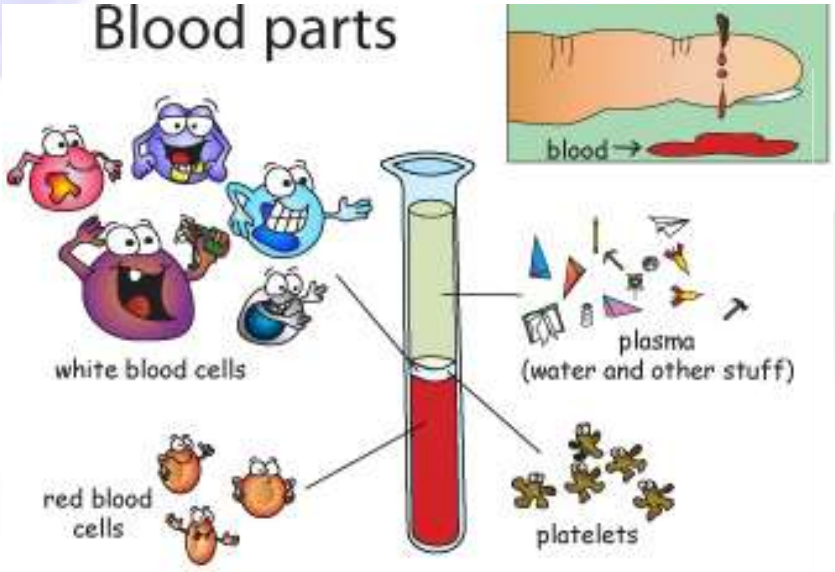
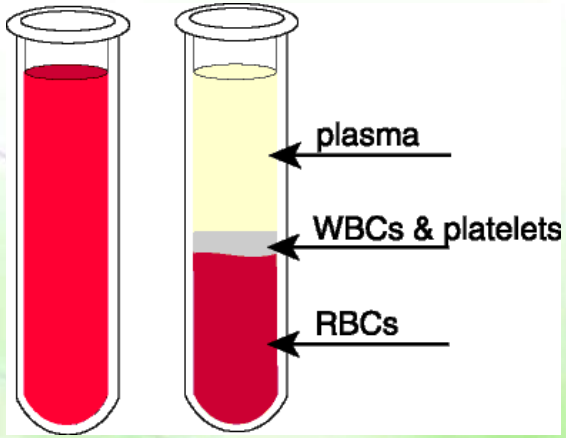
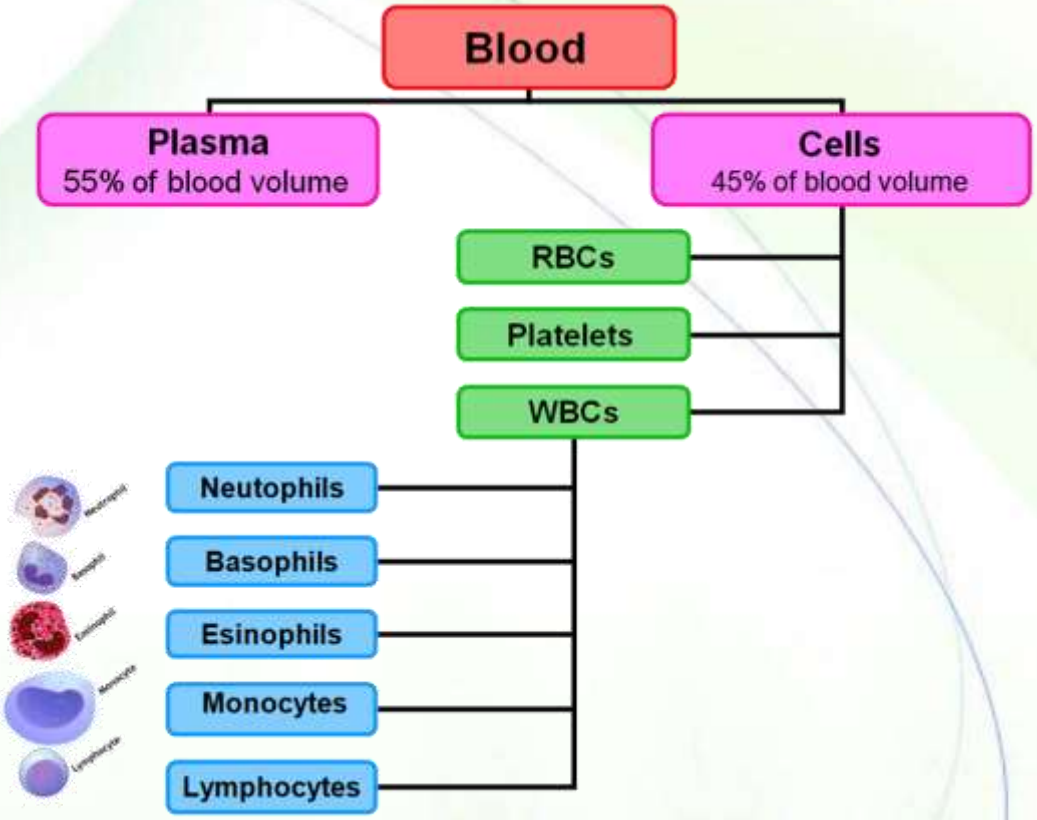
Plasma Proteins

