IMMUNOGLOBULINS

BIOCHEMISTRY

Immunity

- body's ability to resist or eliminate potentially harmful foreign materials or abnormal cells
- consists of following activities:
  - Defense against invading pathogens (viruses & bacteria)
  - Removal of 'worn-out' cells (e.g., old RBCs) & tissue debris (e.g., from injury or disease)
  - Identification & destruction of abnormal or mutant cells (primary defense against cancer)
  - Rejection of 'foreign' cells (e.g., organ transplant)

- Inappropriate responses:
  - Allergies - response to normally harmless substances
  - Autoimmune diseases

- **PLASMA IMMUNOGLOBULINS PLAY A MAJOR ROLE IN THE BODY'S DEFENSE MECHANISMS**

- The immune system of the body consists of two major components:
- **B lymphocytes and T lymphocytes.**
- **The B lymphocytes** are mainly derived from bone marrow cells in higher animals and from the bursa of Fabricius in birds.
- **The T lymphocytes** are of thymic origin.

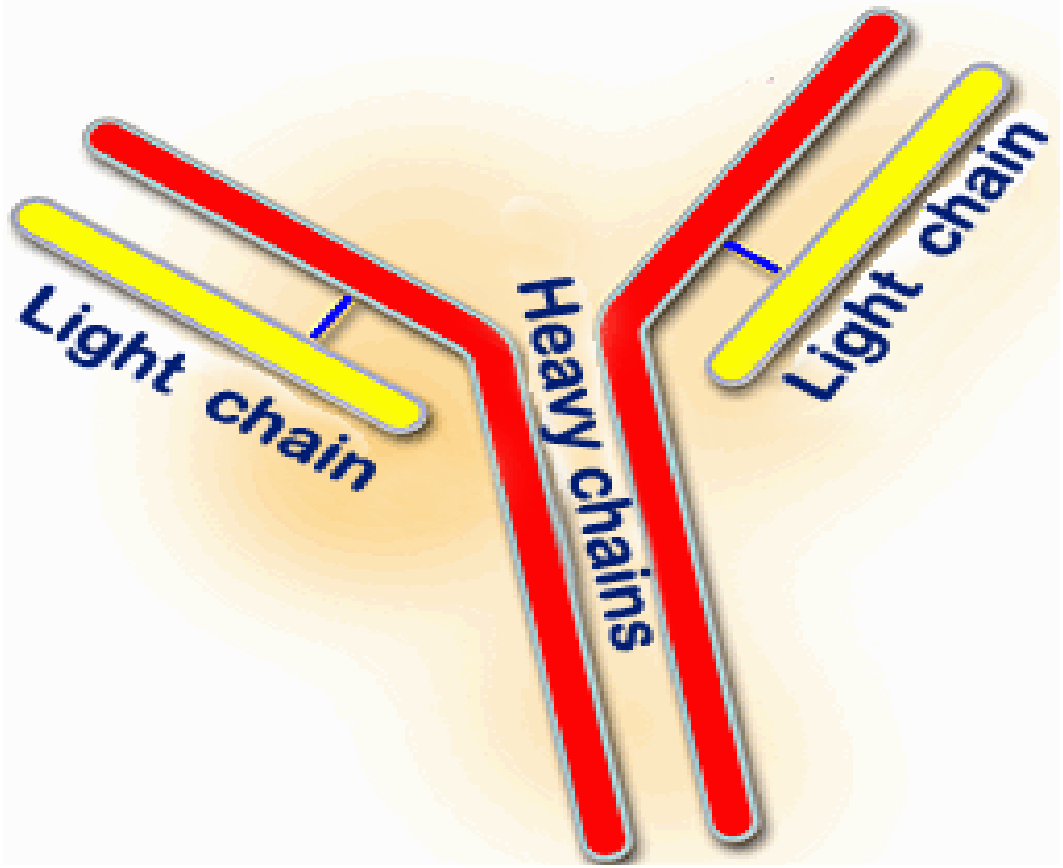
- The **B cells are responsible for the synthesis of circulating** humoral antibodies, also known as **immunoglobulins.**
- The **T cells are involved in a variety of important cell mediated immunologic processes such as:**

1. graft rejection
2. hypersensitivity reactions, and
3. defense against malignant cells and many viruses

Plasma Immunoglobulins

- Plasma Immunoglobulins, are synthesized mainly in **plasma cells.**
- **These are specialized cells** of B cell lineage that synthesize and secrete immunoglobulins into the plasma in response to exposure to a variety of **antigens.**

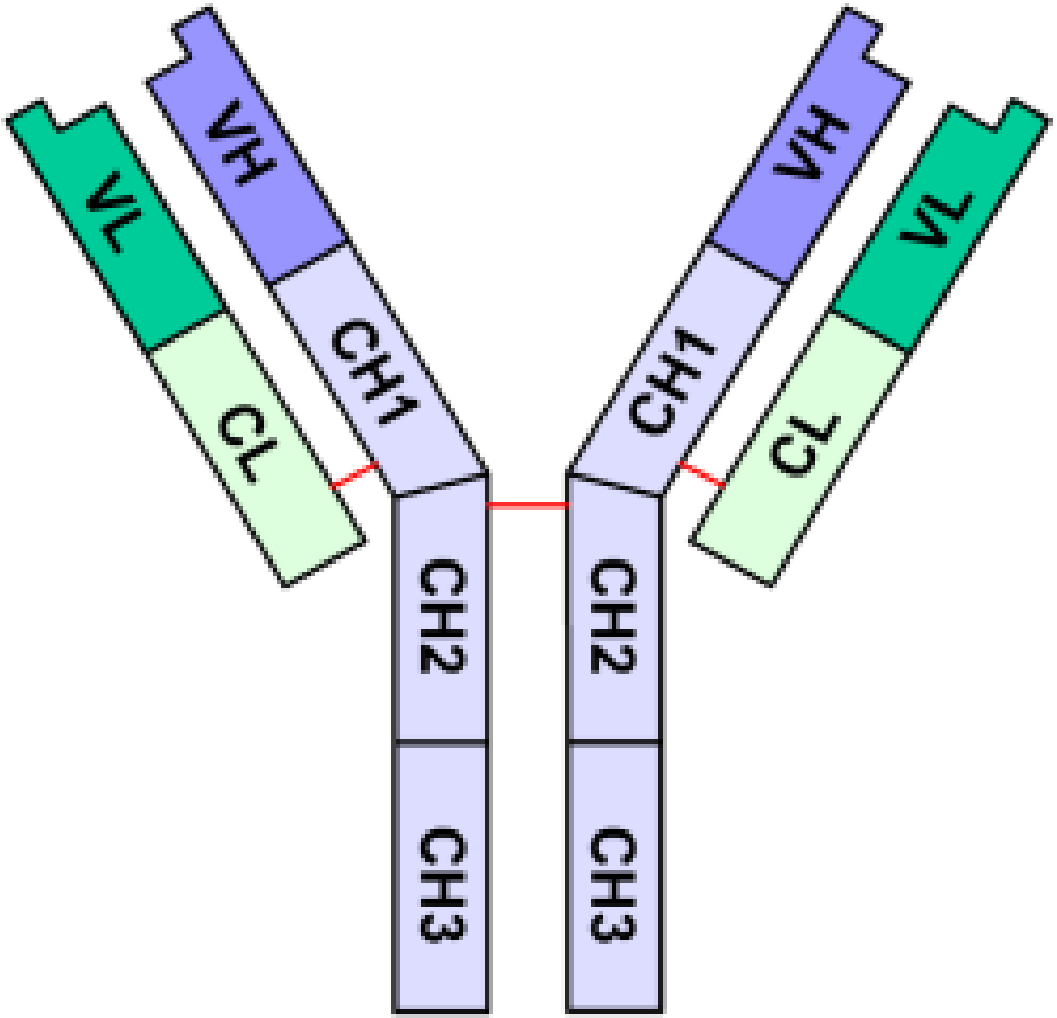
- Immunoglobulins contain a minimum of two identical light (L) chains (23 kDa) and two identical heavy (H) chains (53–75 kDa), held together as a tetramer (L2H2) by disulfide bonds.


