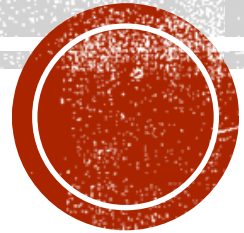
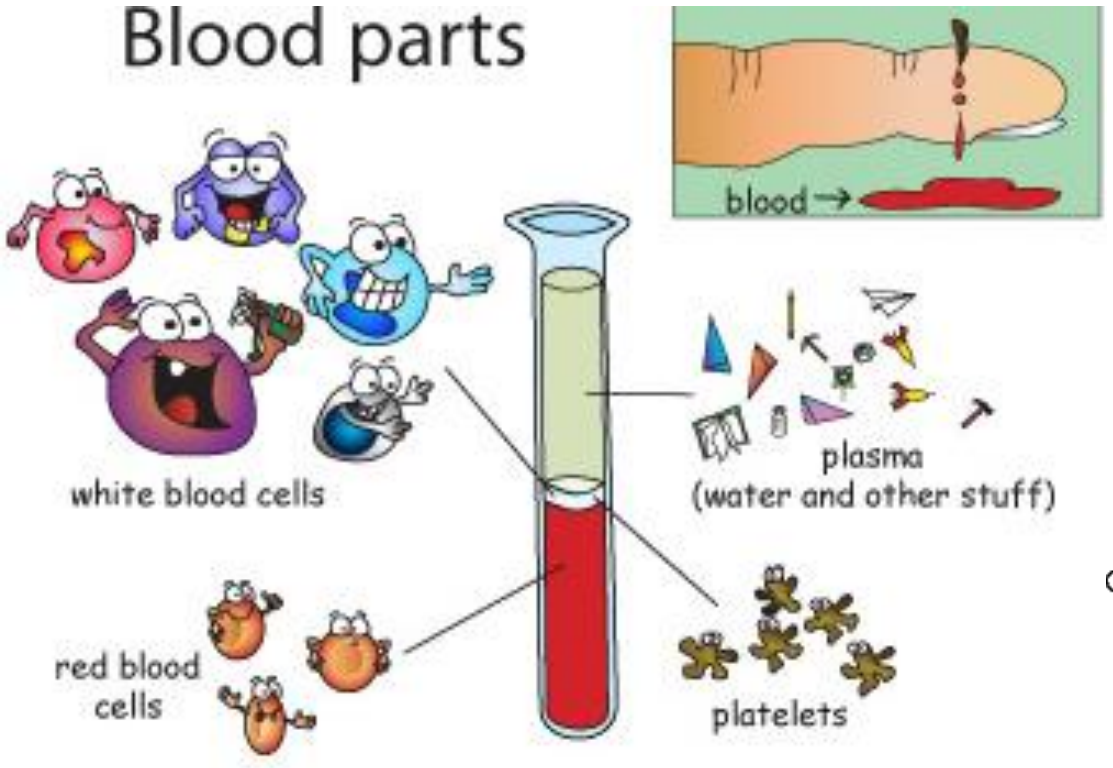
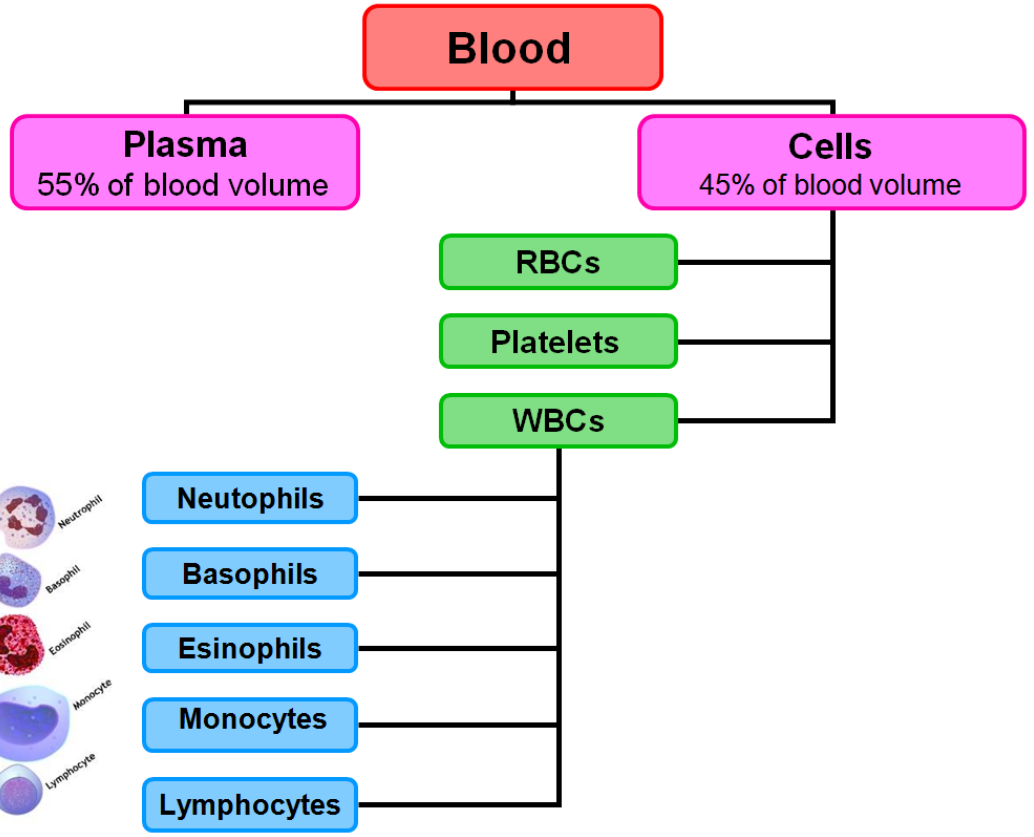
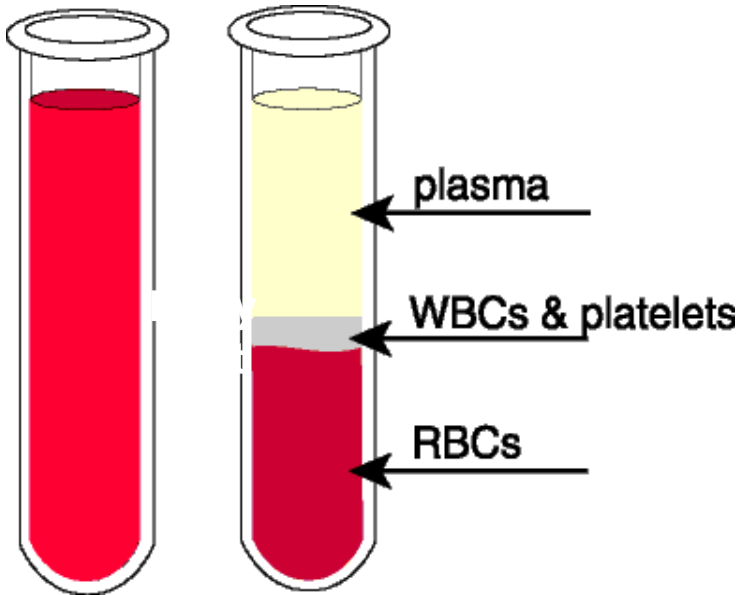
PLASMA PROTEINS



BLOOD

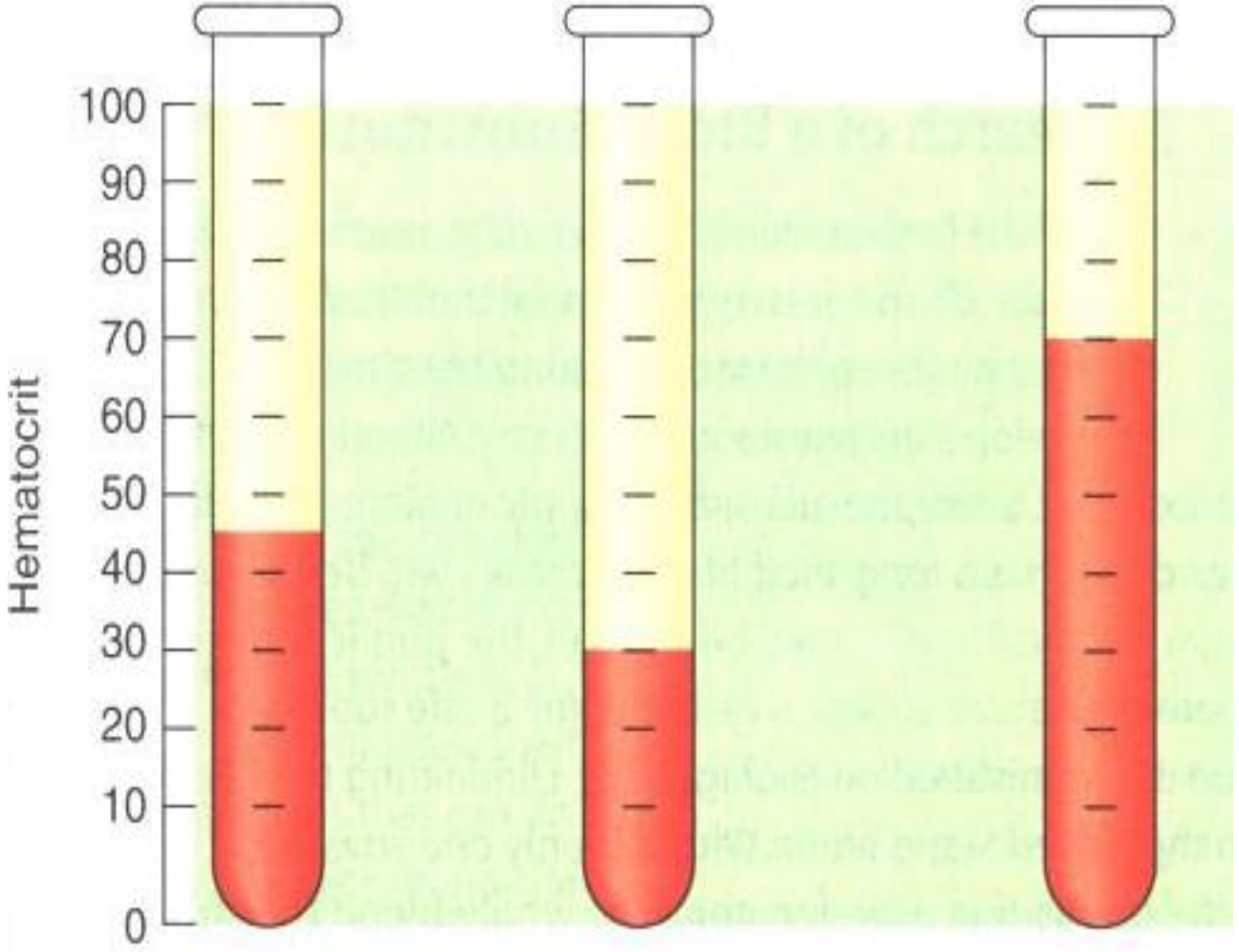

Blood parts
blood
white blood cells
plasma
(water and other stuff)
red blood
cells
platelets


