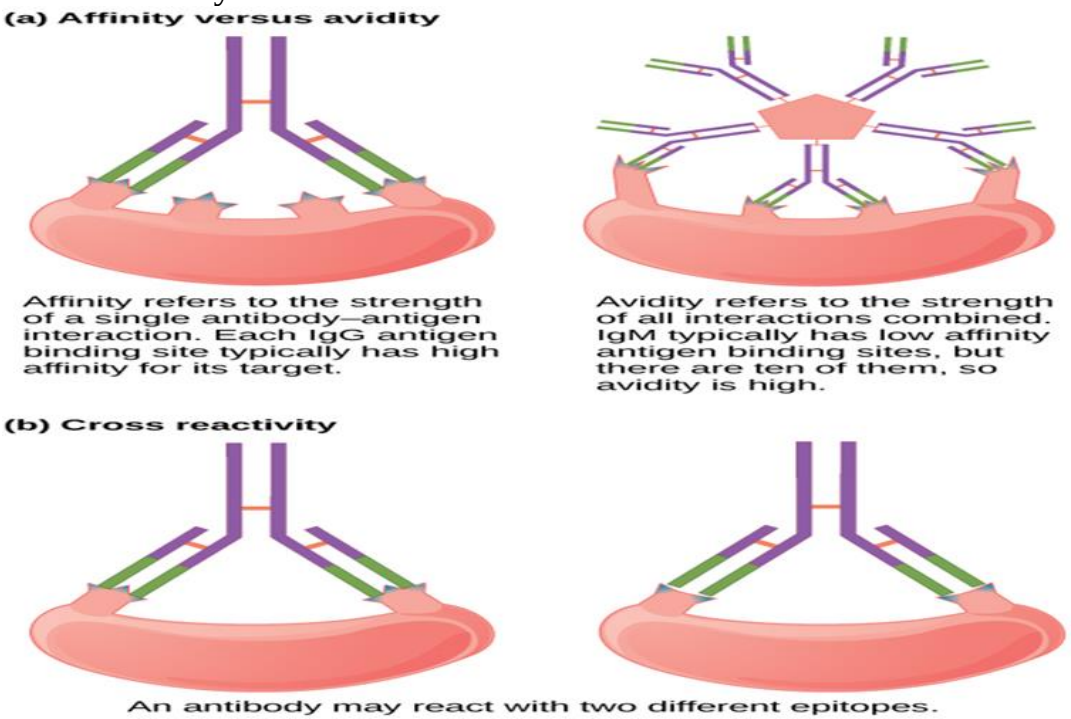
4- Viral neutralization .

5-Antibody dependent cell cytotoxicity .

6-Diagnostic importance.

Affinity and Avidity

The strength of the single bond between Ag and Ab is known as the Ab-affinity, it is the sum of the attractive and repulsive forces.
Whereas the overall strength of interaction between the Ab and Ag indicates Ab-avidity.
The avidity is likely to be more relevant than affinity, as naturally occurring Ags are multivalent.
When some of the epitopes of an Ag are shared by another Ag then a proportion of the Abs directed to that Ag and this phenomenon is termed cross-reactivity.



Generation of Ab-diversity:

Abs are remarkably diverse and provide enough different combining sites to recognize the millions of antigenic shapes in the environment.

In fact, we produce more types of Ab than there are genes in our genome.

All these diversity generated by:

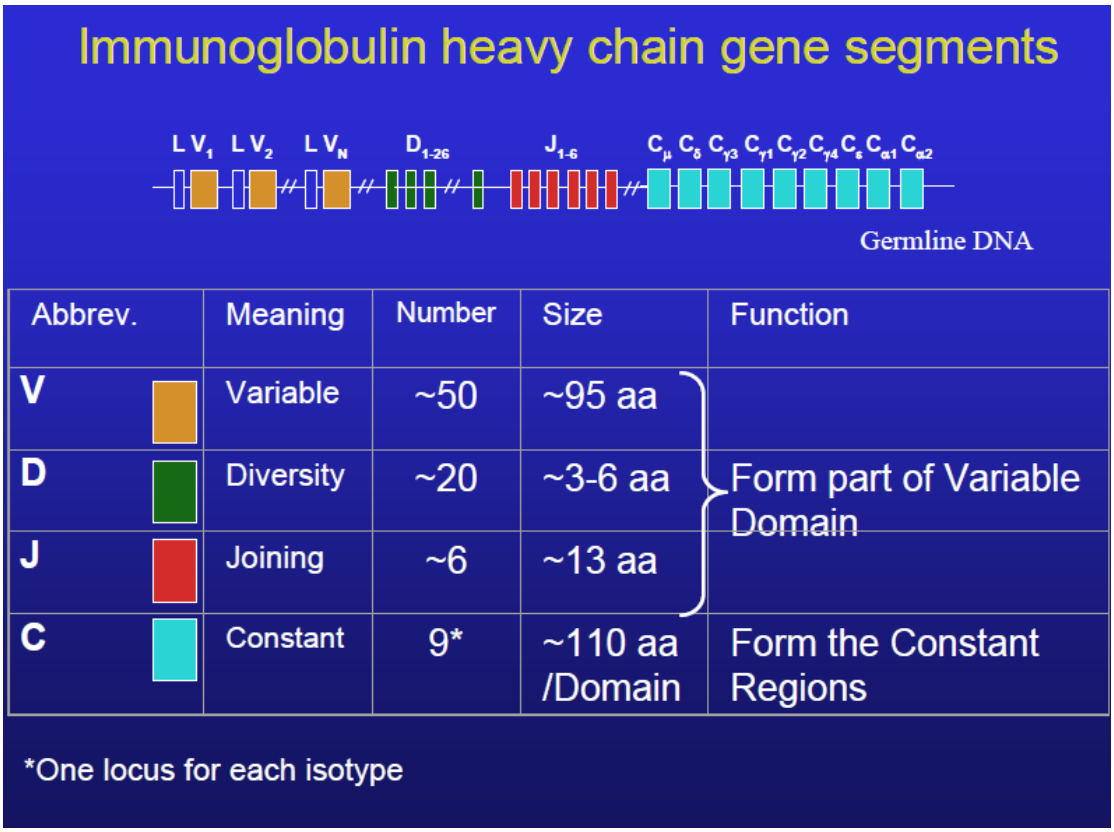
-multiple V-region genes in the germ line; i.e many gene coding for the variable (V) region.

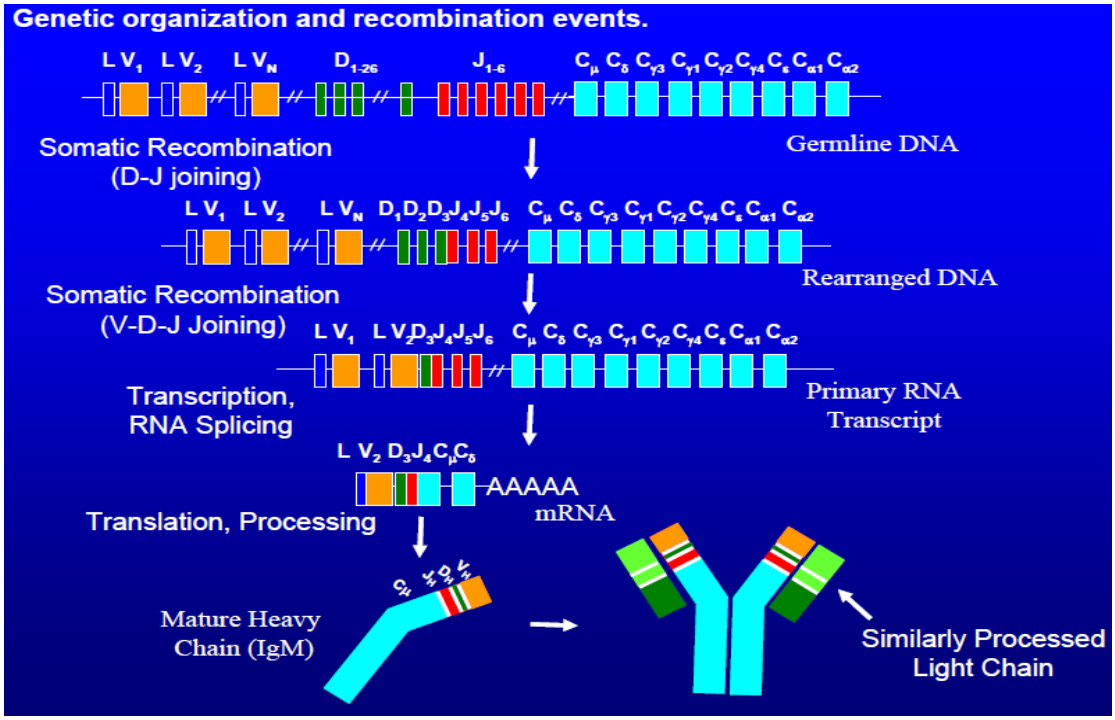
-Somatic recombination between elements forming a V-region gene.i.e a number of gene segments could recombine to give a complete V-gene.

