Plasma proteins

The major plasma proteins are:

1. Albumin
2. Globulin
3. Fibrinogen

The normal value of plasma proteins are:

- Total protein 6 to 8 gm%
- Albumin 3.5 to 6 gm%
- Globulin 2 to 3.5 gm%
- Fibrinogen 200 to 400 mg%
- A/G ratio 1.2:1 to 2.5:1

Synthesis of Plasma Proteins

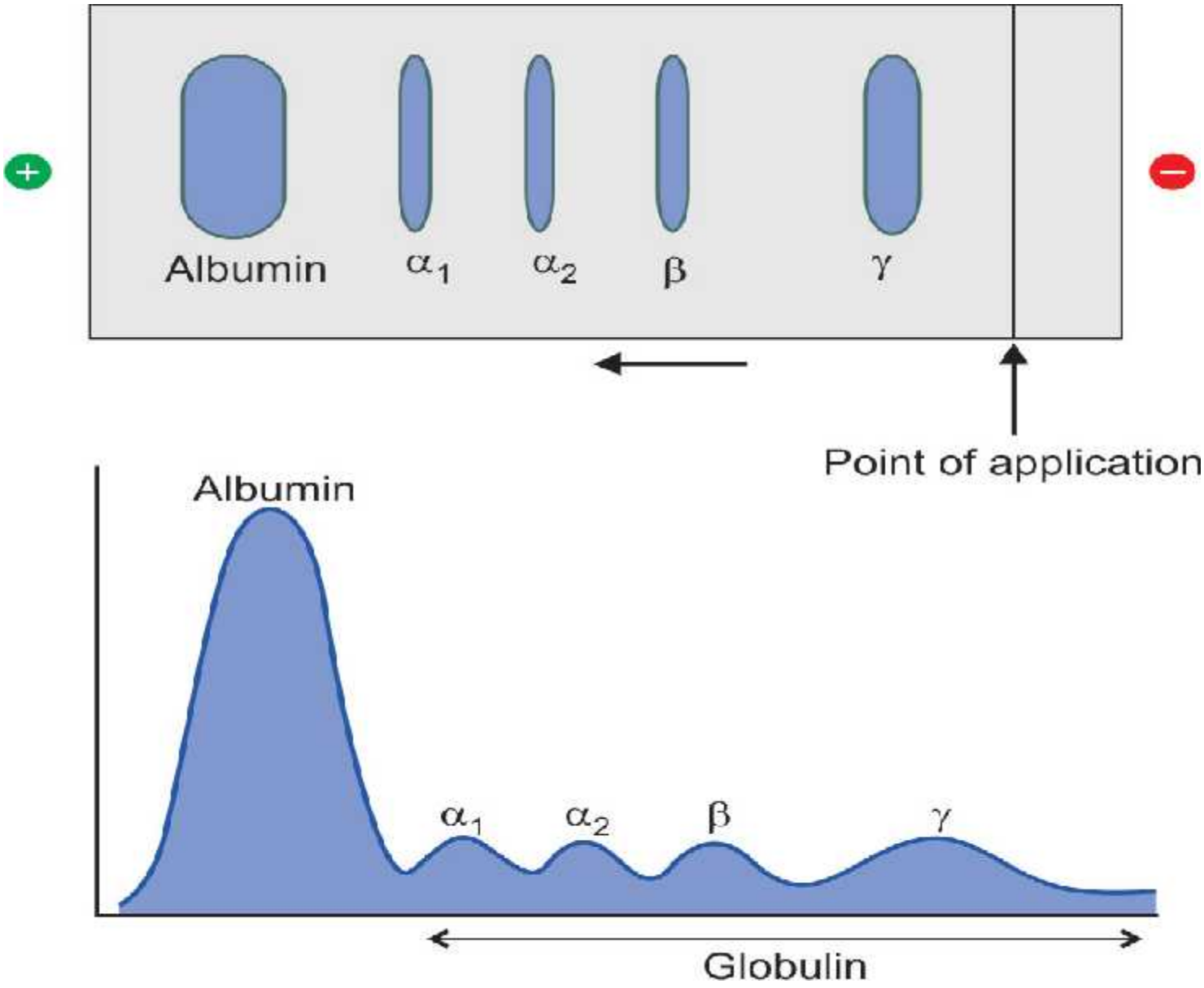
- All the albumin and fibrinogen are synthesized by the liver only
- Similarly 50 to 80% of the globulin is formed in the liver
- The remainder of the globulins are formed almost entirely in the lymphoid tissues.
- The A/G ratio can be altered in the liver disease.