Blood
Plasma
55% of blood volume
Cells
45% of blood volume
RBCs
Platelets
WBCs
Neutophils
Basophils
Esinophils
Monocytes
Lymphocytes

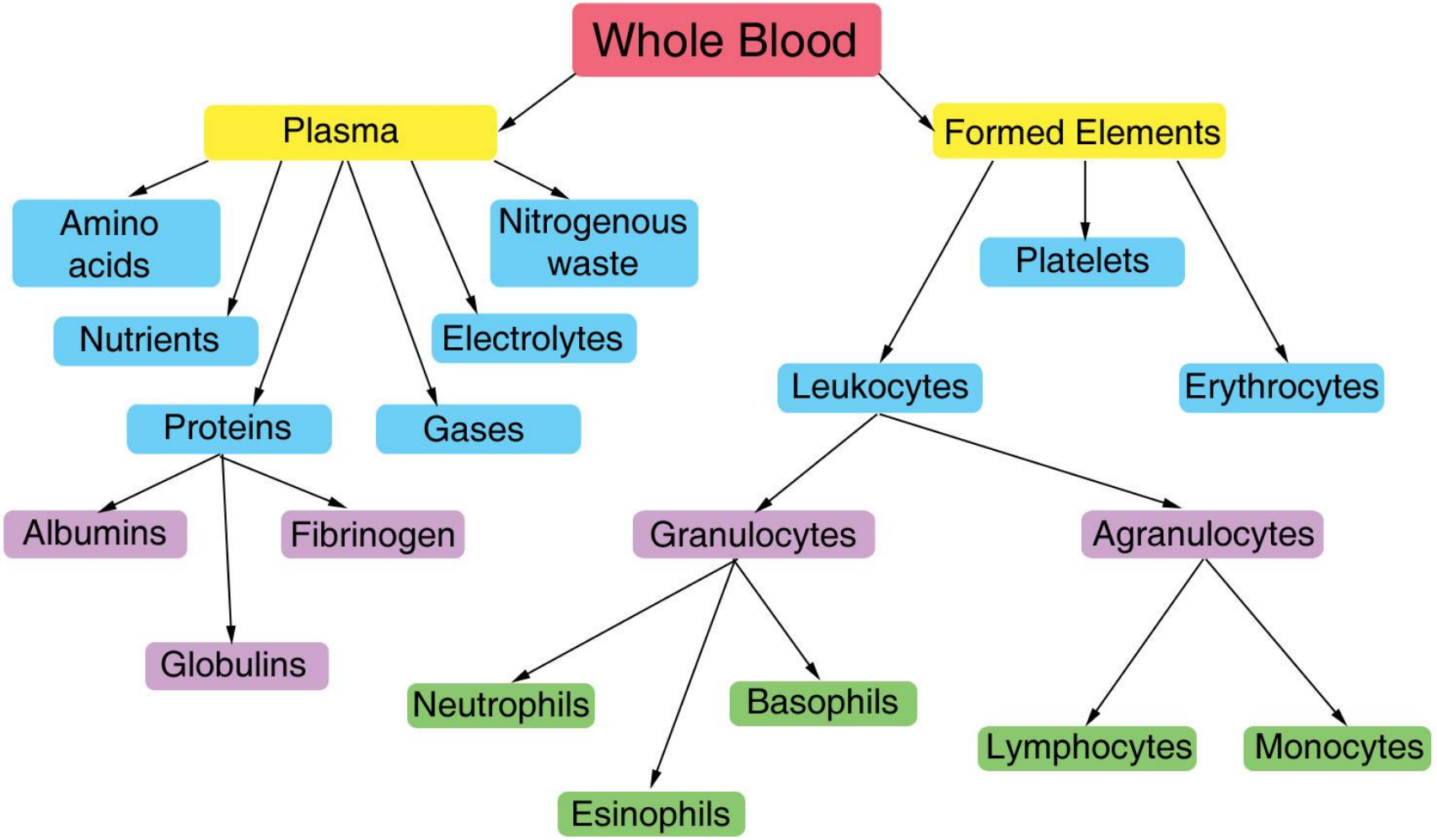

plasma
WBCs & platelets
RBCs

BLOOD: PLASMA VS. HEMATOCRIT

- Hematocrit or packed cell volume (Adult male: 47 %, Adult females: 42 %)



BLOOD: WHAT IS INSIDE PLASMA

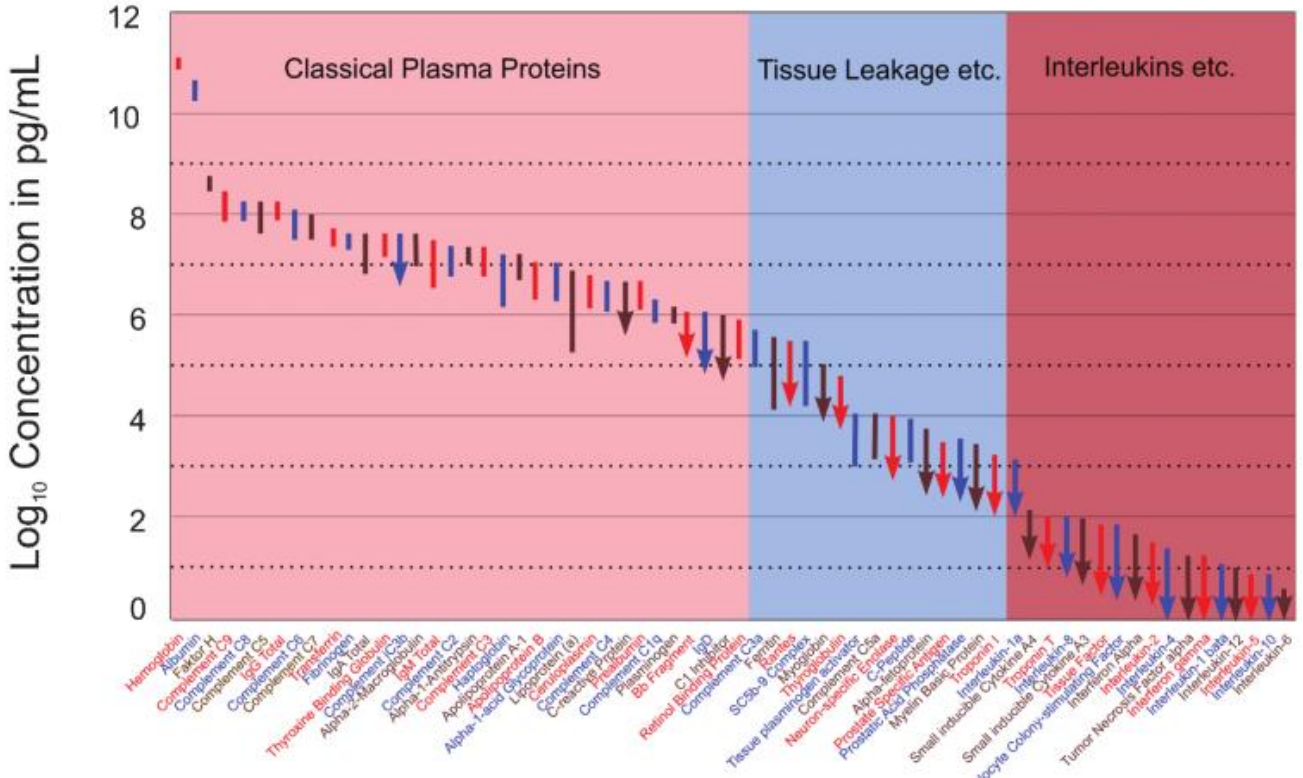


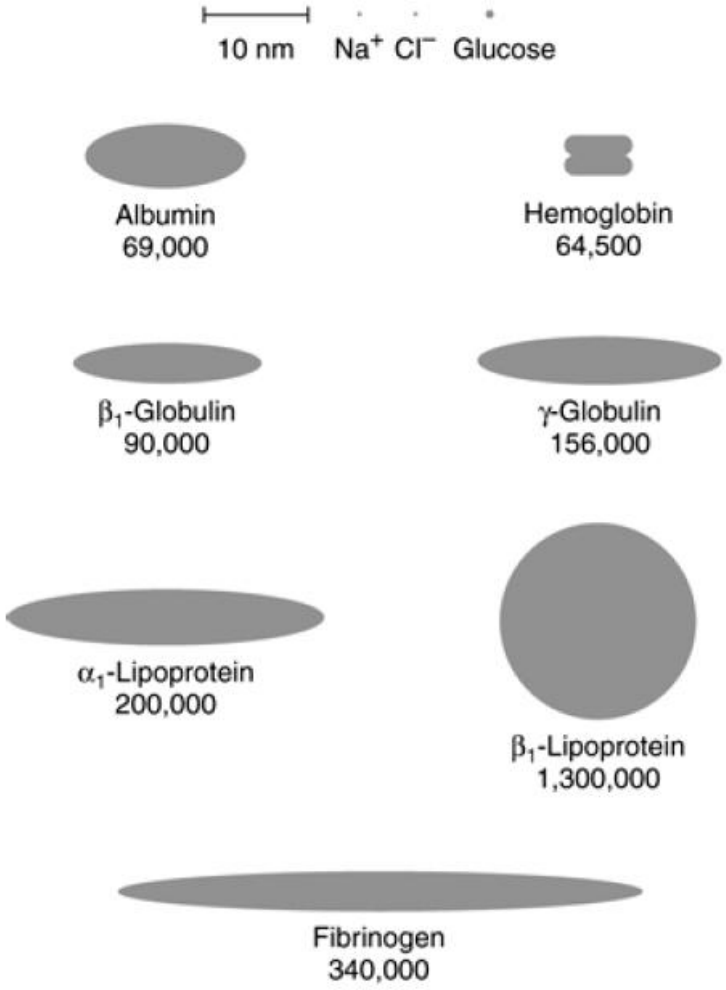
PLASMA

- **Liquid medium where cells are suspended**
- **Composition:** - **Water (92%)** - **Solids (8%)**
  - **<u>Organic:</u>**
    - **Plasma proteins: Albumin, Globulins & Fibrinogen**
    - **Non-protein nitrogenous compounds: urea, free amino acids, uric acid, creatinine, creatine & NH_3**
    - **Lipids: Cholesterol, TG, phospholipids, free fatty acids**
    - **Carbohydrates: Glucose, fructose, pentose**
    - **Other substances as: Ketone bodies, bile pigments, vitamins, enzymes & hormones**
  - **<u>Inorganic:</u> Na^+,K^+,Ca^{2+},Mg^{2+},Cl^-,HCO_3^-,HPO_4^{2-}, SO_4^{2-}**