Summer 2024

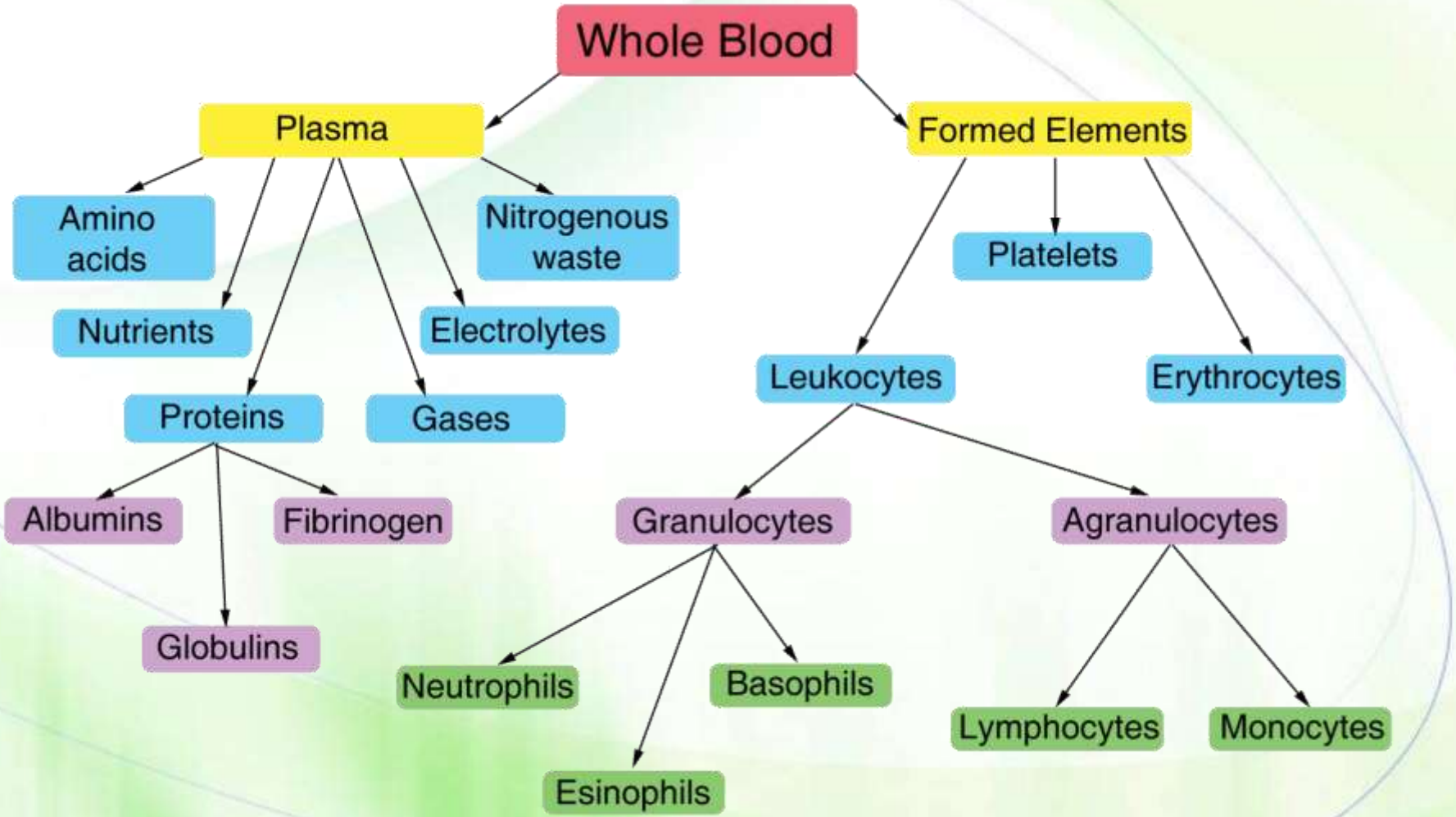
Blood


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


plasma
WBCs & platelets
RBCs


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

Blood: plasma vs. cells

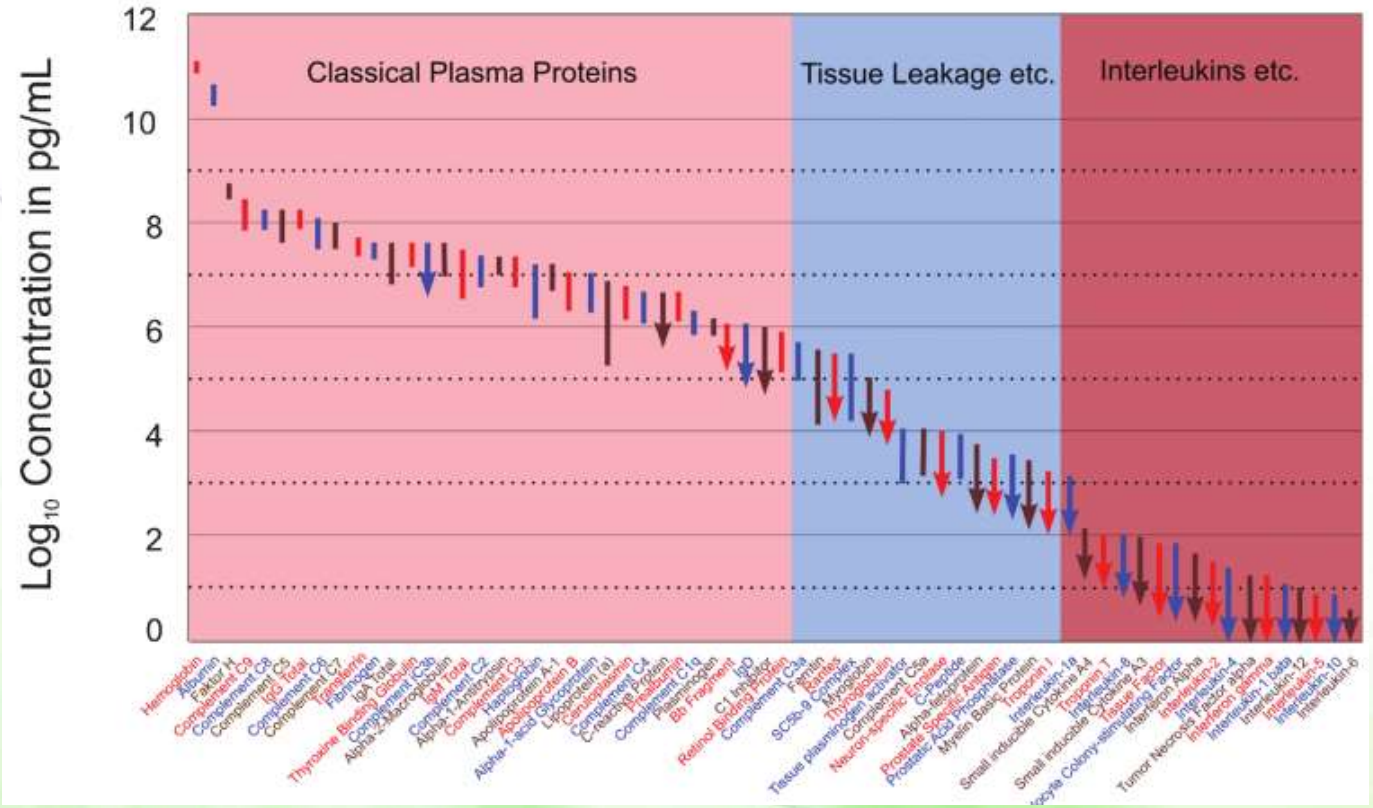


Plasma

- It is the liquid medium in which blood cells are suspended.
- Composition: ▪ Water (92%) ▪ Solids (8%)
  - Organic:
    - Plasma proteins: Albumin, Globulins & Fibrinogen
    - Non-protein nitrogenous compounds: urea, free amino acids, uric acid, creatinine, creatine & NH3
    - Lipids: Cholesterol, TG, phospholipids, free fatty acids
    - Carbohydrates: Glucose, fructose, pentoses
    - Other substances as: Ketone bodies, bile pigments, vitamins, enzymes & hormones
  - Inorganic: 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 & lipoproteins)