Separation of Plasma Proteins

The plasma proteins can be separated by :

- Salting out
- Electrophoresis
- Ultracentrifugation
- Immunoelectrophoresis.

Electrophoretic separation of serum proteins



Major classes of plasma proteins, their functions, and diagnostic importance.

Classes	*Examples*	*Principal functions*	*Diagnostic importance*
Prealbumin	❑ Thyroxine-binding prealbumin (TBPA) ❑ Retinal-binding prealbumin (RBPA)	❑ Transport of hormone thyroxine ❑ Transport of vitamin A	❑ Liver disease, thyrotoxicosis malnutrition
Albumin		❑ Exert colloidal osmotic pressure and transport function	❑ Malnutrition, liver, kidney, and GI disease, malignancy
α_1-gloublin	❑ Retinal-binding protein (RBP)	❑ Transport of vitamin A	—
	❑ α_1-fetoprotein (AFP)	❑ Unknown	❑ Neural tube defects, also as a tumor marker
	❑ α_1-protease inhibitor (API) or α_1-antitrypsin (AAT)	❑ Antiprotease, natural inhibitor of proteolytic enzyme elastase	❑ API deficiency in lung disorders
	❑ α_1-acid glycoprotein (AAG)	❑ Tissue repair	❑ Inflammatory disease of GIT and malignant neoplasm
	❑ Prothrombin	❑ Blood clotting	❑ Coagulation screen, also as a liver function test

α_2-globulins	❑ Ceruloplasmin	❑ Transport of copper	❑ Wilson's disease
	❑ Haptoglobin	❑ Conservation of iron by binding free hemoglobin	❑ Hemolytic disorders
	❑ Thyroxine-binding protein (TBG)	❑ Transport thyroxine hormone	❑ Thyroid disease
	❑ α_2-macroglobulin (AMG)	❑ Natural antiprotease inhibits thrombin, trypsin, and pepsin	❑ Myeloma, peptic ulcer nephrotic syndrome, cirrhosis, collagen disease
β-globulins	❑ Hemopexin	❑ Binds heme and prevents loss of iron	❑ Hemolytic disorders
	❑ Transferrin	❑ Transport of iron	❑ Iron deficiency
	❑ C-reactive protein (CRP)	❑ Body's defense mechanism	❑ Nonspecific test that may be used instead of ESR
	❑ β_2-microglobulin (BMG)	❑ Body's defense mechanism	❑ Monitoring myeloma, renal failure

γ-globulins	❑ Immunoglobulins IgG, IgA, IgM, IgD, and IgE	❑ Body's defense mechanisms	❑ Liver disease, infections, autoimmune disease, and paraproteinemia
Fibrinogen		❑ Blood coagulation	

Quick review of plasma protein

- Most abundant plasma protein: Albumin
- Least abundant plasma protein: α_1-Globulin
- Plasma protein with fastest electrophoretic mobility: Prealbumin, transthyretin followed by albumin.
- Plasma protein with slowest electrophoretic mobility: Gamma globulin
- Plasma protein not synthesized in liver: Immunoglobulins (by plasma cells of B-lymphocyte lineage)
- Plasma protein not a glycoprotein: albumin.
- Plasma protein exclusively synthesized in liver: albumin.

ALBUMIN

- Albumin is a globular protein with 585 amino acid residues accounting for approximately 50% of plasma protein
- Albumin is synthesized exclusively by the liver.

Functions of albumins

Albumin plays a predominant role in:

- Maintenance of plasma oncotic pressure.

- Transport of metabolites which are poorly soluble in water :
  - Fatty acids
  - Bilirubin
  - Calcium
  - Certain steroid hormones
  - Copper
  - Some of the plasma tryptophan
  - A variety of drugs, like sulfonamides, penicillin G, dicumarol, aspirin, and digoxin

- Buffering function: albumin has maximum buffering capacity
- Nutritive function : Degradation of albumin provide essential amino acids during malnutrition.