PLASMA PROTEINS ARE A MIXTURE

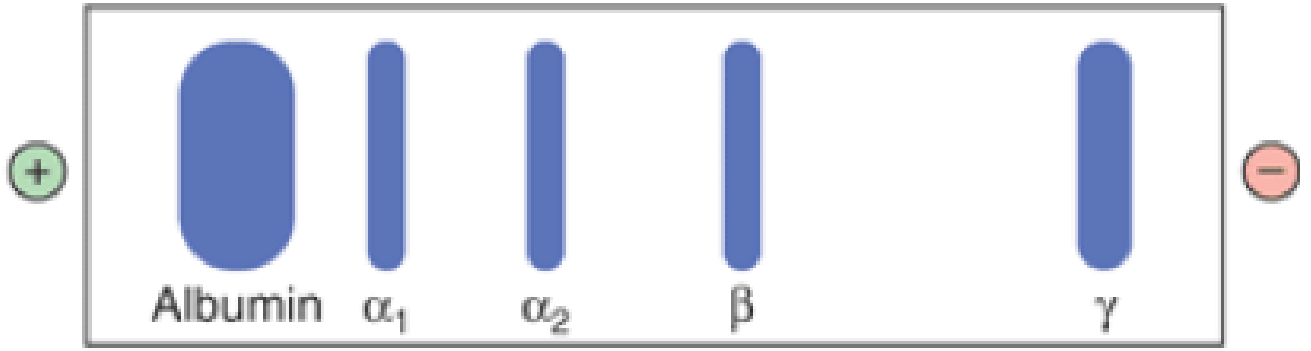
- More than 500 plasma proteins have been identified
- Normal range 6-8 g/dl (the major of the solids)
- Simple & conjugated proteins (glycoproteins & lipoprot





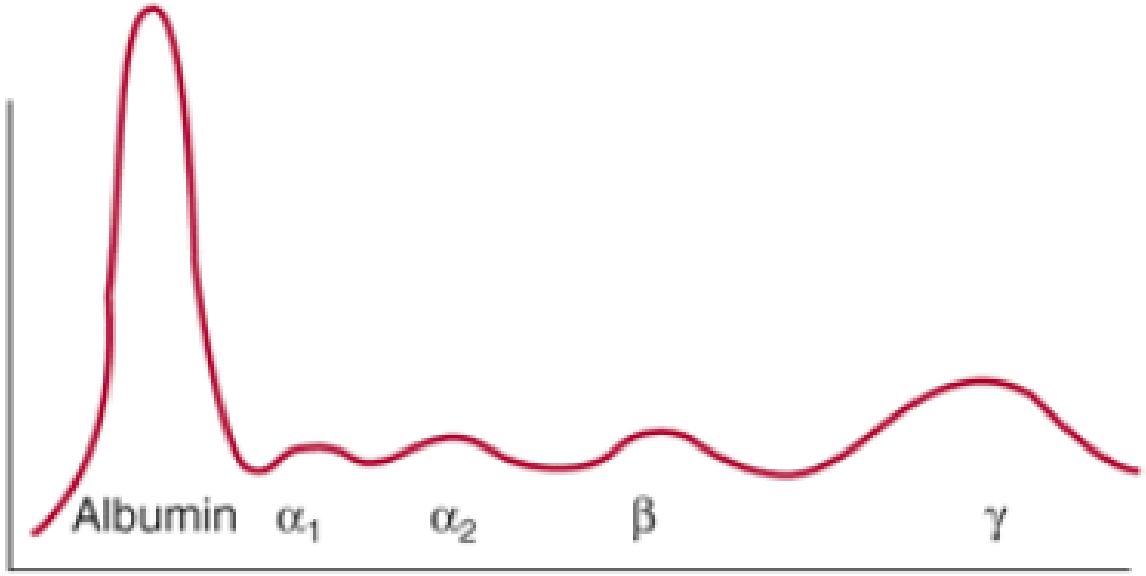
SEPARATION OF PLASMA PROTEINS

- Salting-out (ammonium sulfate): fibrinogen, albumin, and globulins
- Electrophoresis (most common): serum (defebrinated plasma), five bands (albumin, α1 , α2 , β, and γ)



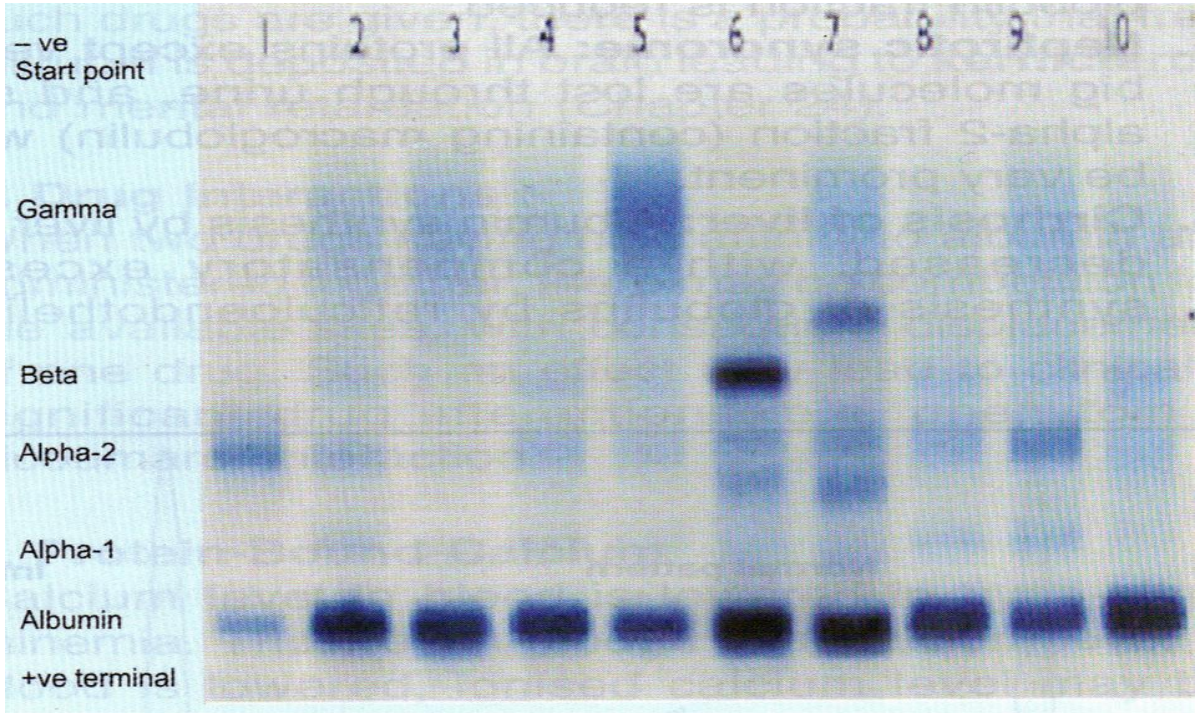
NORMAL VALUES:

Name	Absolute values (g/l)	Relative values (%)
Albumins	35 – 55	50 – 60
α1-globulins	2 – 4	4.2 – 7.2
α2-globulins	5 – 9	6.8 – 12
β-globulins	6 – 11	9.3 – 15
γ-globulins	7 – 17	13 – 23



ELECTROPHORESIS OF PLASMA PROTEINS

- Albumin is smaller than globulin, and slightly negatively charged
- Globulins (3 bands):
- α band:
  - α1 region consists mostly of α1-antitrypsin
  - α2 region is mostly haptoglobin, α2-macroglobulin, & ceruloplasmin
- β band: transferrin, LDL, complement system proteins
- γ band: the immuno-globulins



SYNTHESIS OF PLASMA PROTEINS

- Mostly liver (albumin, globulins), γ-globulins (plasma cells; lymph nodes, bone marrow, spleen)
- Most plasma proteins are synthesized as preproproteins (signal peptide)
- Various posttranslational modifications (proteolysis, glycosylation, phosphorylation, etc.)
- Transit times (30 min to several hours)
- Most plasma proteins are Glycoproteins (N- or O-linked). Albumin is the major exception

POLYMORPHISMS AND HALF-LIVES

Polymorphisms

- A mendelian or monogenic trait
- Exists in population in at least two phenotypes, neither is rare
- The ABO blood groups are the best-known examples
- α1-antitrypsin, haptoglobin, transferrin, ceruloplasmin, and immunoglobulins
- Electrophoresis or isoelectric focusing

Half-Lives

- Determined through isotope labeling studies (I^{131})
- Albumin & haptoglobin (20 & 5 days)
- Diseases can affect half-lives (ex. Crohn's disease), albumin may be reduced (1 day)
- Protein-losing gastro-enteropathy