Light chain
Heavy chains
Light chain

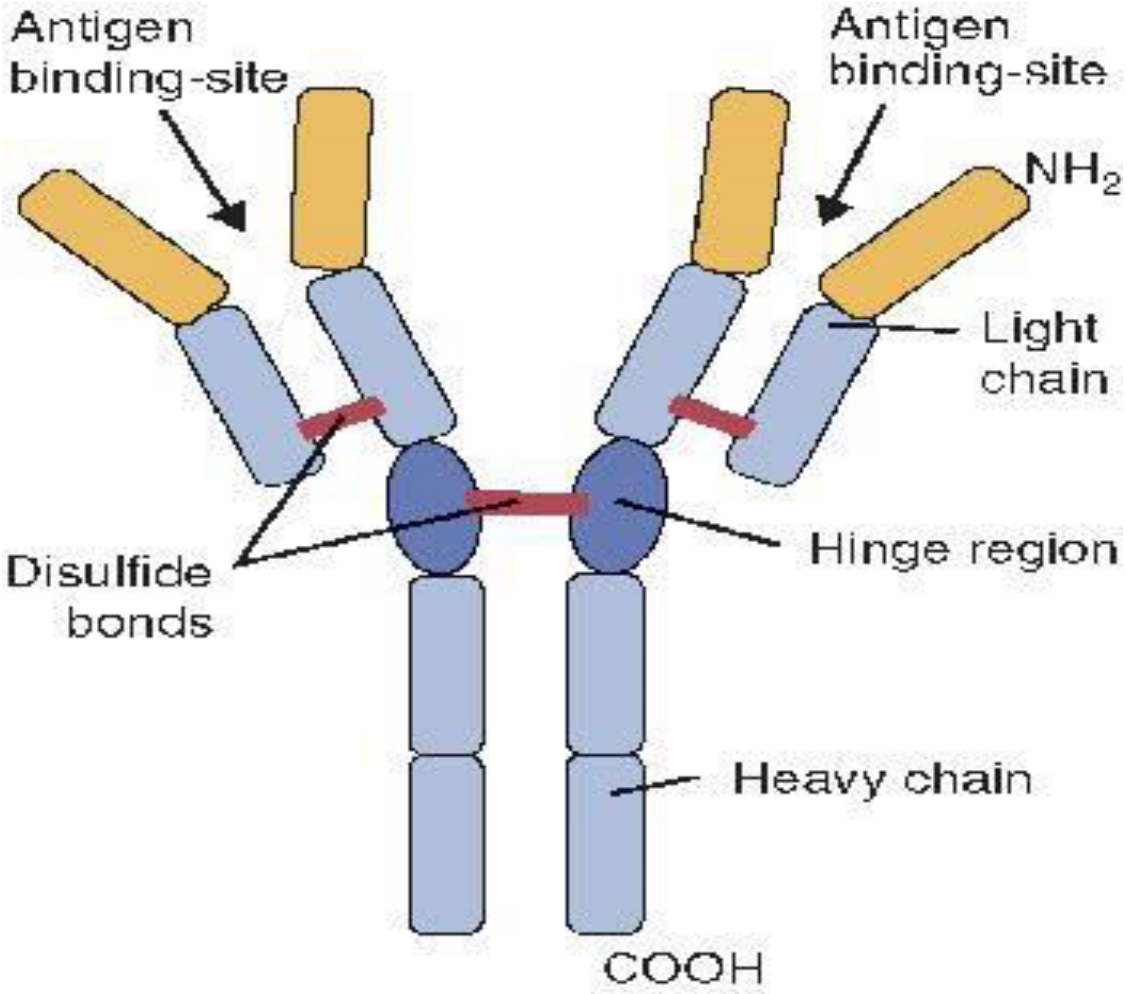
- Each chain can be divided into specific domains:

- The half of the **light (L)** chain toward the carboxyl terminal is referred to as the constant region (CL), while the amino terminal half is the variable region of the light chain (VL).