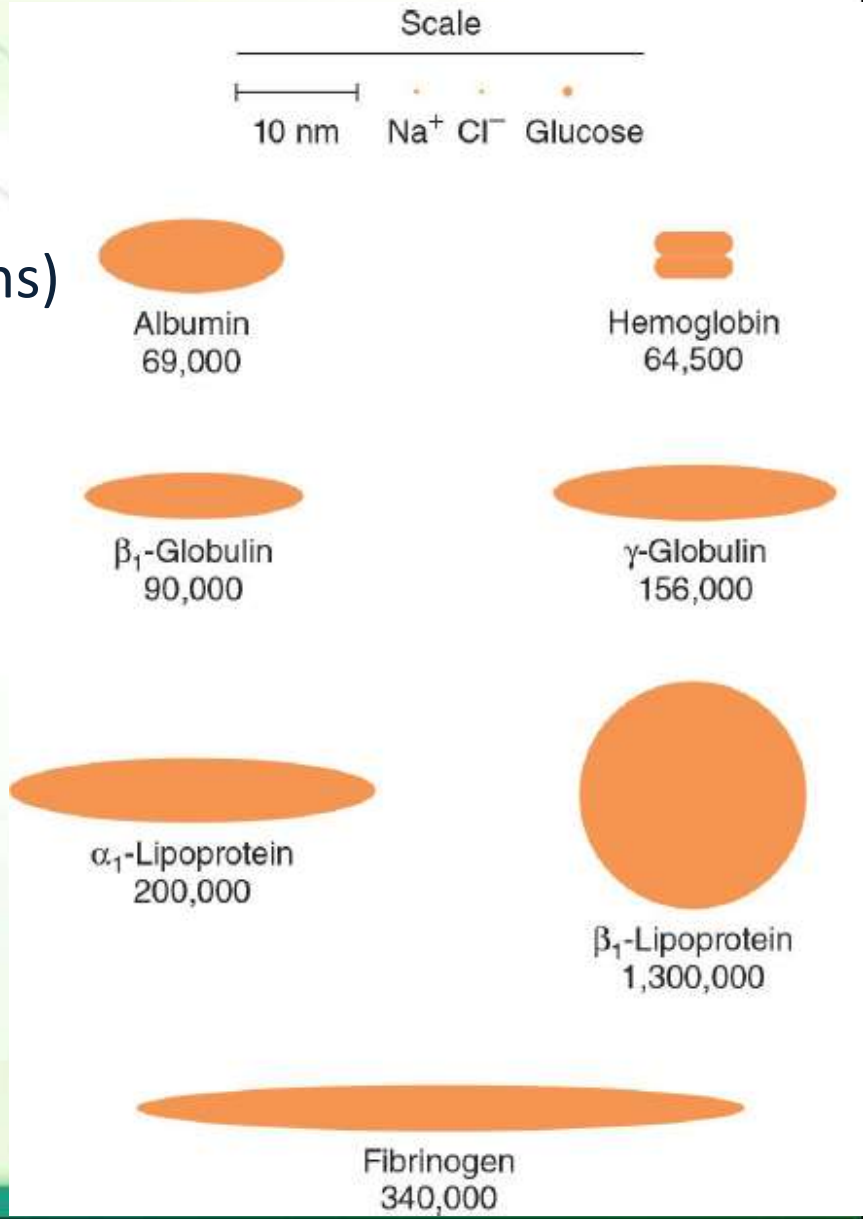
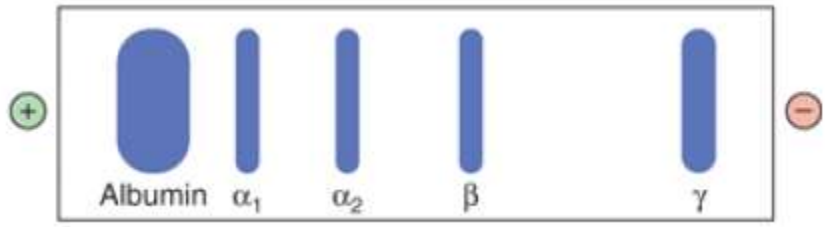