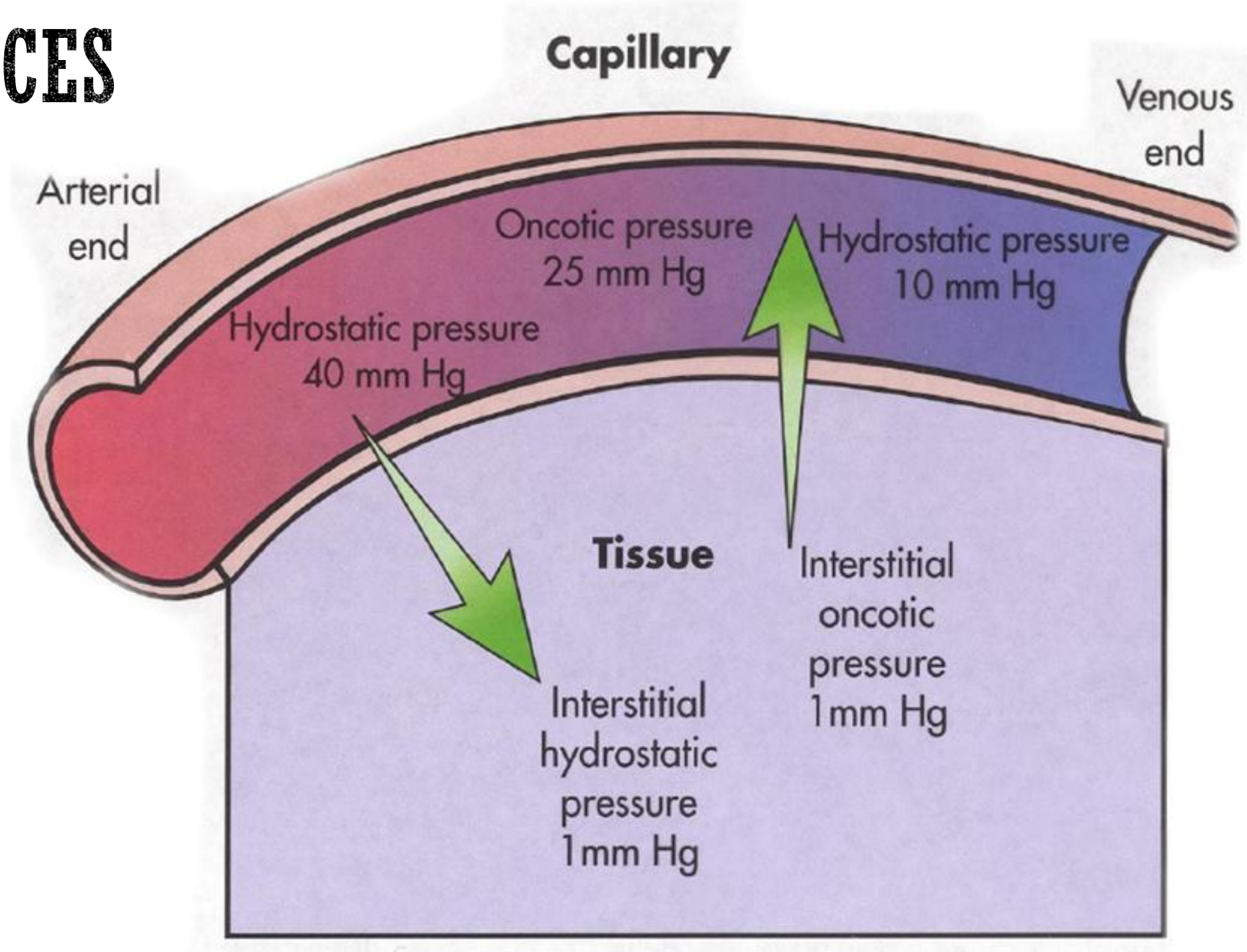
GENERAL AND SPECIFIC FUNCTIONS OF PLASMA PROTEINS

- A nutritive role
- Maintenance of blood pH (amphoteric property)
- Contributes to blood viscosity
- Maintenance of blood osmotic pressure

- Enzymes (e.g. rennin, coagulation factors, lipases)
- Humoral immunity (immunoglobulins)
- Blood coagulation factors
- Hormonal (Erythropoietin)
- Transport proteins (Transferrin, Thyroxin binding globulin, Apolipoprotein)

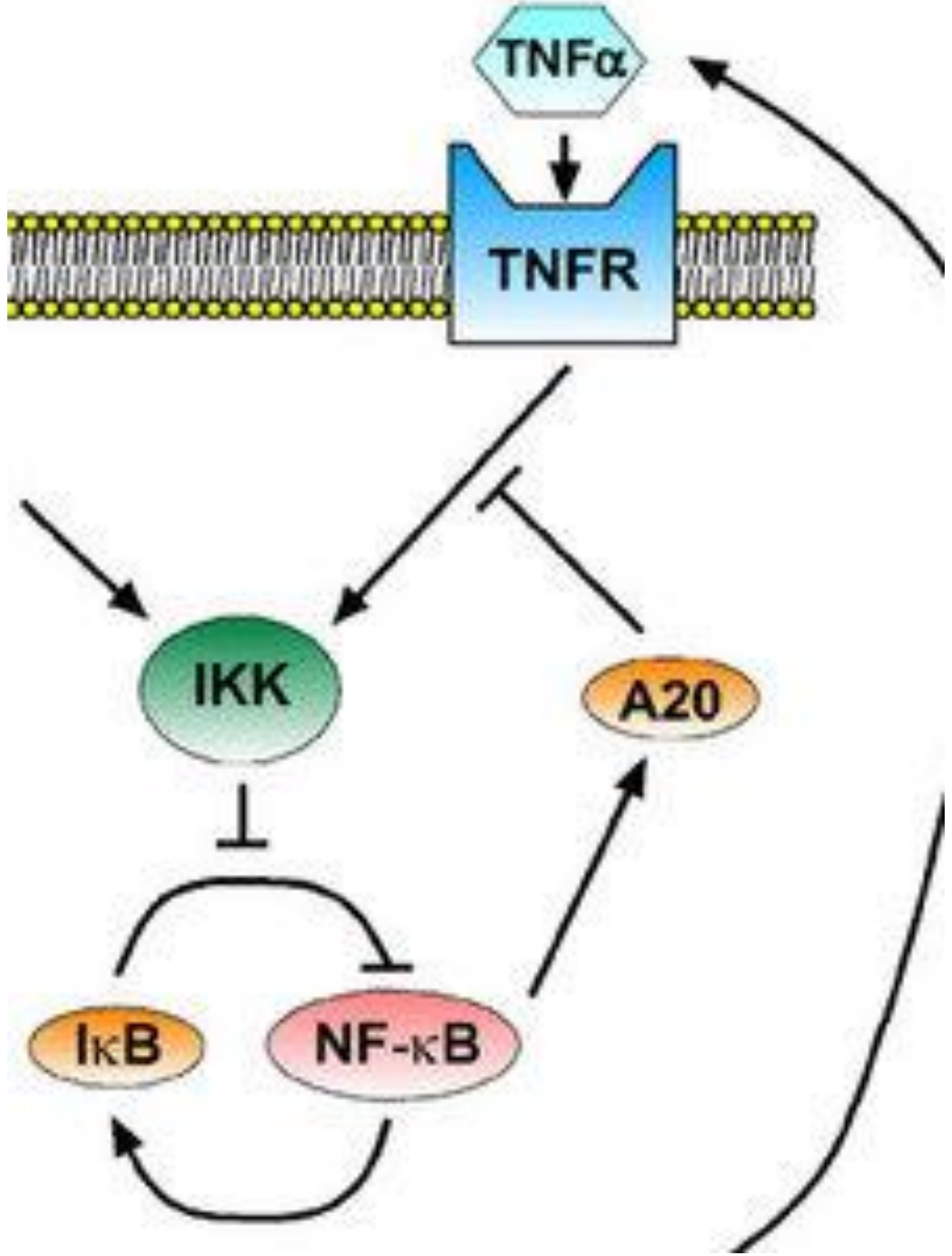
STARLING FORCES

- Edema can be a result of protein deficiency



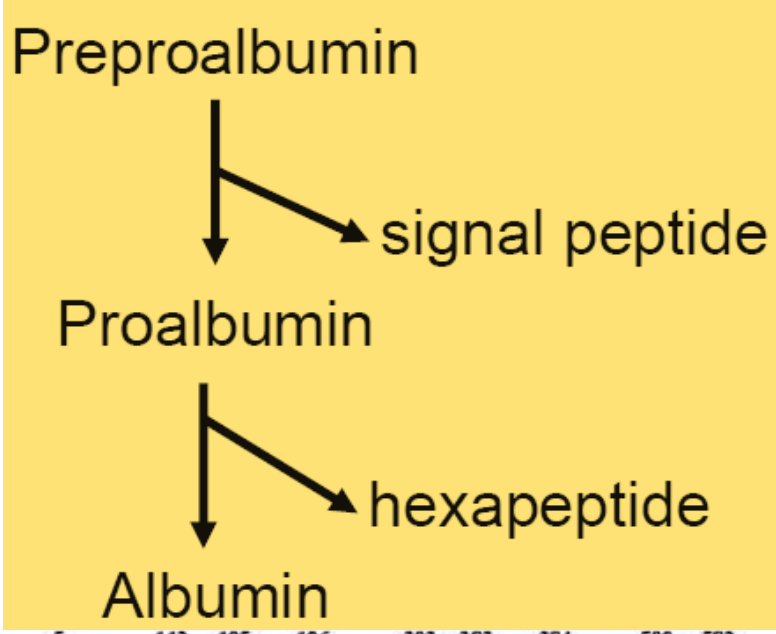
ACUTE-PHASE PROTEINS

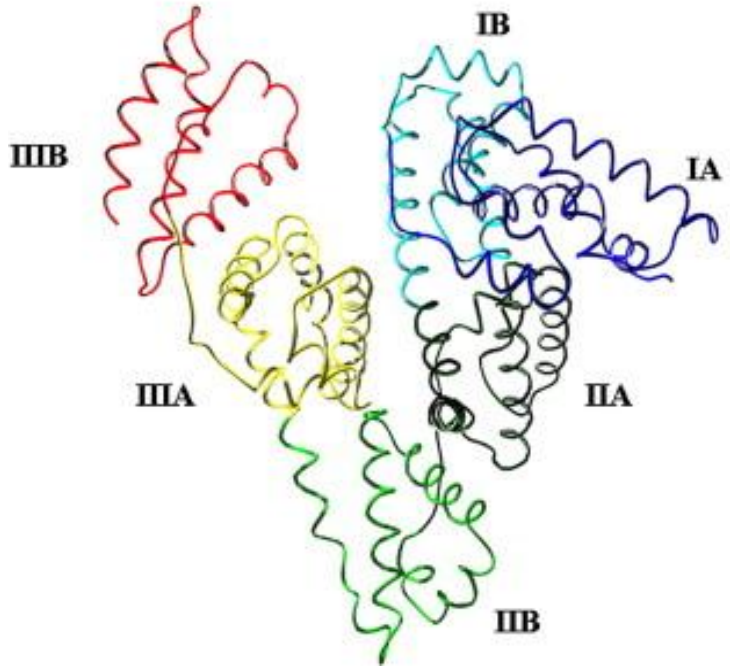
- Levels increase (up to 1000 folds), acute inflammation, tissue damage, chronic inflammation & cancer. C-reactive protein (CRP), α1 -antitrypsin, haptoglobin, & fibrinogen
- Interleukin-1 (IL-1), main stimulator (gene transcription)
- Nuclear factor kappa-B (NFkB): Exist in an inactive form in cytosol, activated and translocated to nucleus (interleukin-1)
- Negative acute phase proteins: prealbumin, albumin, transferrin