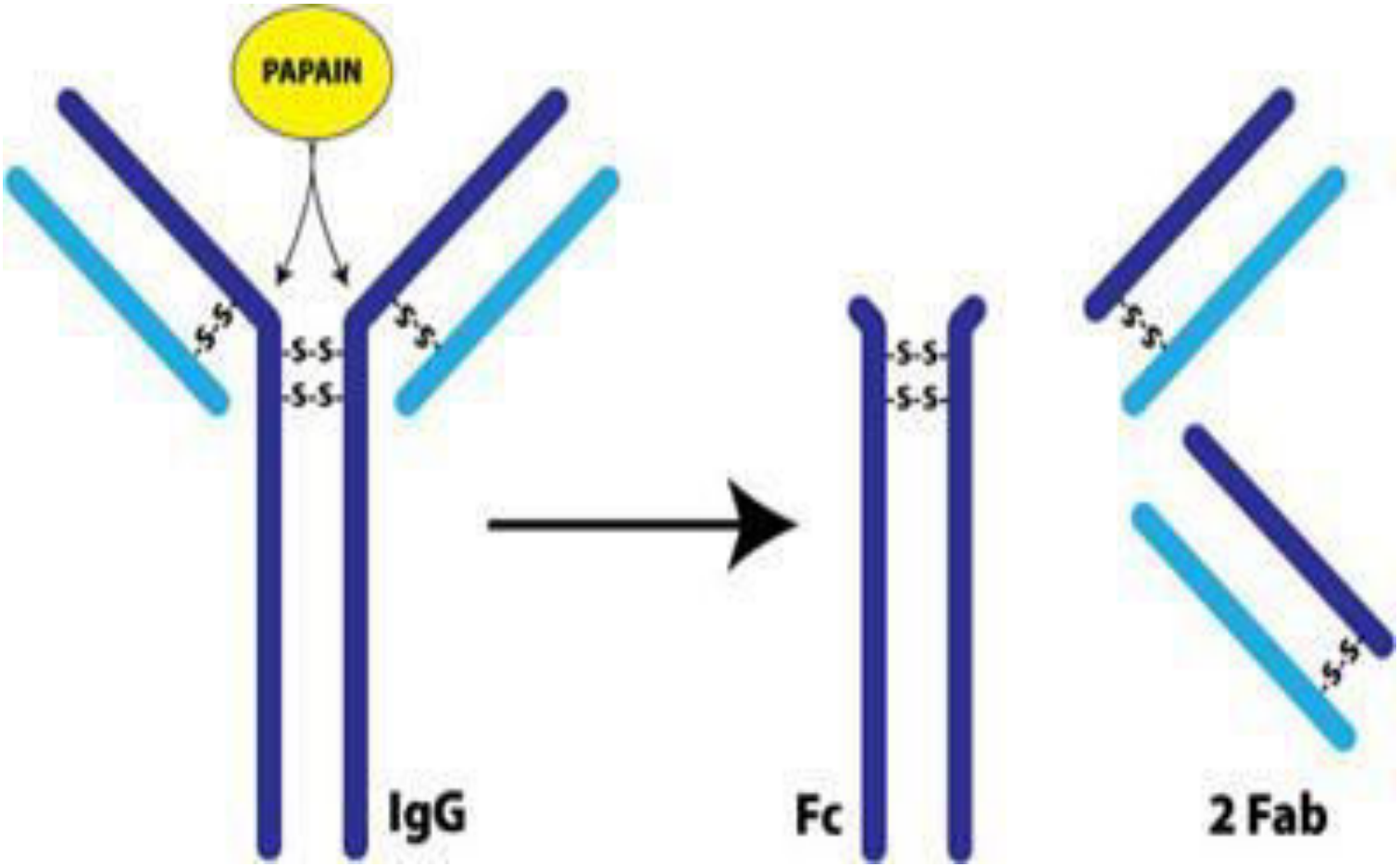
- one-quarter of the **heavy (H)** chain at the amino terminals is referred to as its variable region (VH), and the other three-quarters of the heavy chain are referred to as the constant regions (CH1, CH2, CH3) of that H chain.

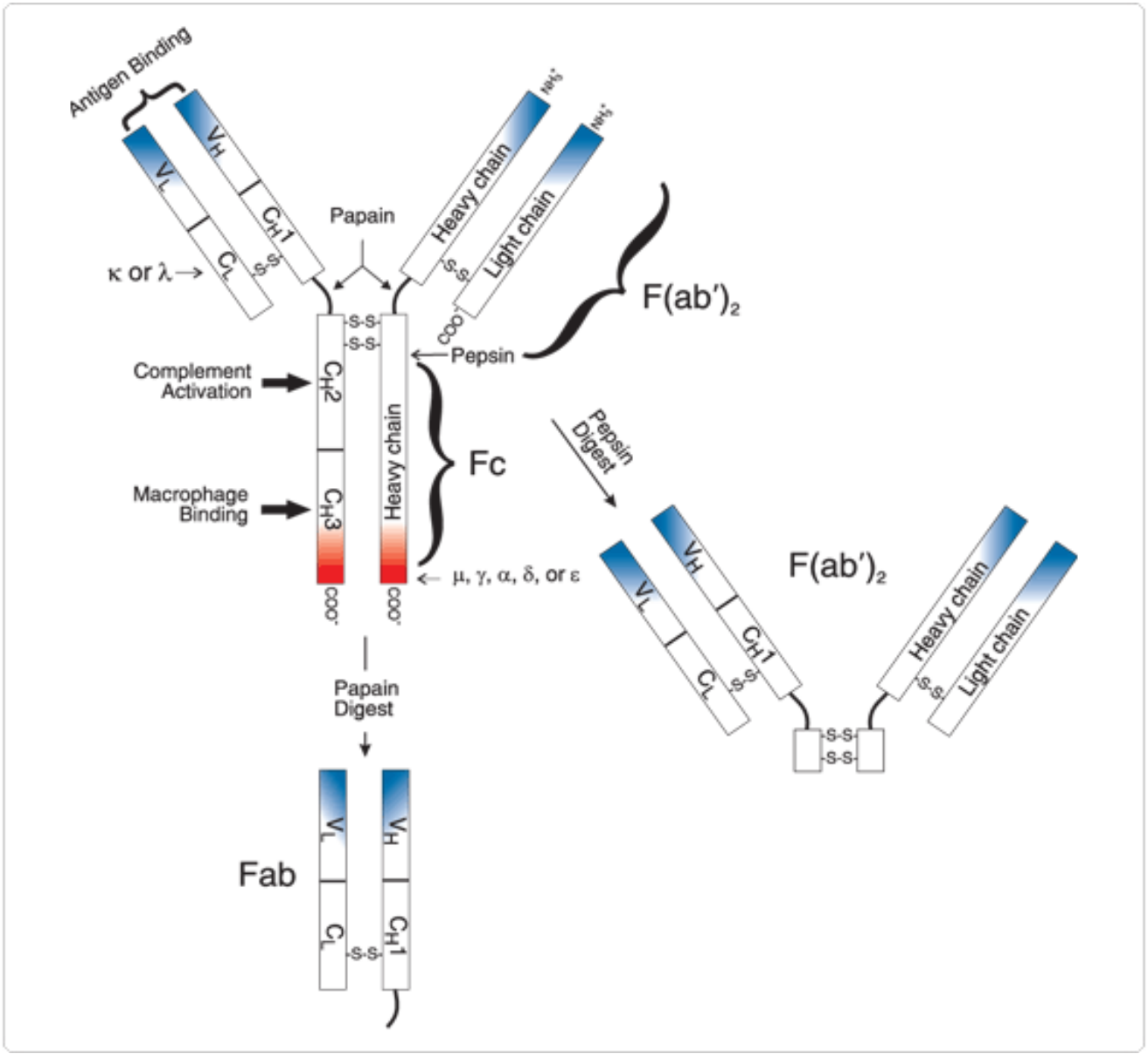


- The portion of the immunoglobulin molecule that **binds the specific antigen** is formed by the amino terminal portions (**variable regions**) of both the H and L chains—ie, the VH and VL domains.