TABLE 52–2 Major Functions of Blood

1. **Respiration**—transport of oxygen from the lungs to the tissues and of CO_2 from the tissues to the lungs
2. **Nutrition**—transport of absorbed food materials
3. **Excretion**—transport of metabolic waste to the kidneys, lungs, skin, and intestines for removal
4. Maintenance of the normal **acid–base balance** in the body
5. Regulation of **water balance** through the effects of blood on the exchange of water between the circulating fluid and the tissue fluid
6. Regulation of **body temperature** by the distribution of body heat
7. **Defense** against infection by the white blood cells and circulating antibodies
8. Transport of **hormones** and regulation of metabolism
9. Transport of **metabolites**
10. **Coagulation**

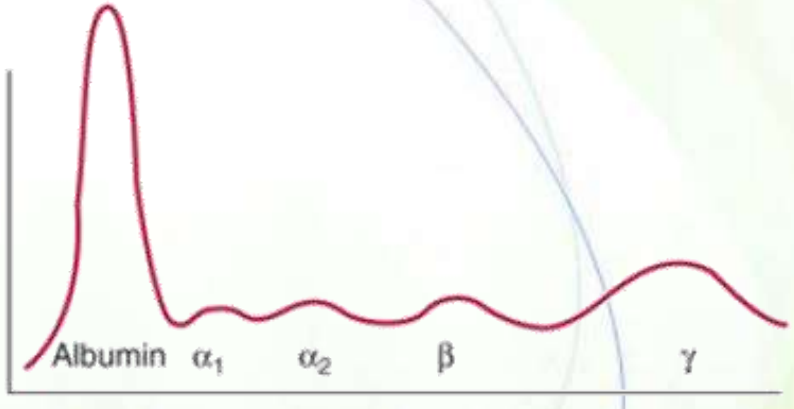
The separation of plasma proteins

- Electrophoresis (most common): serum (defebrinated plasma), five bands (albumin, α1 , α2 , β, and γ)



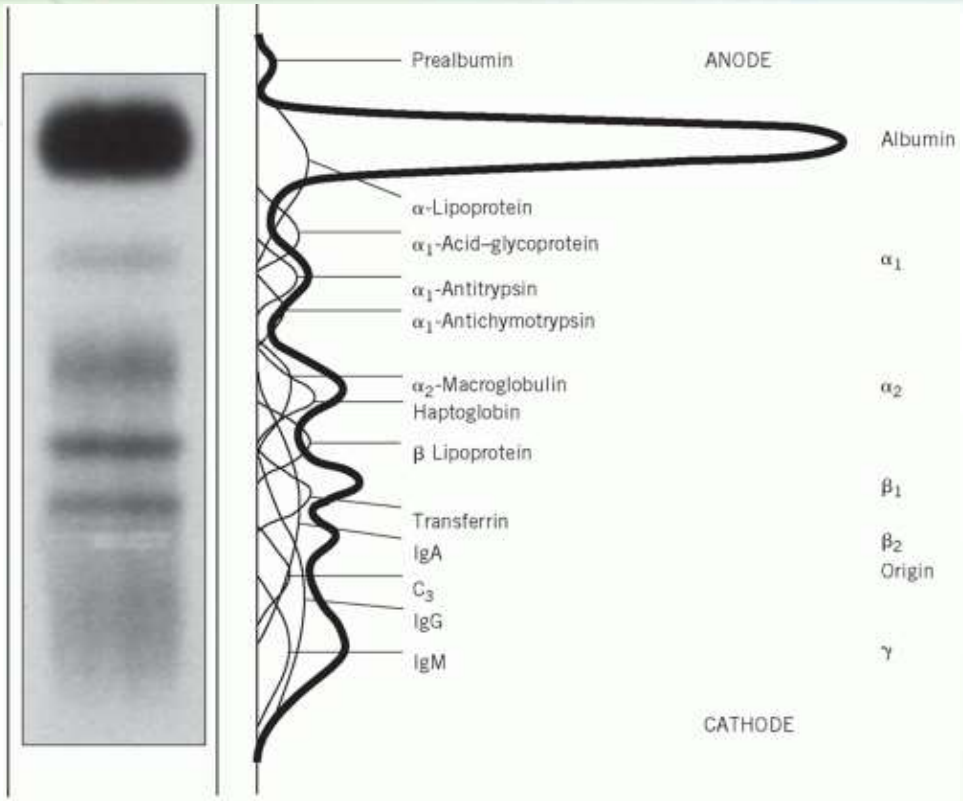
NORMAL VALUES:

Name	Absolute values (g/l)	Relative values (%)	
Albumins	35 – 55	50 – 60	
α1-globulins	2 – 4	4.2 – 7.2	5 %
α2-globulins	5 – 9	6.8 – 12	9 %
β-globulins	6 – 11	9.3 – 15	12 %
γ-globulins	7 – 17	13 – 23	18 %