Clinical significance

Hypoalbuminaemia: Malnutrition, nephrotic syndrome, cirrhosis of liver

Hyperalbuminaemia: Acute dehydration have no clinical significance.

Analbuminaemia (less than 1gm/l , normal= 3.5 to 6gm/dl):

Analbuminaemia is a rare hereditary abnormalities there may be no symptoms or signs not even edema due to compensatory increase in plasma globulin concentration.

Causes of hypoalbuminemia.

Physiological	*Pregnancy physical exercise*
Pathological	**Impaired synthesis, e.g.** ❑ Malnutrition ❑ Malabsorption ❑ Chronic liver disease **Increased catabolism, e.g. in:** ❑ Injury, e.g. major surgery or trauma ❑ Infection ❑ Fever ❑ Malignant disease

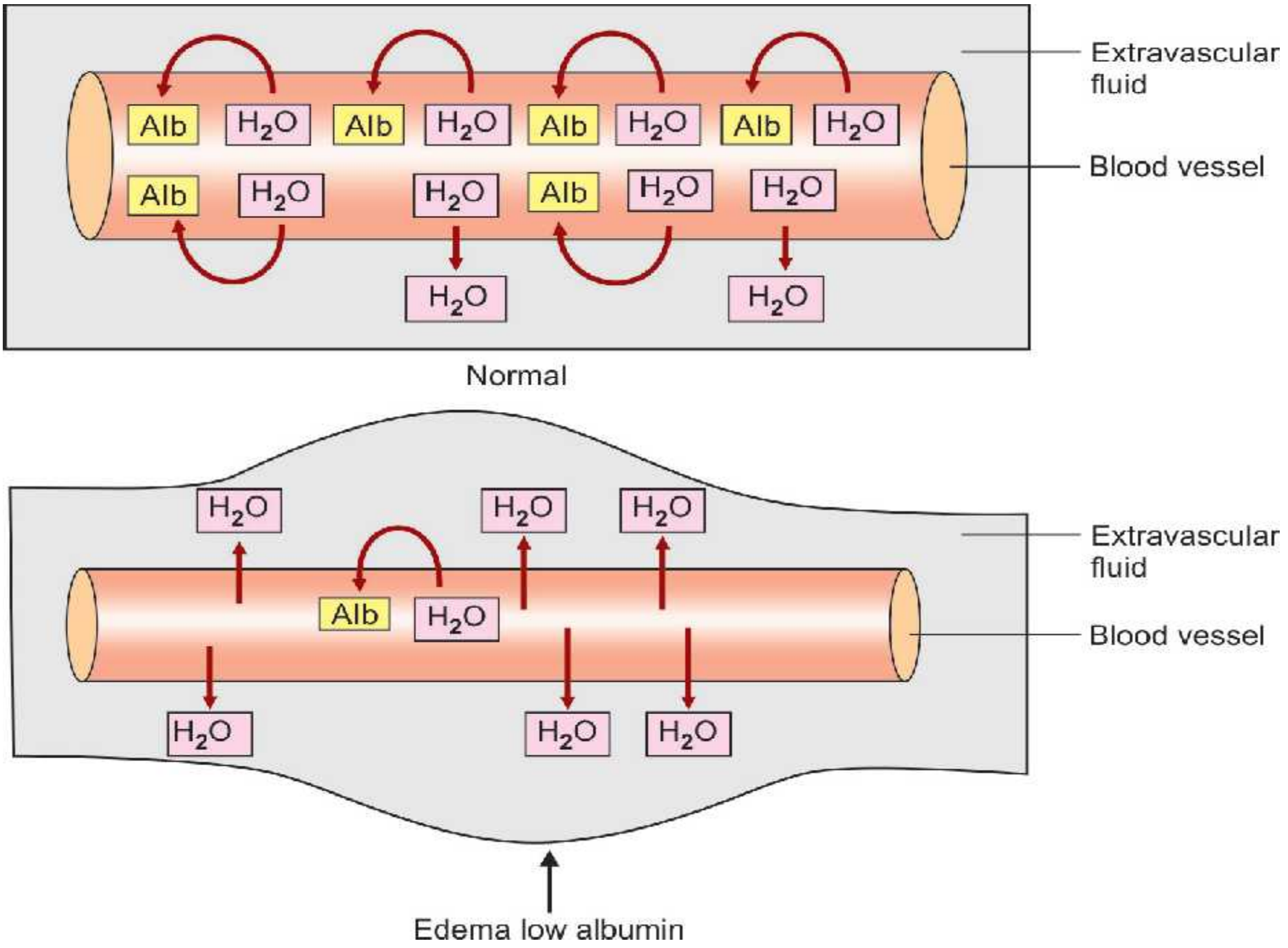
Abnormal distribution

- Severe burns
- Edema
- Ascites

Abnormal or excessive losses, e.g. in:

- Nephrotic syndrome
- Gastrointestinal tract diseases
- Burns or certain skin diseases
- Hemorrhage
- Inflammation

Overhydration due to hemodilution


Alb
H_2O
Extravascular fluid
Blood vessel
Normal
Edema low albumin

Globulins

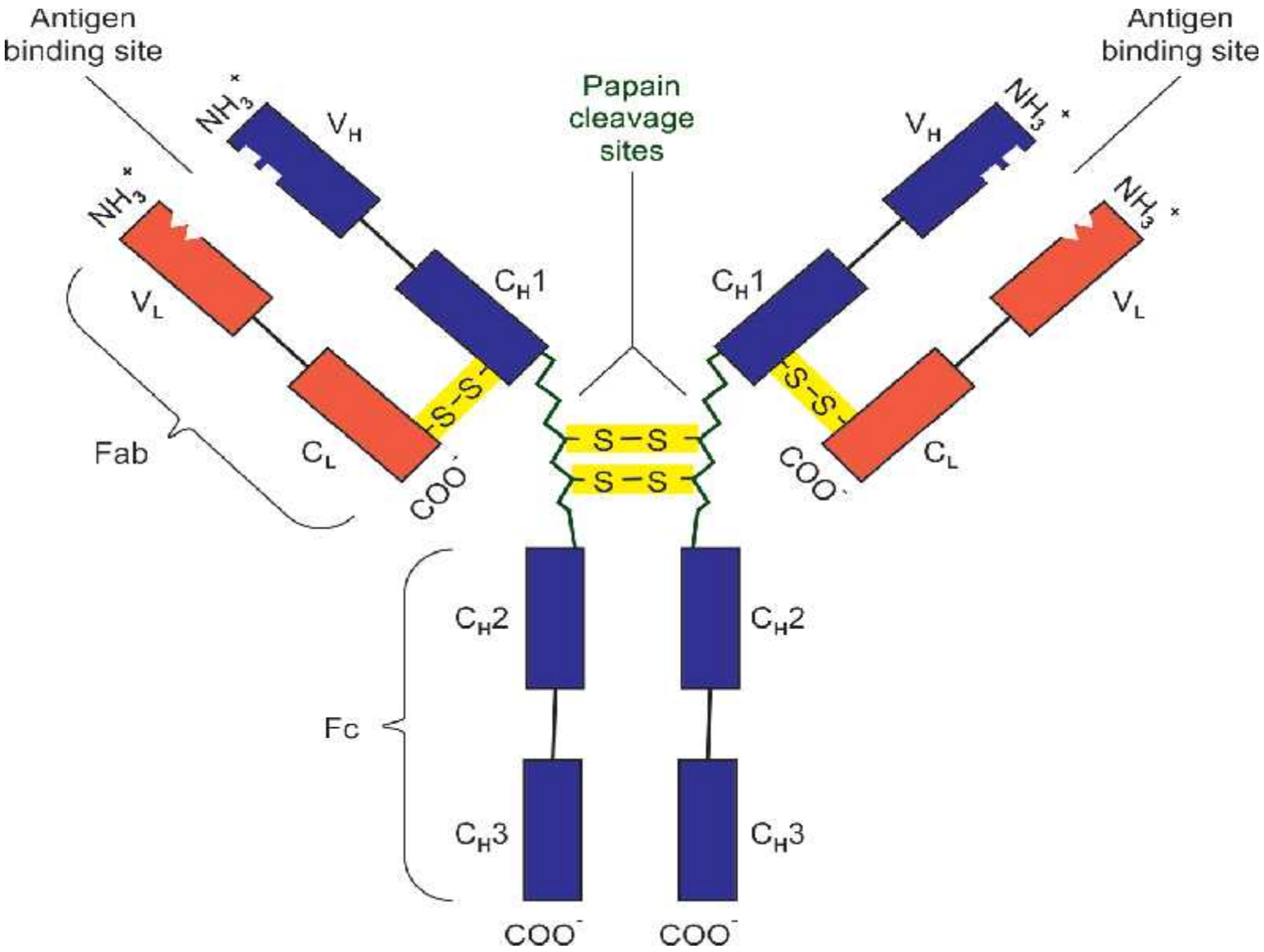
Globulins constitute several fractions.