ALBUMIN

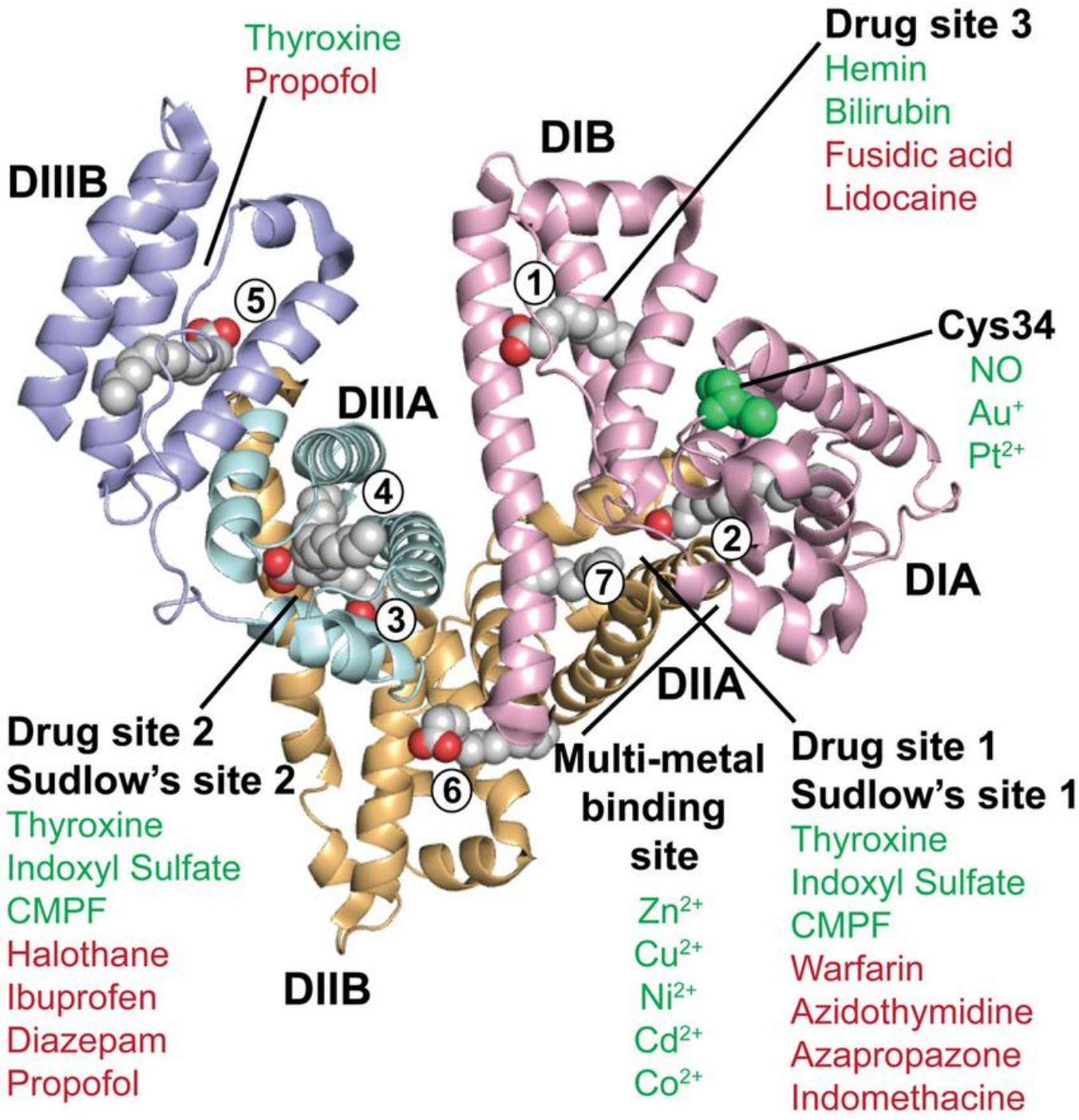
- The Major Protein in Human Plasma, 69 kDa, half-life (20 days)
- The main contributor to the osmotic pressure (75-80%)
- Liver: 12 g/day (25% of total protein synthesis) (liver function test)
- Synthesized as a preproprotein
- One polypeptide chain, 585 amino acids, 17 disulfide bonds
- Proteases subdivide albumin into 3 domains
- Ellipsoidal shape (viscosity) vs. fibrinogen
- Anionic at pH 7.4 with 20 negative charges





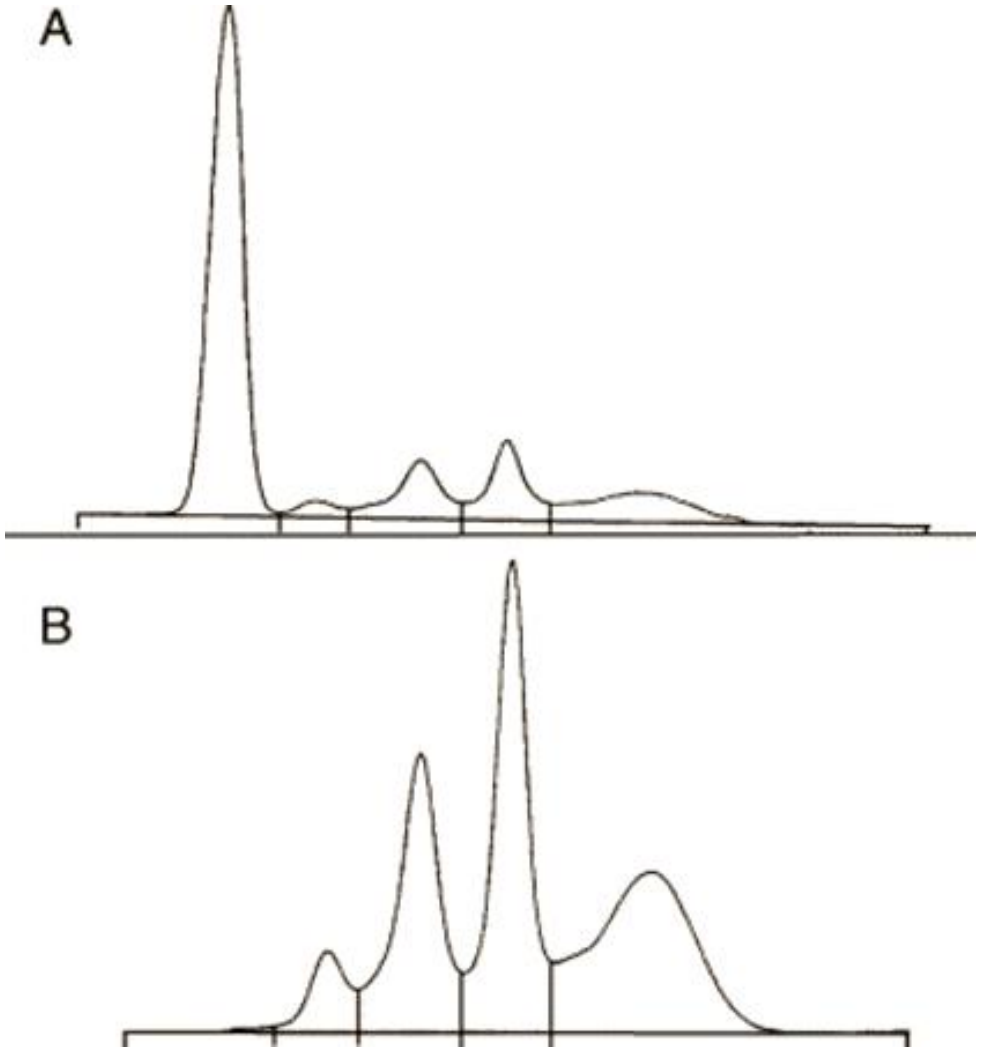
ALBUMIN BINDING CAPACITY

- binds various ligands:
  - Free fatty acids (FFA)
  - Certain steroid hormones
  - Bilirubin
  - Plasma tryptophan
  - Metals: Calcium, copper and heavy metals
  - Drugs: sulfonamides, penicillin G, dicumarol, aspirin (drug-drug interaction)



ANALBUMINEMIA

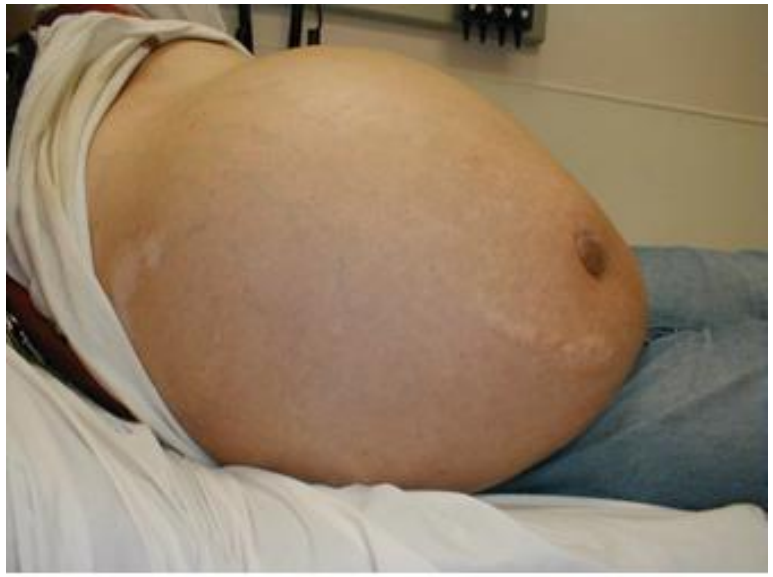
- There are human cases of analbuminemia (rare)
- Autosomal recessive inheritance
- One of the causes: a mutation that affects splicing
- Patients show moderate edema!!!