Electrophoresis of plasma proteins

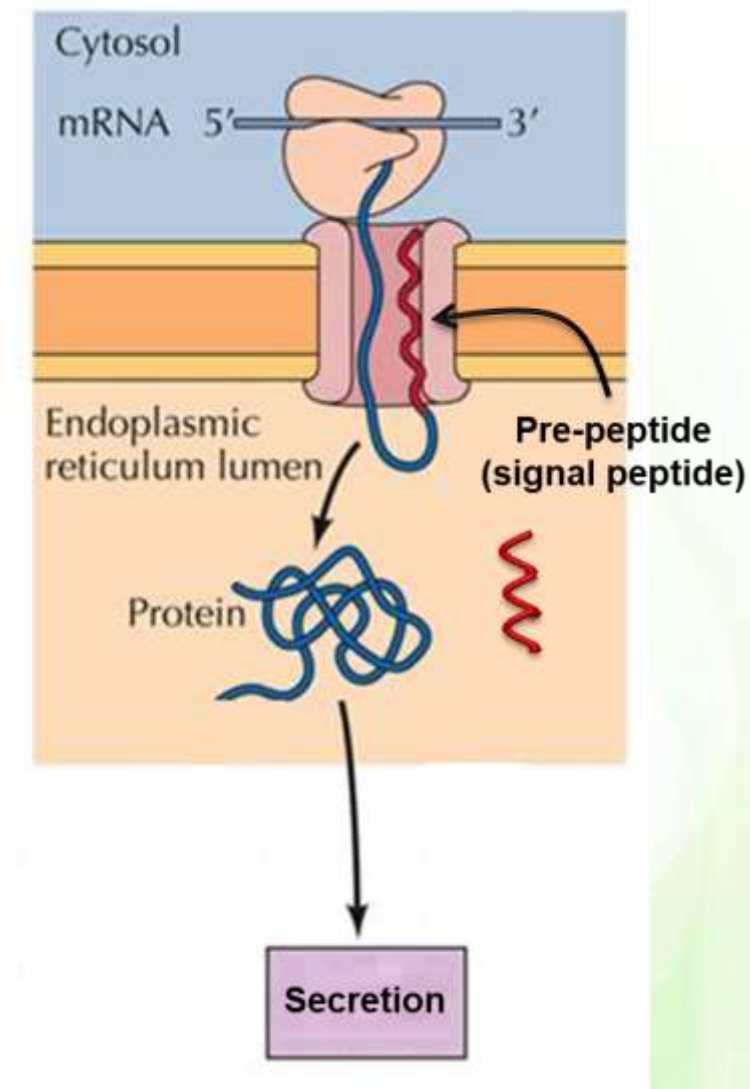
- Albumin is smaller than globulin, and slightly negatively charged
- Globulins (3 bands):
  - α band:
    - α1 region consists mostly of α1-antitrypsin



  - α2 region is mostly haptoglobin, α2-macroglobulin, & ceruloplasmin
- β band: transferrin, LDL, complement system proteins
- γ band: the immunoglobulins

Synthesis of plasma proteins

- Mostly liver (albumin, globulins), γ-globulins (plasma cells; lymph nodes, bone marrow, spleen).
- Most plasma proteins are synthesized as preproteins (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.



Plasma Proteins & genetic variation

(genetic polymorphism)

- The follow a mendelian or monogenic trait.
- They exist in population in at least two phenotypes.
  - The ABO blood groups are the best-known examples
- Electrophoresis or isoelectric focusing is used for analysis.

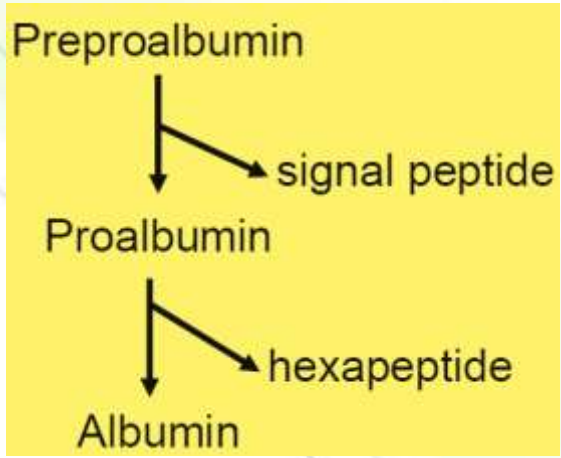
Plasma Proteins Half-Lives

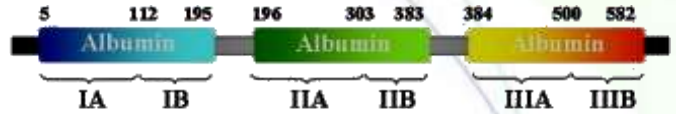
- Albumin & haptoglobin (20 & 5 days, respectively)
- Diseases can affect half-lives
  - In protein-losing gastroenteropathy such as Crohn's disease, albumin may be reduced (1 day).