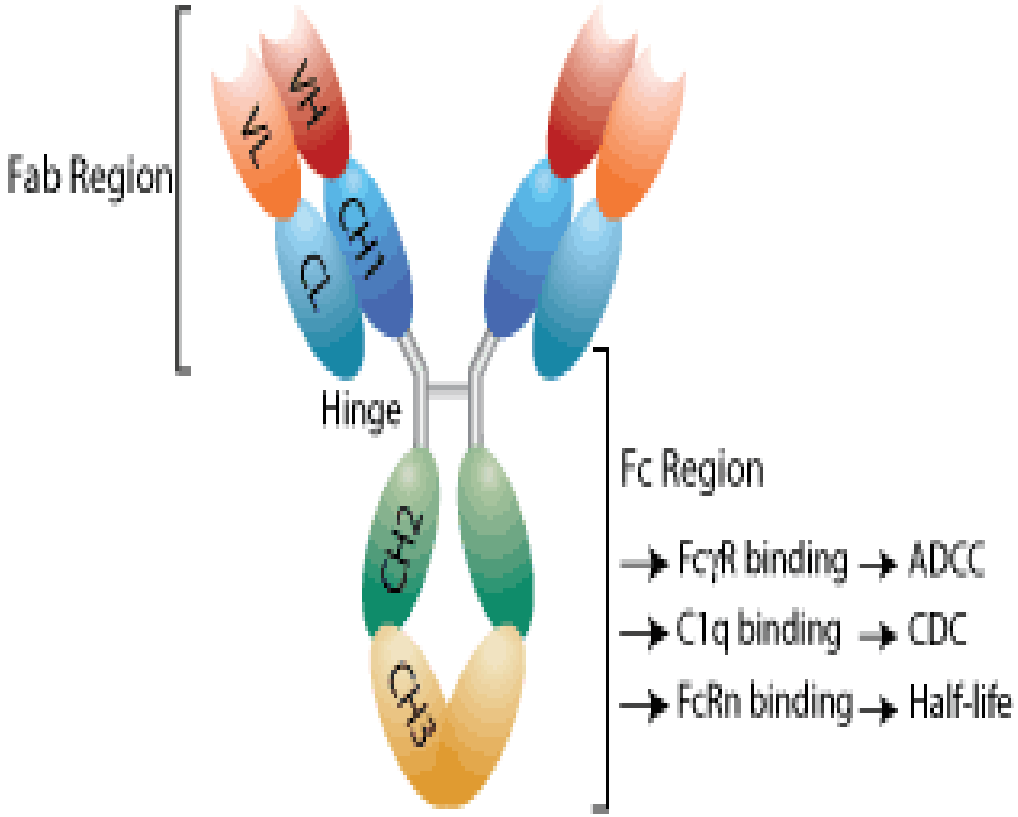


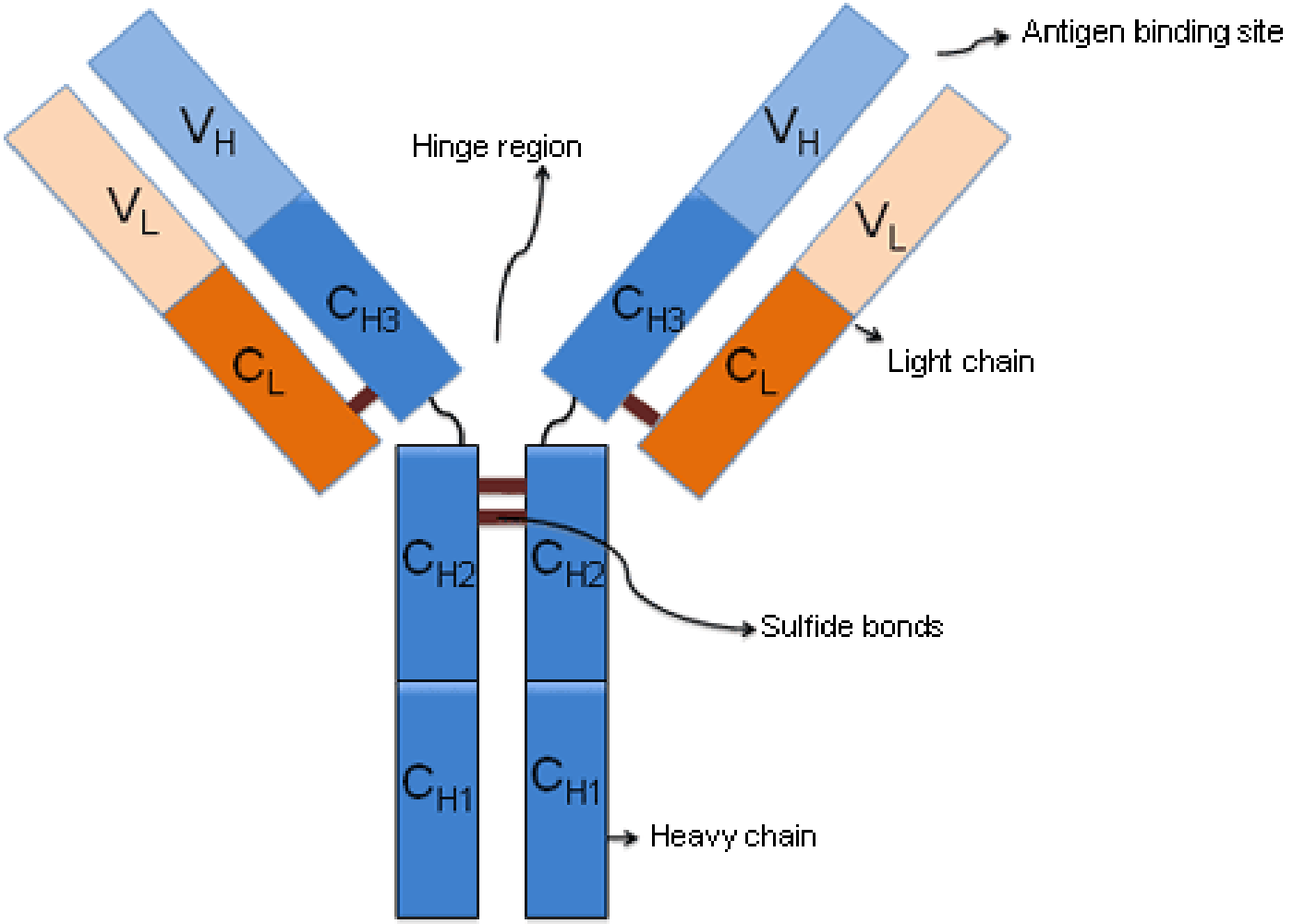
- digestion of an immunoglobulin by the enzyme **papain produces two** antigen-binding fragments (Fab) and one crystallizable fragment (Fc), which is responsible for functions of immunoglobulins other than direct binding of antigens.