- α_1-globulin
- α_2-globulin
- β-globulin and
- γ-globulin

Immunoglobulins (Ig)

- The immunoglobulins are *γ* -globulins, called antibodies.
- Constitute about 20% of all the plasma proteins
- produced by plasma cells and by lymphocytes in response to a variety of antigen.

Schematic structure of immunoglobulin G.



- The basic immunoglobulin is Y shaped consist of four polypeptide chains:
  - two H and
  - two L chains
- The four chains are linked by disulfide bond
- L chain may be either of two types, Kappa (κ) or Lambda (λ) but not both

- The heavy chains may be of five types and are designated by Greek letter:
  - alpha (α)
  - gamma (γ),
  - delta (δ),
  - mu (μ) and
  - epsilon (ε)
- Immunoglobulins are named as per their heavy chain type as IgA, IgG, IgD, IgM and IgE

Different classes of immunoglobulins corresponding to the type of heavy chains.

Ig classes	*Types of H chains*
IgG	γ (gamma)
IgA	α (alpha)
IgM	μ (mu)
IgD	δ (delta)
IgE	ε (epsilon)

- The L and H chains are subdivided into variable (towards the carboxyl terminal end) and constant (towards the amino terminal end) regions.

- L chain consists of one variable (VL) and one constant (CL) domain or region.

- Most H-chains consist of one variable (VH) and three constant (CH-1, CH-2, and CH-3) domains.

- The hinge region between the CH-1 and CH-2 domains confers flexibility and allows both Fab arms to move independently , thus helping them to bind to antigenic site

Light chain type

- Light chain may be either of two types, Kappa (k) or Lambda (l) but not both.
- In a given immunoglobulin either 2k or 2 l but not the mixture of kappa and lambda
- Most abundant light chain in human is k

- Enzyme (papain) digestion splits the immunoglobulin molecule into two fragments

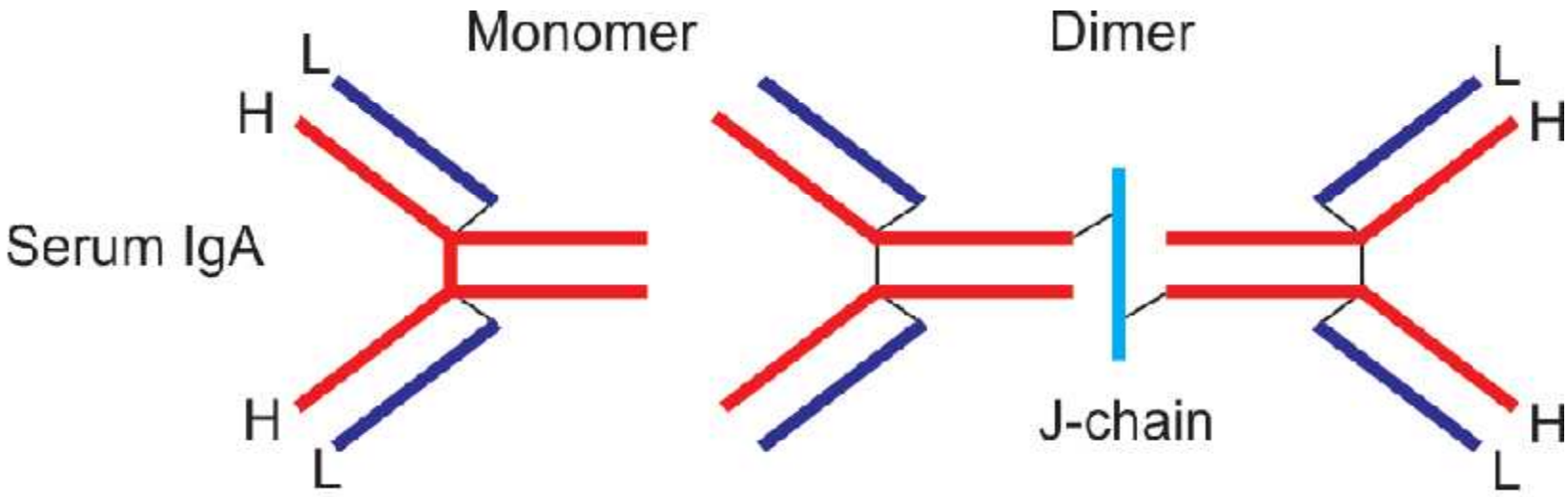
  1. Fab: Fragment for antigen binding. Located in variable region.
  2. Fc: Crystallisable fragment or fragment for complement binding