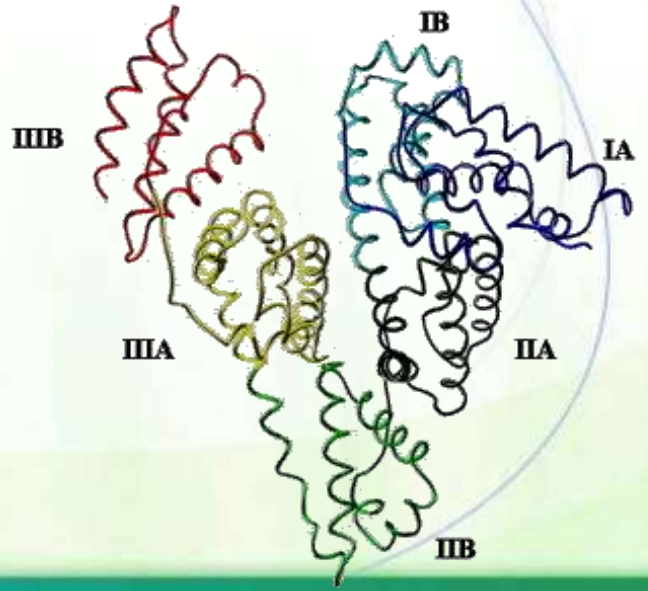
Albumin

- 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)
- 3/5 total plasma proteins (3.4-4.7g/dL)
- Synthesized as a preproprotein
- Monomeric
- Ellipsoidal shape (does not increase viscosity like fibrinogen)