PAPAIN
IgG
Fc
2 Fab



- The area in which papain cleaves the immunoglobulin molecule— ie, the region between the CH1 and CH2 domains— is referred to as the **“hinge region.”**

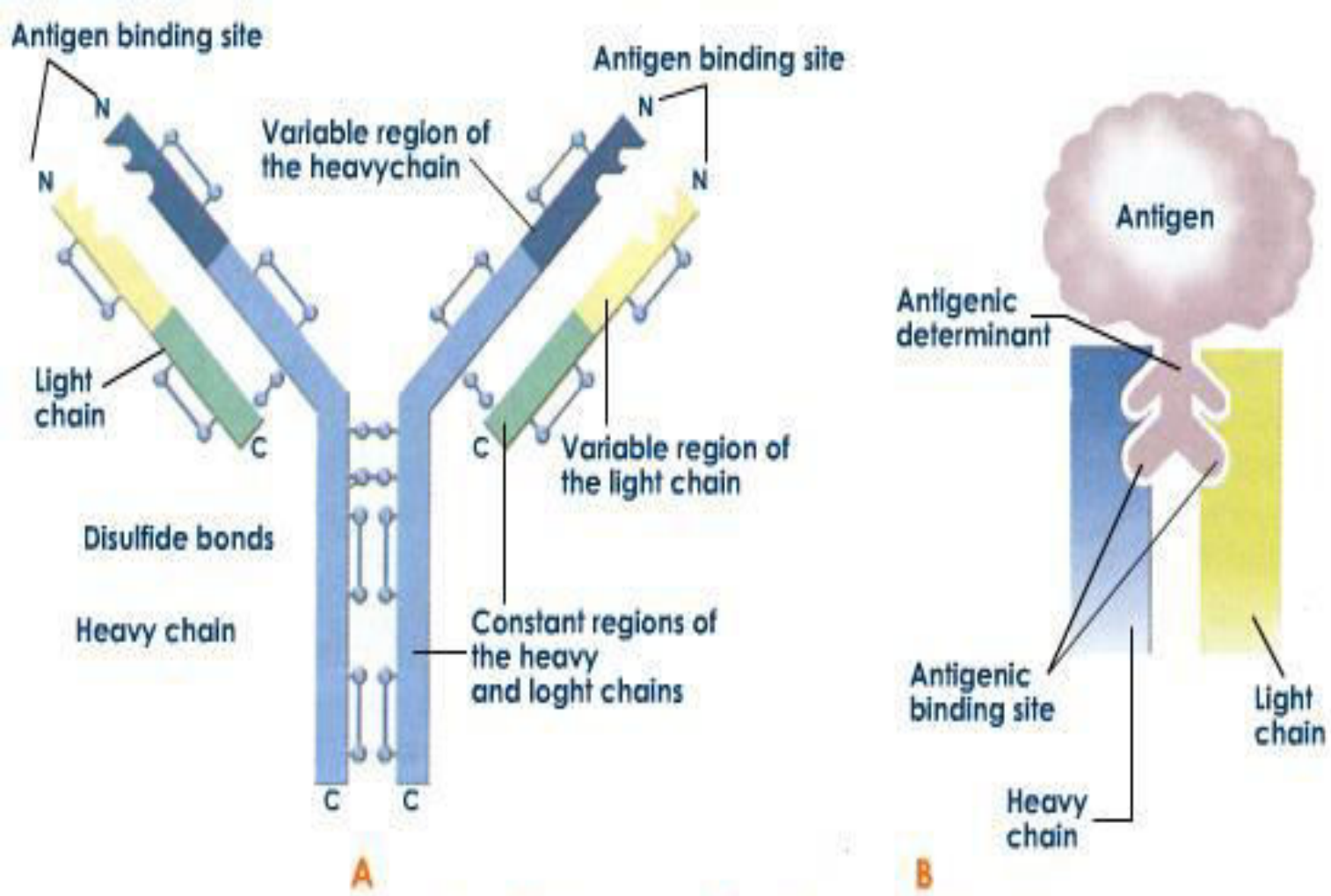




- **The hinge** region confers flexibility and allows both Fab arms to move independently, thus helping them to bind to antigenic sites that may be variable distances apart (eg, on bacterial surfaces).

- The site on the antigen to which an antibody binds is termed an **antigenic determinant, or epitope.**

- Fc and hinge regions differ in the different classes of antibodies, but the overall model of antibody structure for each class is similar.



Immunoglobulins : A. Structure, B. Antigen binding site

All Light Chains Are Either Kappa or Lambda in Type

- There are two general types of light chains, kappa (κ) and lambda (λ), which can be distinguished on the basis of structural differences in their CL regions.
- A given immunoglobulin molecule always contains two κ or two λ light chains—never a mixture of κ and λ. .
- In humans, the κ chains are more frequent than λ chains in immunoglobulin molecules.