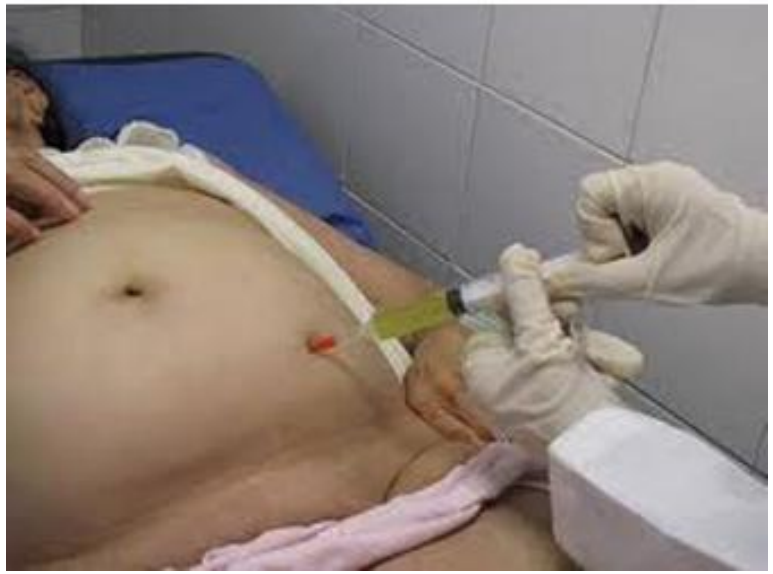


OTHER CLINICAL DISORDERS

- Hypoalbiminemia: edema seen in conditions where albumin level in blood is less than 2 g/dl
  - Malnutrition (generalised edema)
  - Nephrotic syndrome
  - Cirrhosis (mainly ascites)
  - Gastrointestinal loss of proteins

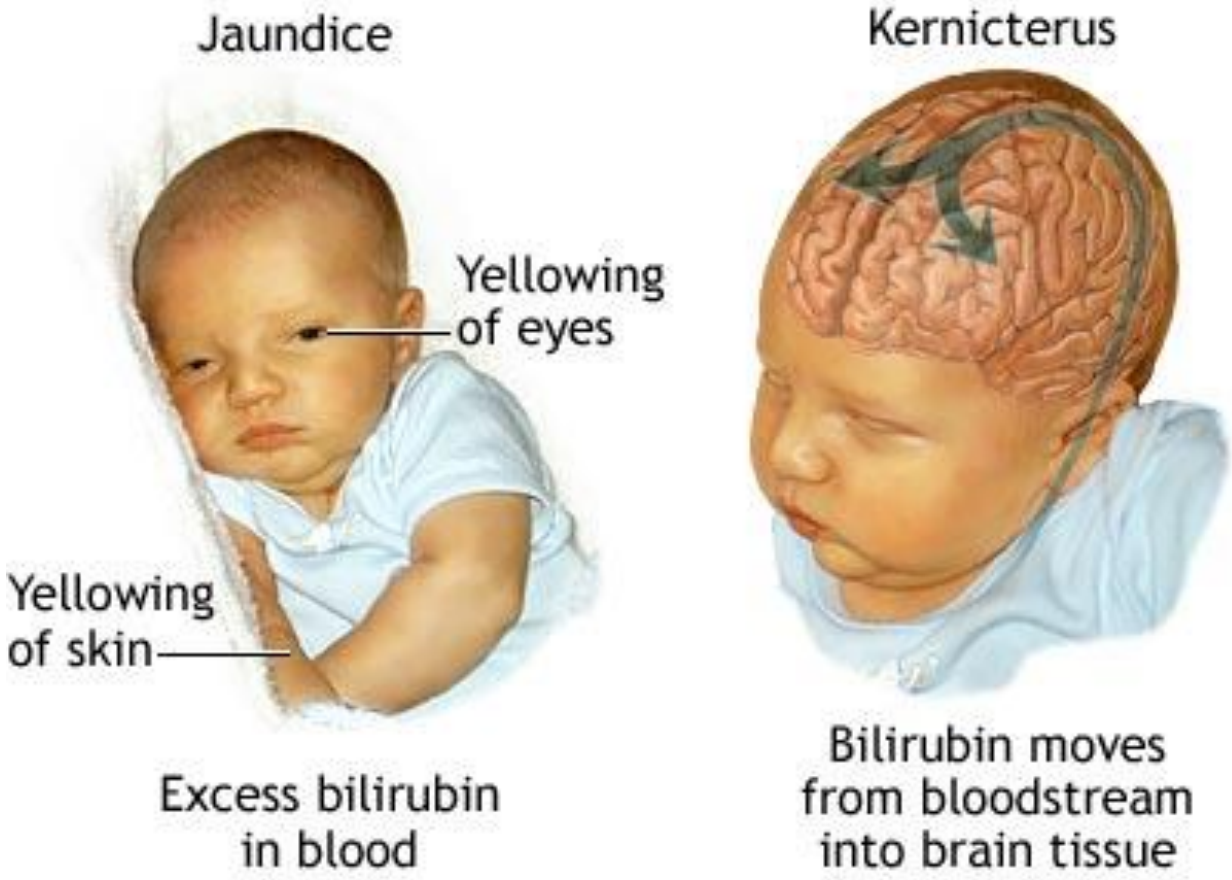
- Hyperalbuminemia: dehydration (relative increase)





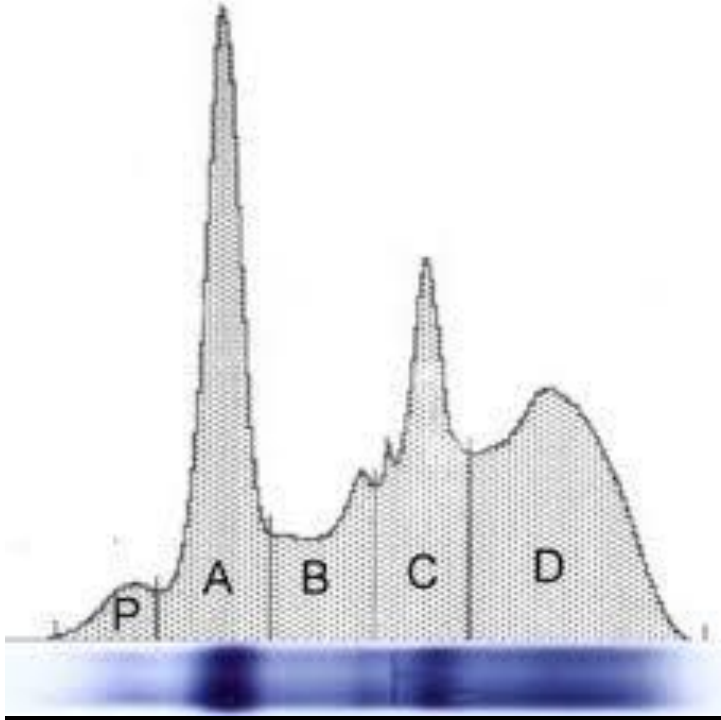
OTHER CLINICAL DISORDERS

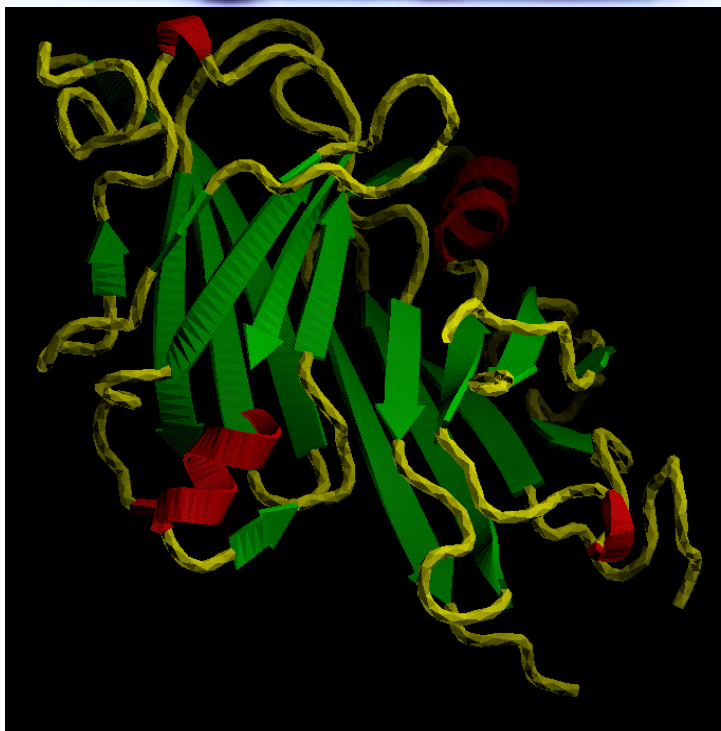
- Drug-drug interaction:
- Bilirubin toxicity (aspirin is a competitive ligand of albumin): kernicterus and mental retardation, Reye's syndrome
- Phenytoin-dicoumarol interaction



PREALBUMIN (TRANSTHYRETIN)

- Migrates ahead of albumin, 62 kDa
- It is a small glycoprotein (rich in tryptophan, 0.5% carbohydrates)
- Blood level is low (0.25 g/L)
- It has short half-life (≈2 days): sensitive indicator of disease or poor protein nutrition
- Main function:
- T4 (Thyroxine) and T3 carrier





GLOBULINS

✓ α1-globulins	✓ α2- globulins	✓ β- globulins	✓ γ-globulins
✓ α1-antitrypsin ✓ α1-fetoprotein ✓ α1- acid glycoprotein ✓ Retinol binding protein	✓ Ceruloplasmin ✓ Haptoglobin ✓ α2-macroglobulin	✓ CRP ✓ Transferrin ✓ Hemopexin ✓ β2-microglobulin	✓ IGG ✓ IGA ✓ IGM ✓ IGD ✓ IGE

α1- ANTITRYPSIN

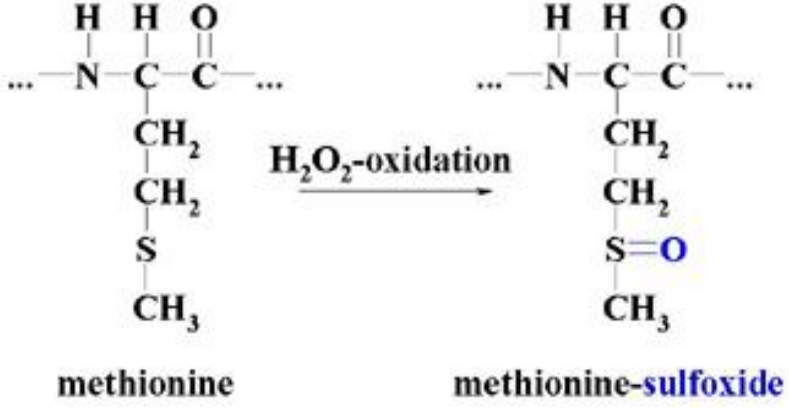
- α1-Antiproteinase (52 kDa)
- Neutralizes trypsin & trypsin-like enzymes (elastase)
- 90% of α1- globulin band
- Many polymorphic forms (at least 75)
- Alleles Pi^M, Pi^S, Pi^Z, Pi^F (MM is the most common)
- Deficiency (genetic): emphysema (ZZ, SZ). MS, MZ usually not affected
- Increased level of α1- antitrypsin (acute phase response)