Structure, functions, and characteristics of different types of immunoglobulins.

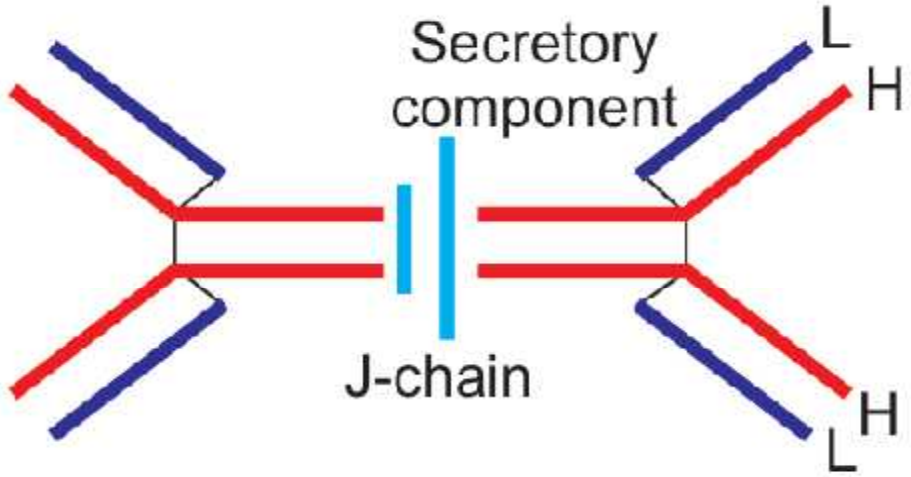
Types	*Structure*	*Approximate percentage of the total immunoglobulin in serum*	*Characteristics*	*Functions*
IgG	Monomer	70%	❑ Main antibody in the secondary response ❑ It is only immunoglobulin which crosses the placenta and is the only maternal antibody which protects the fetus	❑ Neutralizes bacterial toxins and viruses ❑ Opsonizes bacteria, making them easier to phagocytize ❑ Activates complements which enhances bacterial killing
IgA	Monomer or dimer	20%	❑ Major component of colostrum ❑ Also occurs in saliva, tears, and respiratory, intestinal, and genital tract secretions	❑ Secretory IgA prevents attachment of bacteria and viruses to mucous membranes and helps protect mucous surface from antigenic attack ❑ Prevents access of foreign substances to the circulation
IgM	Monomer or pentamer	8–10%	❑ Main antibody in the primary response to an antigen ❑ Produced by fetus	❑ Activates complement, promotes phagocytosis, and causes lysis of antigenic cells (bacteria) ❑ Antigen receptor on the surface of B lymphocytes

lgD	Monomer	Less than 1%	❑ Labile molecules. These facts have made the study of lgD function difficult	❑ Uncertain may function as an antigen recepto No known antibody function
lgE	Monomer	Trace amount 0.004%	❑ Binds mast cells and basophils and leads to rupture of the cell membrane, degranulation, and release of histamine	❑ Antiallergic and antiparasitic ❑ Mediates immediate hypersensitivity by causing release of histamine from mast cells and basophils upon exposure to antigen ❑ Defends against worm infections by causing release of enzymes from eosinophils ❑ Main host defense against parasites like helminths provides protection in the disease schistosomiasis