The Five Types of Heavy Chain

- Five classes of H chain have been found in humans distinguished by differences in their CH regions.
- They are designated γ, α, μ δ, and ε.
- The type of H chain determines the class of immunoglobulin and thus its effector function.
- There are thus five immunoglobulin classes: **IgG, IgA, IgM, IgD, and IgE.**

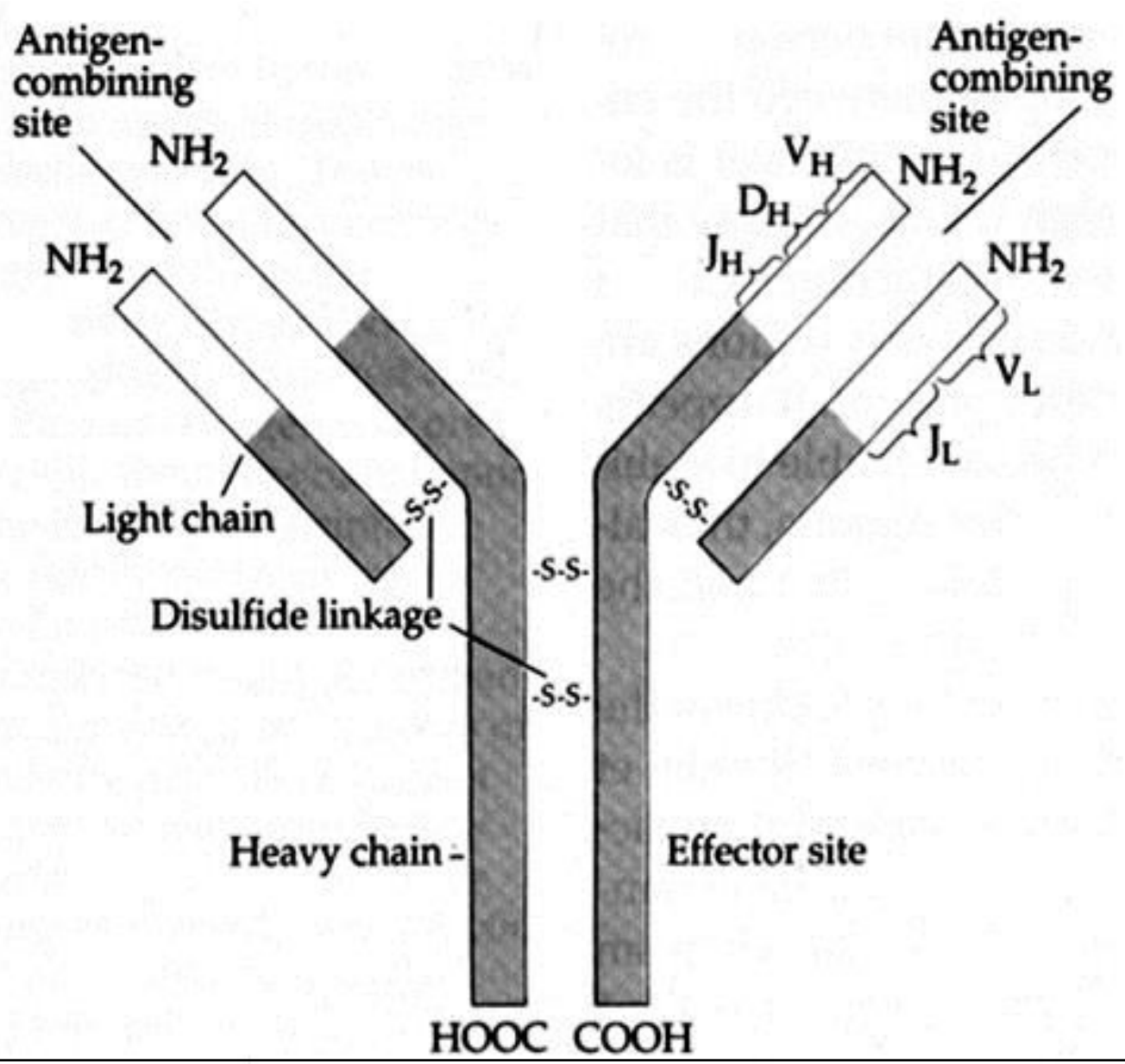
- **No Two Variable Regions Are Identical**
- No two variable regions from different humans have been found to have identical amino acid sequences.
- hypervariable regions are also termed **complementarity-determining regions (CDRs).**

- **The Constant Regions Determine Class-Specific Effector Functions.**

- The L chains and H chains are synthesized as separate molecules and are subsequently assembled within the B cell or plasma cell into mature immunoglobulin molecules, all of which are **glycoproteins.**

- Each immunoglobulin **light chain** is the product of at least three separate structural genes:

1. a variable region (*VL) gene,*
2. a joining region *(J) gene*
3. and a constant region (*CL) gene*.



- Each **heavy chain** is the product of at least four different genes:

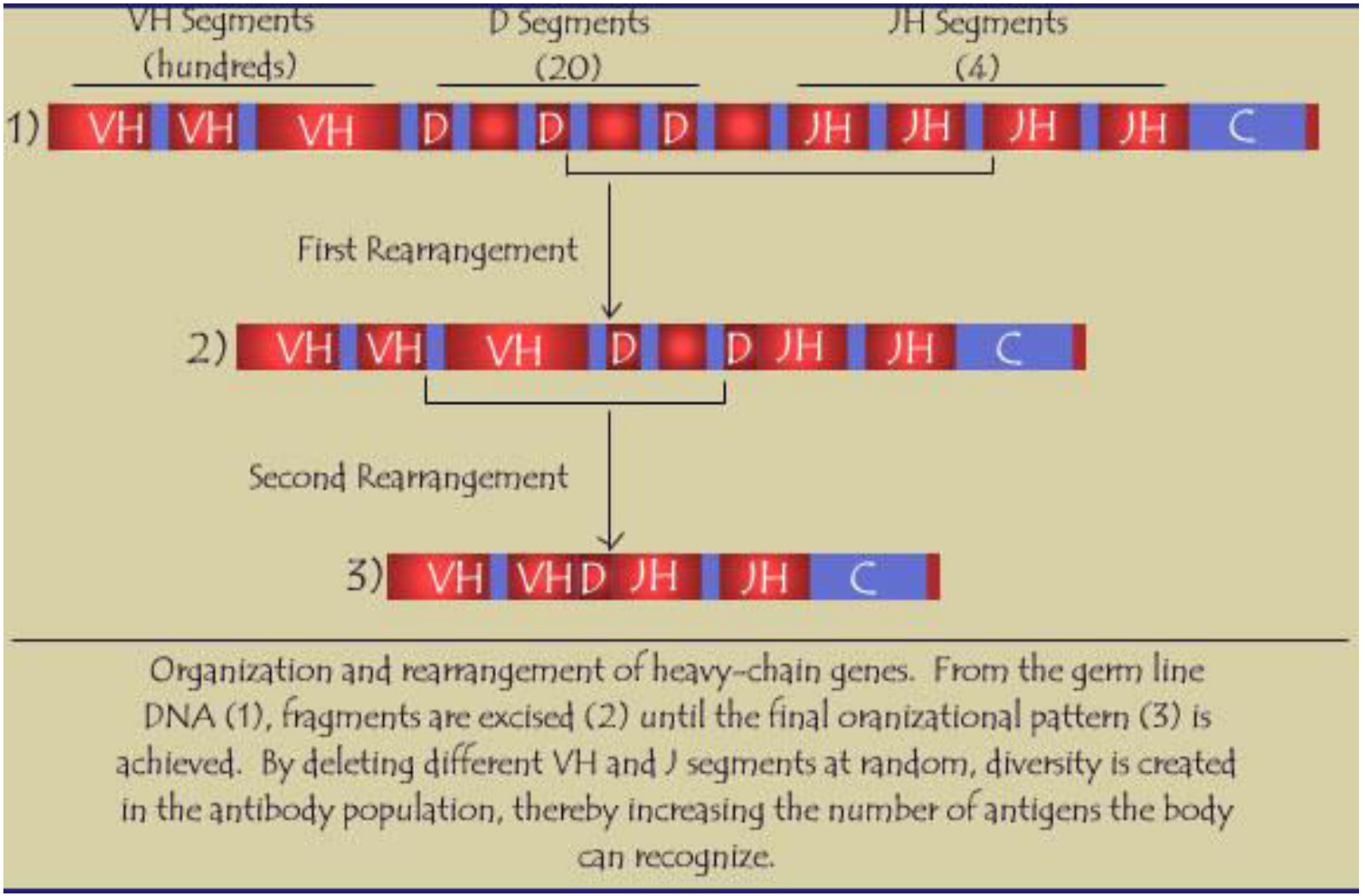
1. a variable region (*VH) gene,*
2. diversity region *(D) gene,*
3. a joining region *(J) gene, and*
4. a constant region (*CH) gene*.

- The generation of antibody diversity depends upon a number of factors:

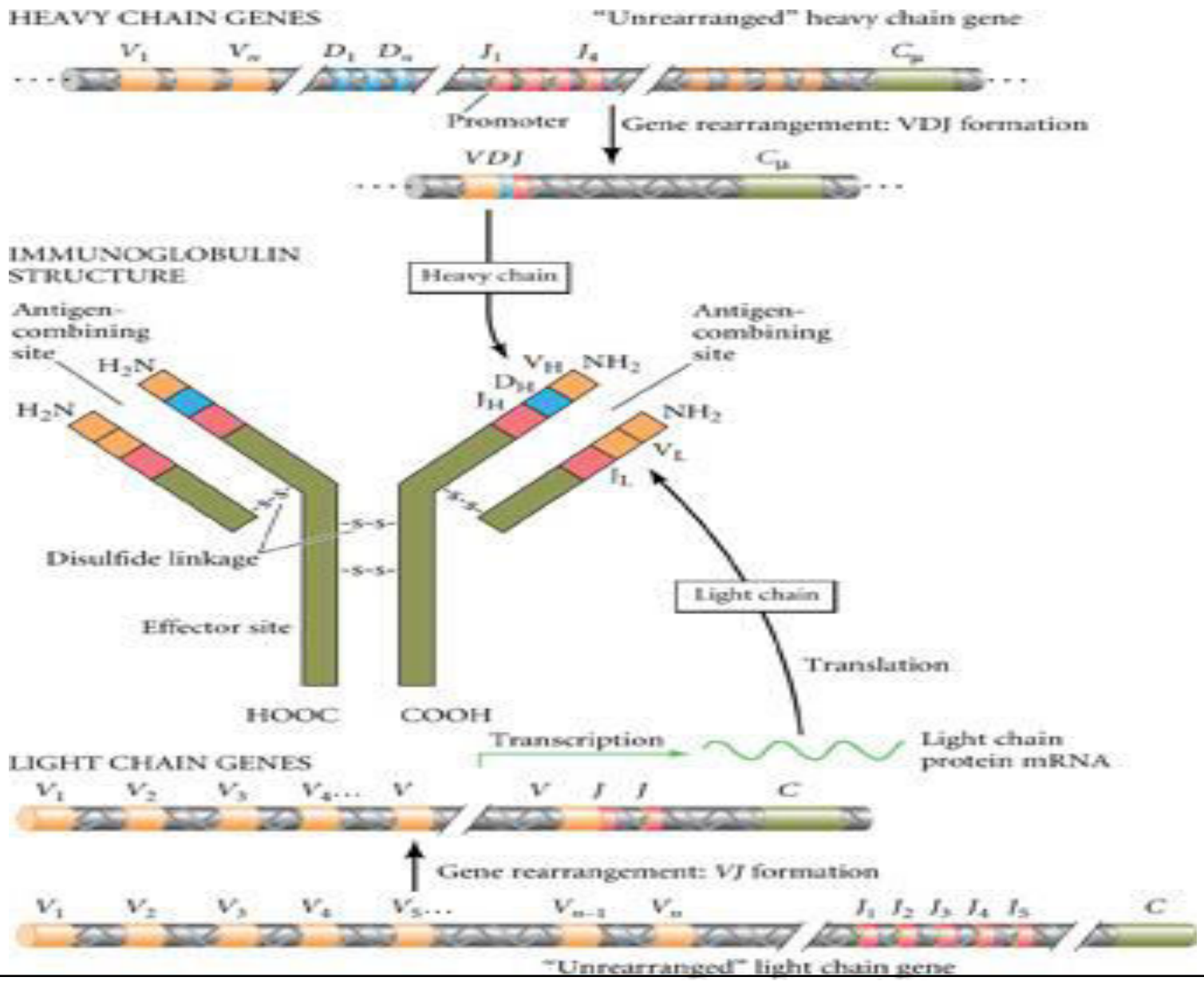
1. including the existence of multiple gene segments (V, C, J, and D segments), their recombinations.

2. The combinations of different L and H chains,

3. Junctional diversity.



Organization and rearrangement of heavy-chain genes. From the germ line DNA (1), fragments are excised (2) until the final oranizational pattern (3) is achieved. By deleting different VH and J segments at random, diversity is created in the antibody population, thereby increasing the number of antigens the body can recognize.