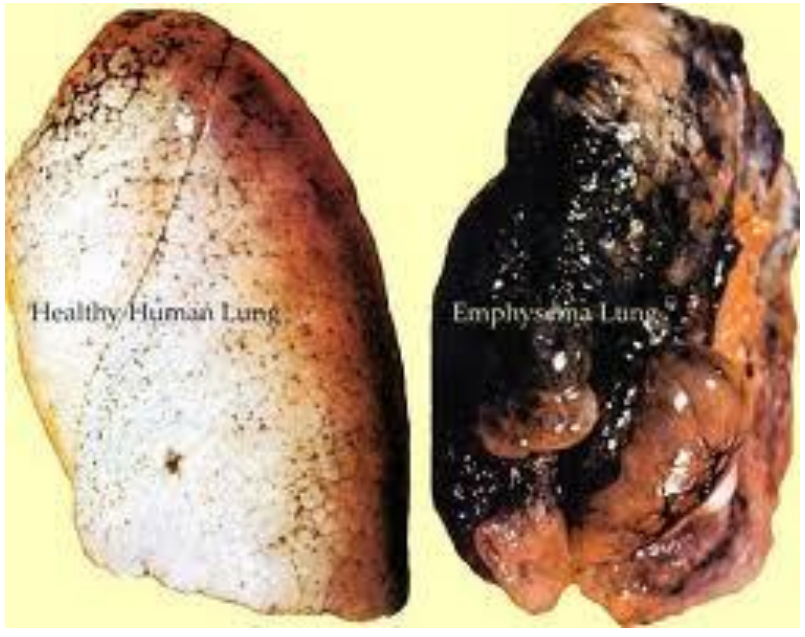
Active elastase + α_1–AT → Inactive elastase: α_1–AT complex → No proteolysis of lung → No tissue damage

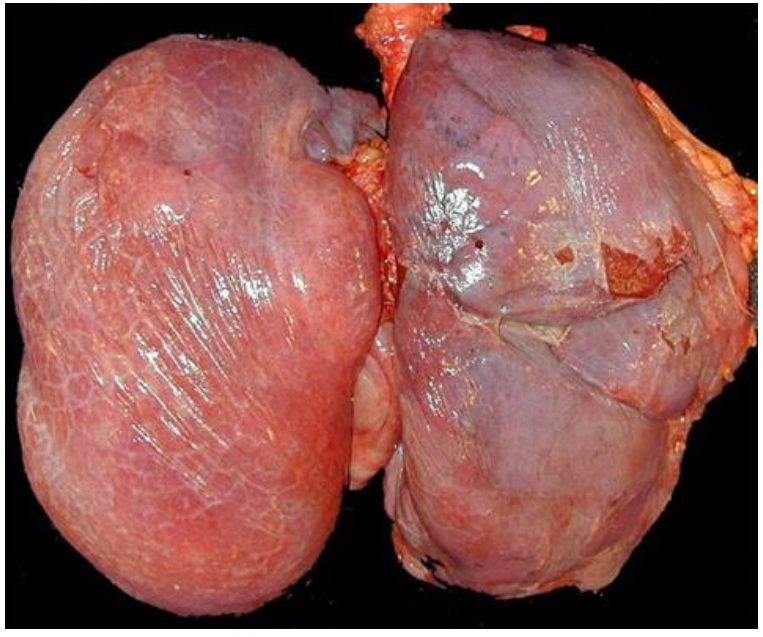
Active elastase + ↓ or no α_1–AT → Active elastase → Proteolysis of lung → Tissue damage

SMOKING & α1- ANTITRYPSIN DEFICIENCY

- Chronic inflammation (neutrophil elastase)
- Oxidation of Met^{358}
- Devastating in patients with PiZZ

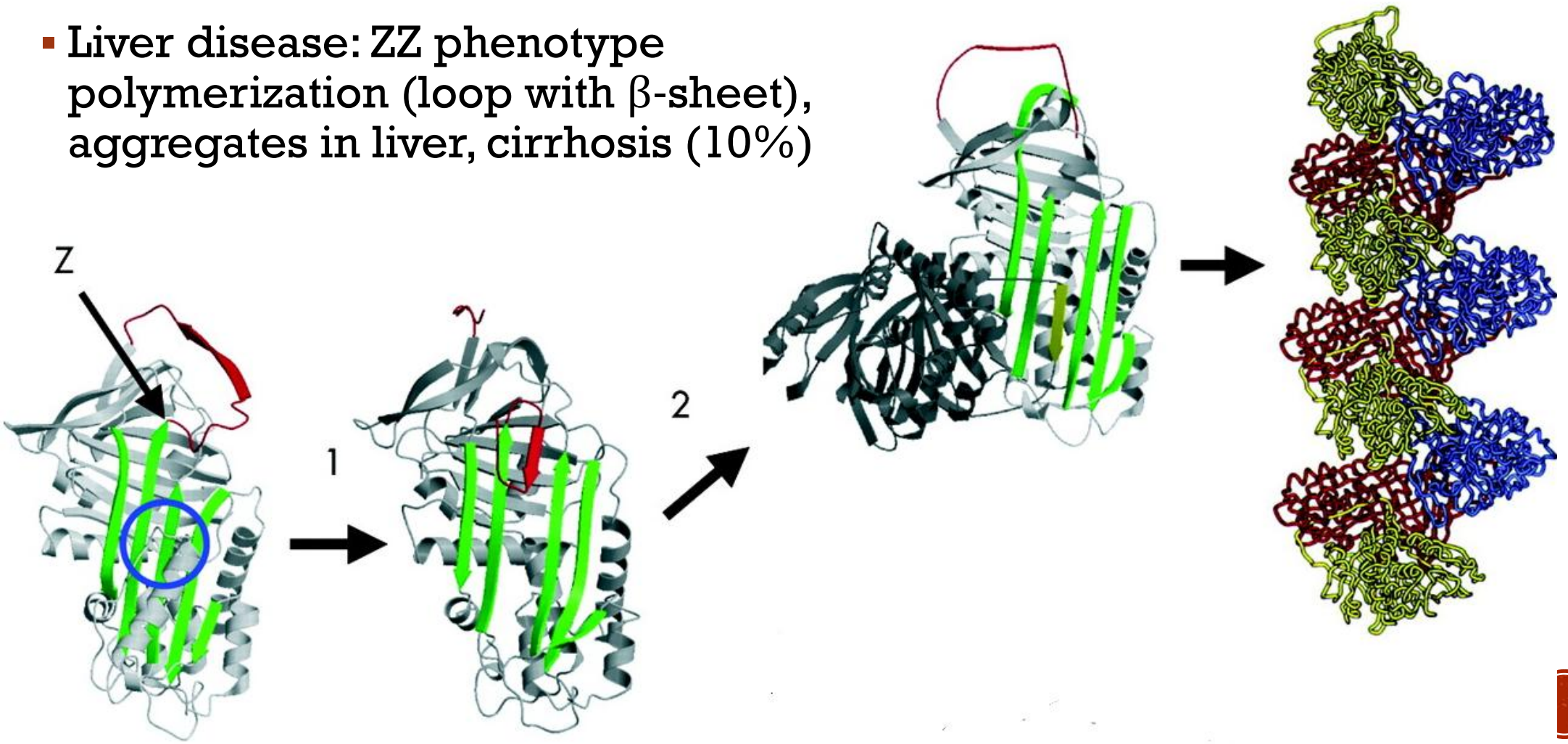






LIVER DISEASE & α1- ANTITRYPSIN DEFICIENCY

- Liver disease: ZZ phenotype polymerization (loop with β-sheet), aggregates in liver, cirrhosis (10%)

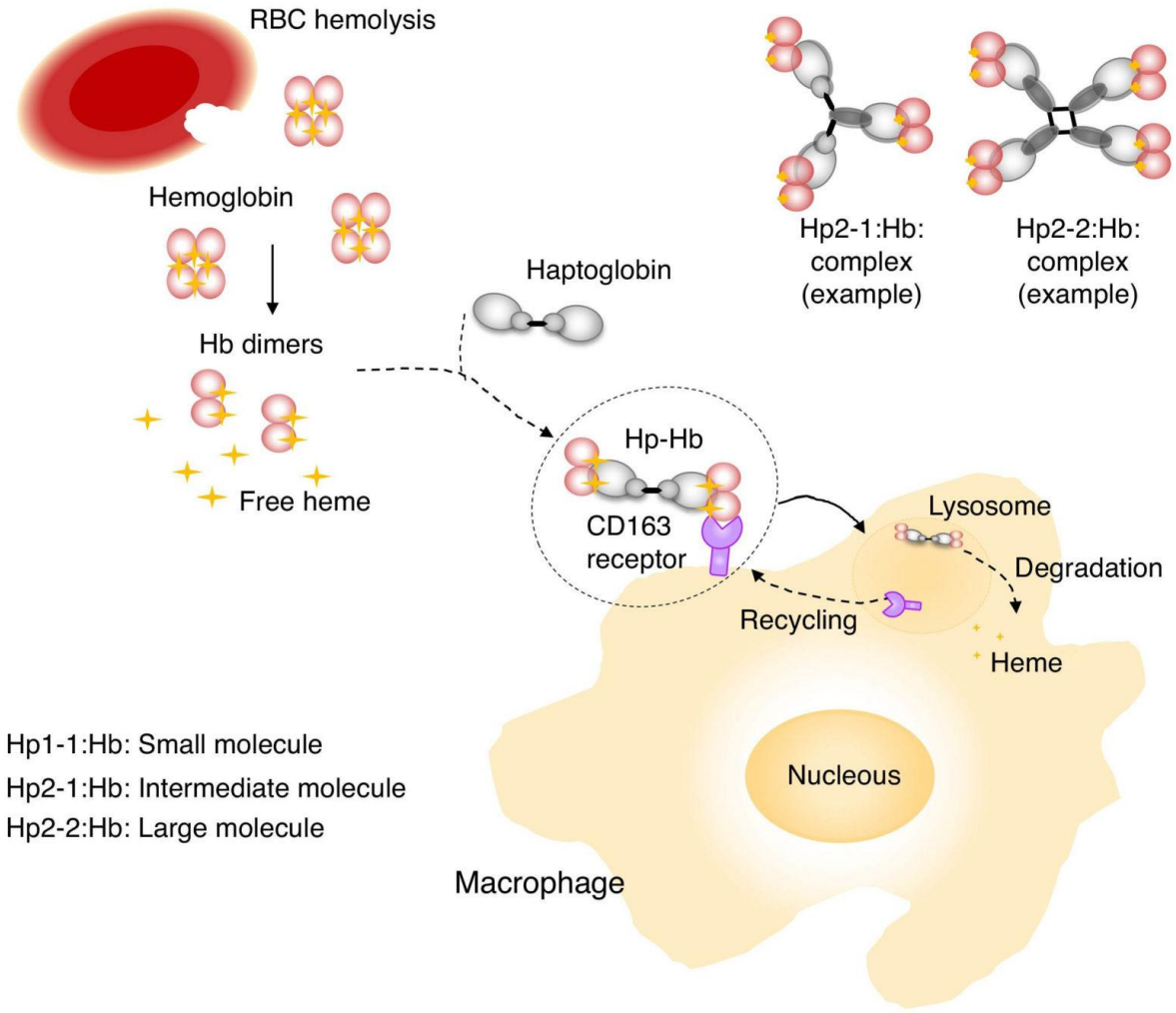


α1- FETOPROTEIN

- Synthesized primarily by the fetal yolk sac and then by liver parenchymal cells
- Very low levels in adult
- Functions of α1-fetoprotein:
- Protect the fetus from immunolytic attacks
- Modulates the growth of the fetus
- Transport compounds e.g. steroids
- Low level: increased risk of Down's syndrome
- Level of α1-fetoprotein increases in:
- Fetus and pregnant women Normally
- Hepatoma & acute hepatitis