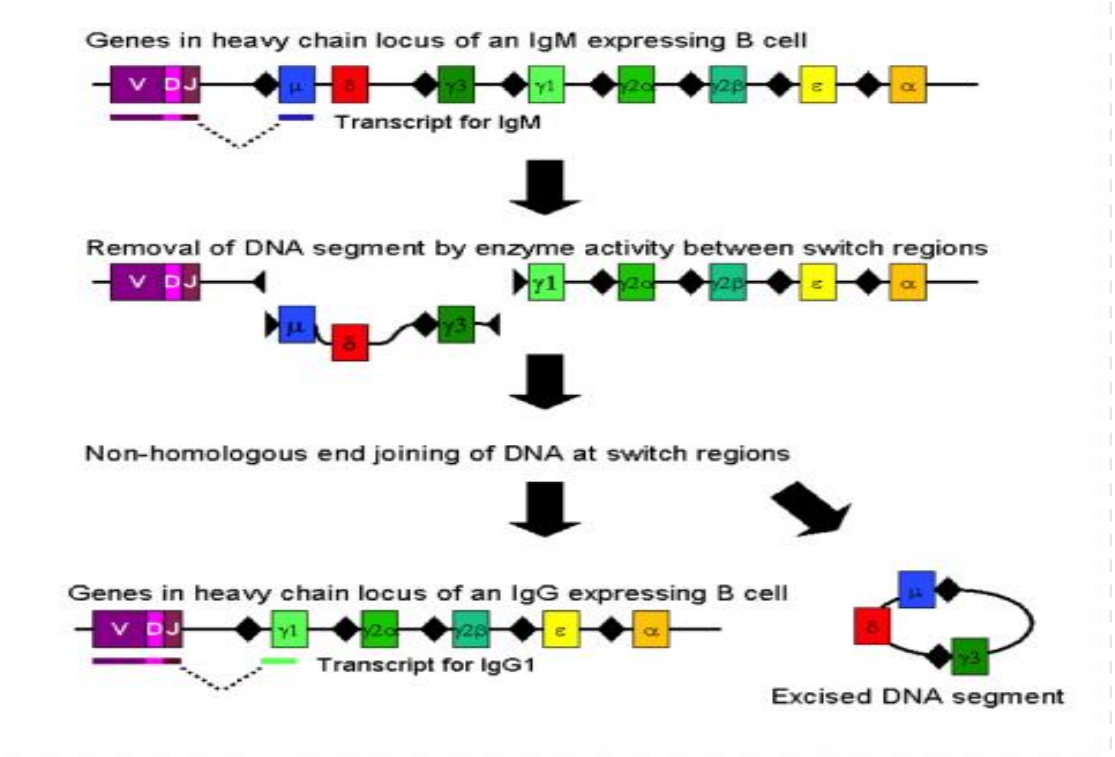
-Gene conversion; a panel of pseudo genes can also be used to alter the sequences within the variable region.

-Nucleotide addition; during cutting and joining of the DNA extra nucleotides may be inserted.

-Somatic mutation; so the relatively few genes give rise to many mutated genes during the lifetime of the individual




Genetic organization and recombination events.
Somatic Recombination
(D-J joining)
Germline DNA
Somatic Recombination
(V-D-J Joining)
Rearranged DNA
Transcription,
RNA Splicing
Primary RNA
Transcript
AAAAA
mRNA
Translation, Processing
Mature Heavy
Chain (IgM)
Similarly Processed
Light Chain


Genes in heavy chain locus of an IgM expressing B cell
Transcript for IgM
Removal of DNA segment by enzyme activity between switch regions
Non-homologous end joining of DNA at switch regions
Genes in heavy chain locus of an IgG expressing B cell
Transcript for IgG1
Excised DNA segment