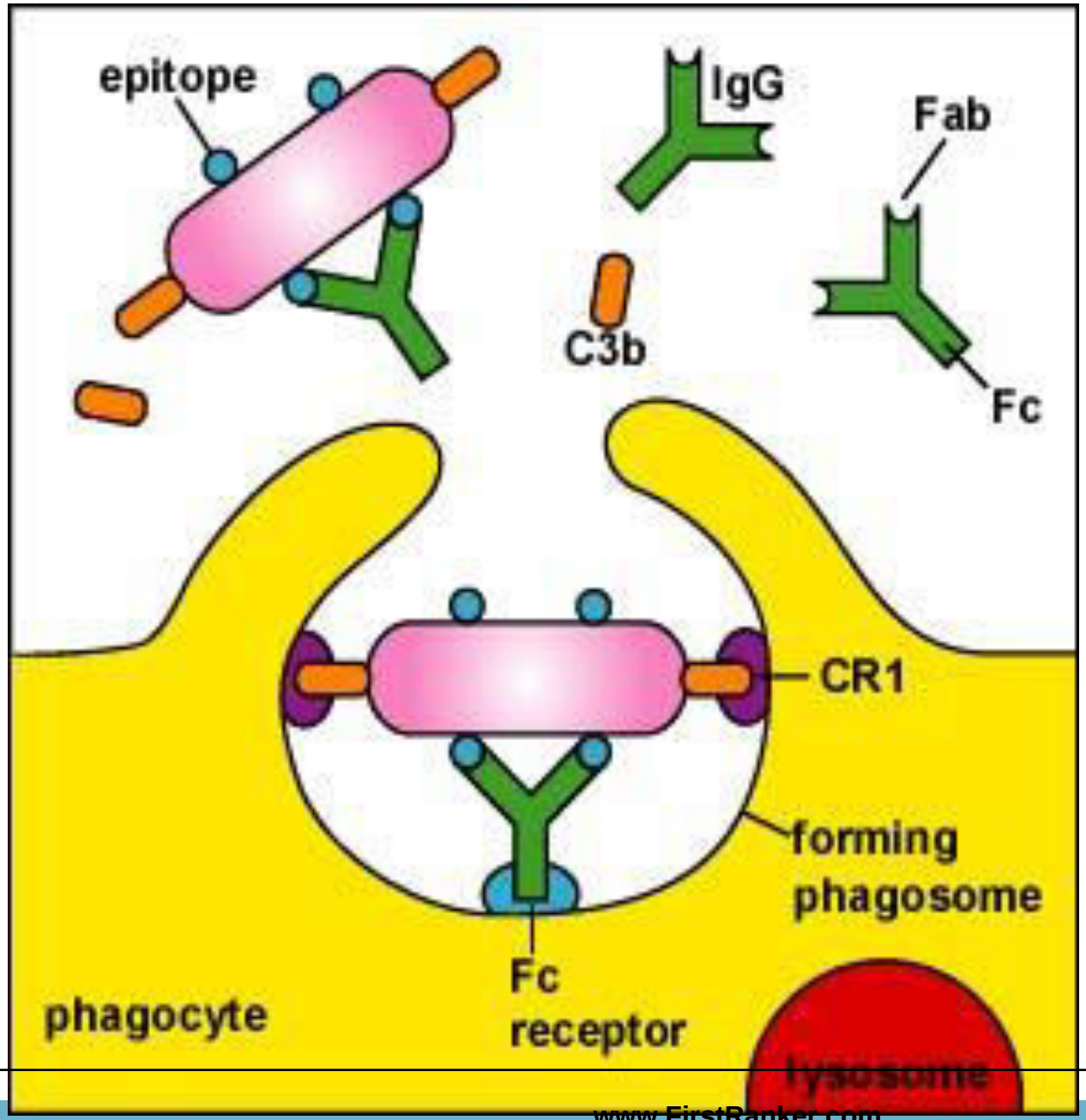

HEAVY CHAIN GENES
"Unrearranged" heavy chain gene
Promoter
Gene rearrangement: VDJ formation
VDJ
IMMUNOGLOBULIN STRUCTURE
Heavy chain
Antigen-combining site
Antigen-combining site
Disulfide linkage
Effector site
Light chain
Translation
HOOC
COOH
Transcription
Light chain protein mRNA
LIGHT CHAIN GENES
Gene rearrangement: VJ formation
"Unrearranged" light chain gene

Major functions of Immunoglobulins

Immunoglobulin G:

- Main antibody in the secondary response.

1. Opsonizes bacteria, making them easier to phagocytose.
2. Fixes complement, which enhances bacterial killing.
3. Neutralizes bacterial toxins and viruses.
4. Crosses the placenta.



- **Complement system:**

- activated by invading organisms &, more often, triggered by antibodies ('complements' action of antibodies)
- consists of 11 plasma proteins produced by liver .

- The complement system is named because it "complements" the white blood cells' forces. it is involved in the MAC attack, which stands for "Membrane Attack Complex:
- first, proteins self-assemble on the cell surface of a bacterium. when they are fully assembled they destroy the membrane
- and the bacterium's insides start to leak out. This happens all over the bacterium and finally, the bacterium lyses .

- **Immunoglobulin A:**

1. Secretory IgA prevents attachment of bacteria and viruses to mucous membranes.
2. Present in the external secretions like milk, tears, saliva, bronchial and intestinal secretions.
3. Does not fix complement.

- **Immunoglobulin M:**

1. It is the first antibody t o appear in the serum when an antigen is injected- primary antibody response, then followed by Ig G
2. Produced in the primary response to an antigen.
3. Activates complement.
4. Does not cross the placenta.
5. Important Ig in autoimmune diseases.

- **Immunoglobulin D:**
  Uncertain

- **Immunoglobulin E:**

1. Mediates immediate hypersensitivity by causing release of mediators from mast cells and basophils upon exposure to antigen (allergen).
2. Defends against worm infections by causing release of enzymes from eosinophils.
3. Does not fix complement.
4. Main host defense against helminthic infections.

- **Bence Jones proteins:**
- Not a normal protein.
- Found in the plasma of multiple myeloma patients, in whom large amounts of one type of antibody is produced.
- Light chains of Igs.
- It is coagulated at 50-60 degrees, but on further heating it dissolves.
- Multiple myeloma- in urine of such patients.