HAPTOGLOBIN (HP)

- It is an acute phase reactant protein
- α2 glycoprotein (90kDa)
- A tetramer (2α, 2β)
- 3 phenotypes:
  - Hp 1-1→ α1, α1 + 2β
  - Hp 2-1→ α1, α2 + 2β
  - Hp 2-2 → α2, α2 + 2β
- Binds the free hemoglobin (65 kDa); prevents loss of hemoglobin & its iron into urine
- Hb-Hp complex has shorter half-life (90 min) than that of Hp (5 days)
- Decreased level in hemolytic anemia

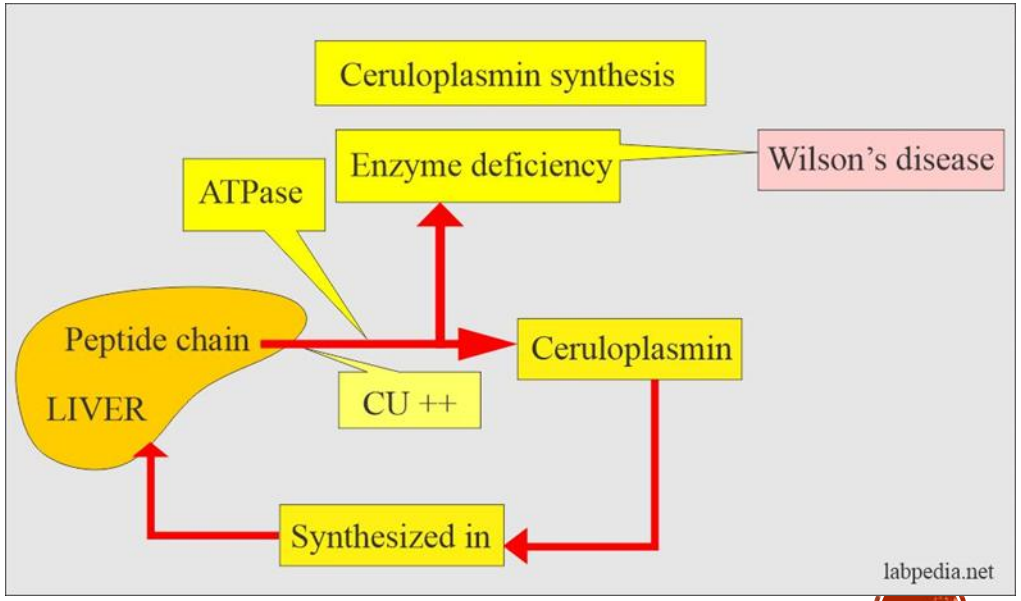


CERULOPLASMIN

- A copper containing glycoprotein (160 kDa)
- It contains 6 atoms of copper
- Metallothioneins (regulate tissue level of Cu)
- Regulates copper level: contains 90% of serum Cu
- A ferroxidase: oxidizes ferrous to ferric (transferrin)
- Albumin (10%) is more important in transport
- Decreased levels in liver disease (ex. Wilson's, autosomal recessive genetic disease)

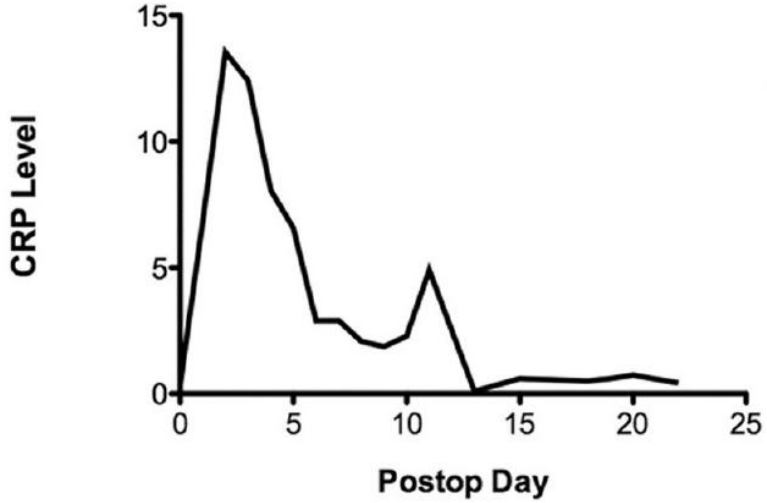
Cu-containing enzymes

- Amine oxidase
- Copper-dependent superoxide dismutase
- Cytochrome oxidase
- Tyrosinase

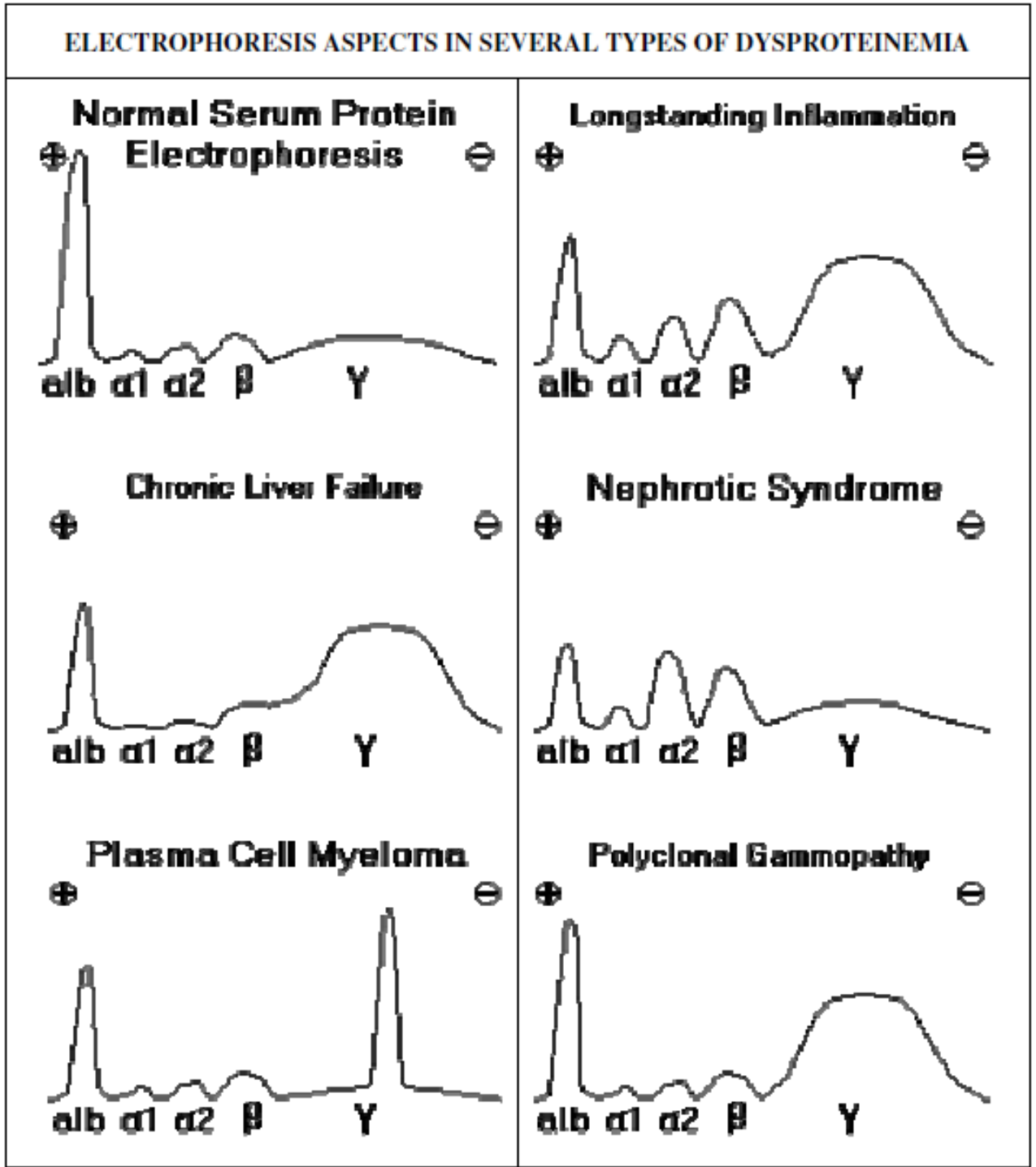


C-REACTIVE PROTEIN (CRP)

- A **homo-pentameric** acute-phase inflammatory protein
- Able to bind to a polysaccharide (fraction C) in the cell wall of pneumococci
- Help in the defense against bacteria and foreign substances
- Undetectable in healthy individuals, detectable in many inflammatory diseases (Acute rheumatic fever, bacterial infection, gout, etc.) & Tissue damage
- Its level reaches a peak after 48 hours of incident (monitoring marker)



DISEASES


ELECTROPHORESIS ASPECTS IN SEVERAL TYPES OF DYSPROTEINEMIA
Normal Serum Protein Electrophoresis
alb α1 α2 β γ
Longstanding Inflammation
alb α1 α2 β γ
Chronic Liver Failure
alb α1 α2 β γ
Nephrotic Syndrome
alb α1 α2 β γ
Plasma Cell Myeloma
alb α1 α2 β γ
Polyclonal Gammopathy
alb α1 α2 β γ

DISEASES