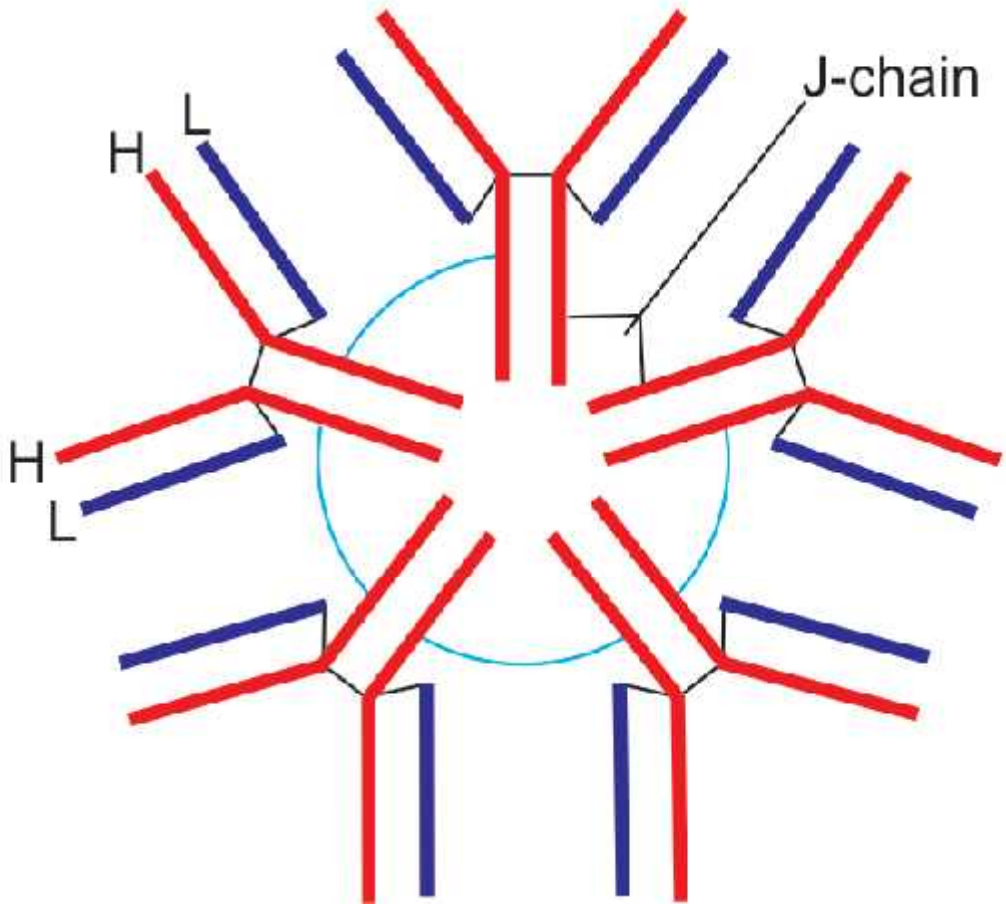
Monomeric, dimeric, and pentameric forms of immunoglobulins.



Secretory IgA
(dimer)



IgM
(pentamer)



- Most common Ig in serum: IgG
- Least common Ig in serum: IgE
- Largest Ig: IgM
- Pentamer Ig: IgM
- Dimmer: Secretary IgA
- Ig fixes the complement: IgG and IgM
- Ig present in secretion: IgA

- Ig can cross placenta: IgG
- IgG can not cross placenta: IgG2Ig involved in primary immune response: IgM
- Ig secondary immune response: IgG
- Ig with J chain: IgM and IgA
- Ig with secretary piece: IgA

Disorders due to changes in immunoglobulins

Quantitative changes in the amount of immunoglobulins in the plasma and urine are known in several pathological conditions in human.

- Multiple Myeloma
- Amyloidosis
- Bence Jones Proteins
- Cryoglobulinaemia
- Waldenstrom’s Macroglobulinaemia