- Anionic at pH 7.4 with 20 negative charges

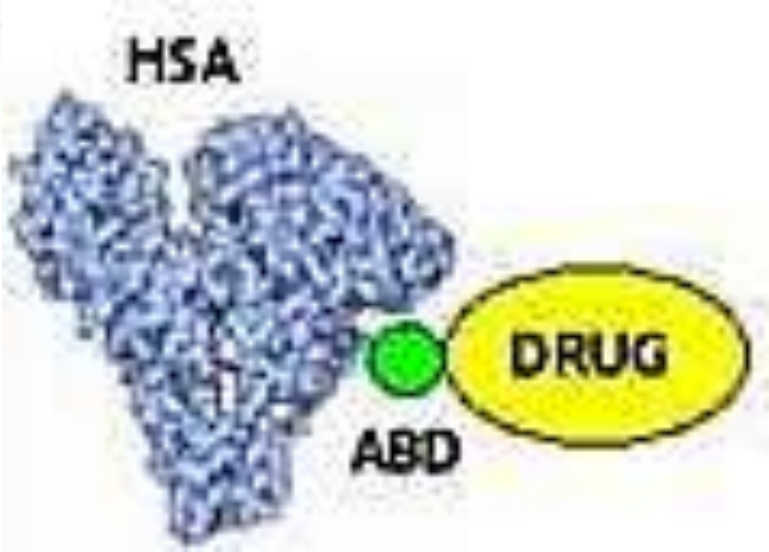






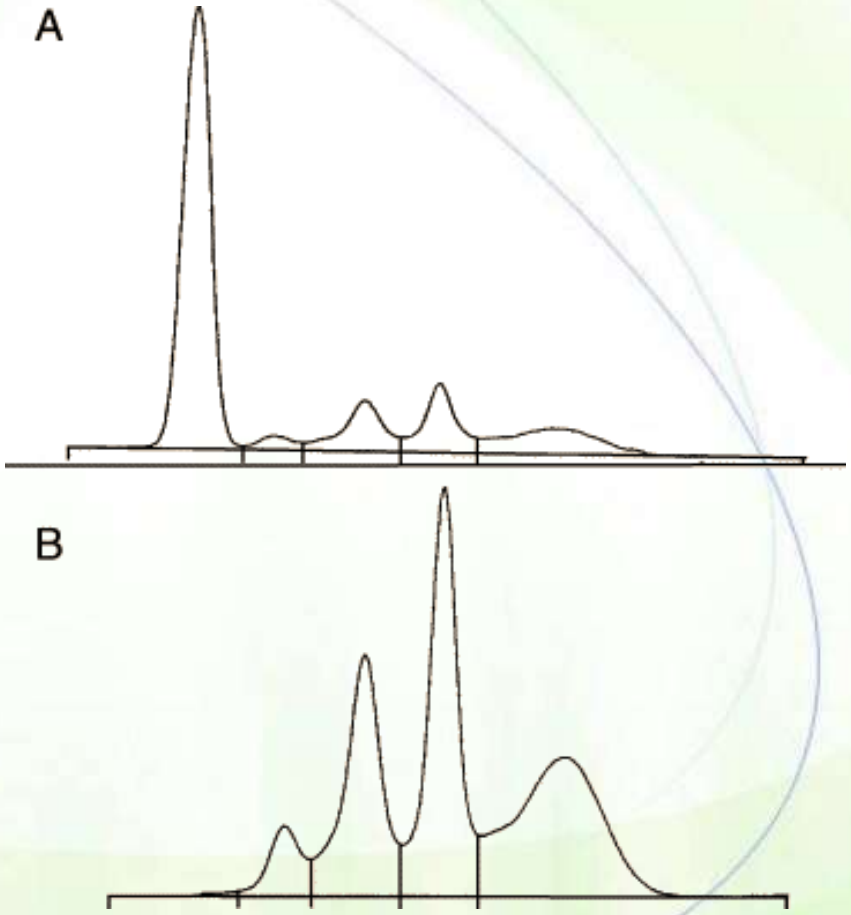
Albumin’s binding capacity

- 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)



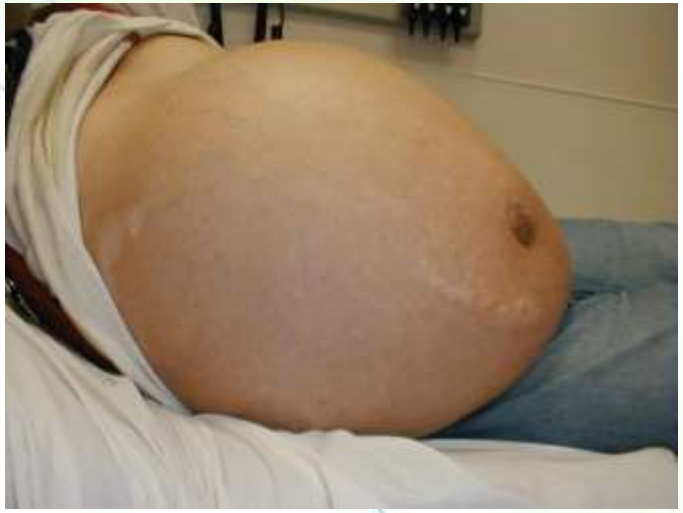
Analbuminemia

- There are human cases of analbuminemia (rare)
- Patients show moderate edema!!!

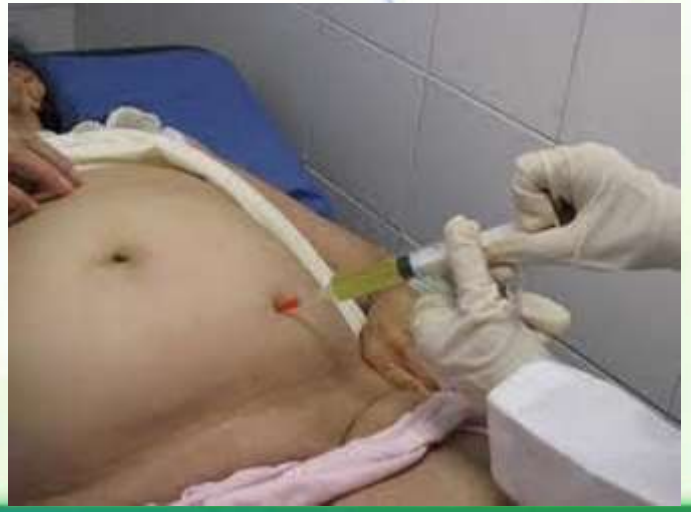


Other clinical disorders

- Hypoalbiminemia: edema seen in conditions where albumin level in blood is less than 2 g/dl
  - Malnutrition (generalized edema)
  - Gastrointestinal loss of proteins

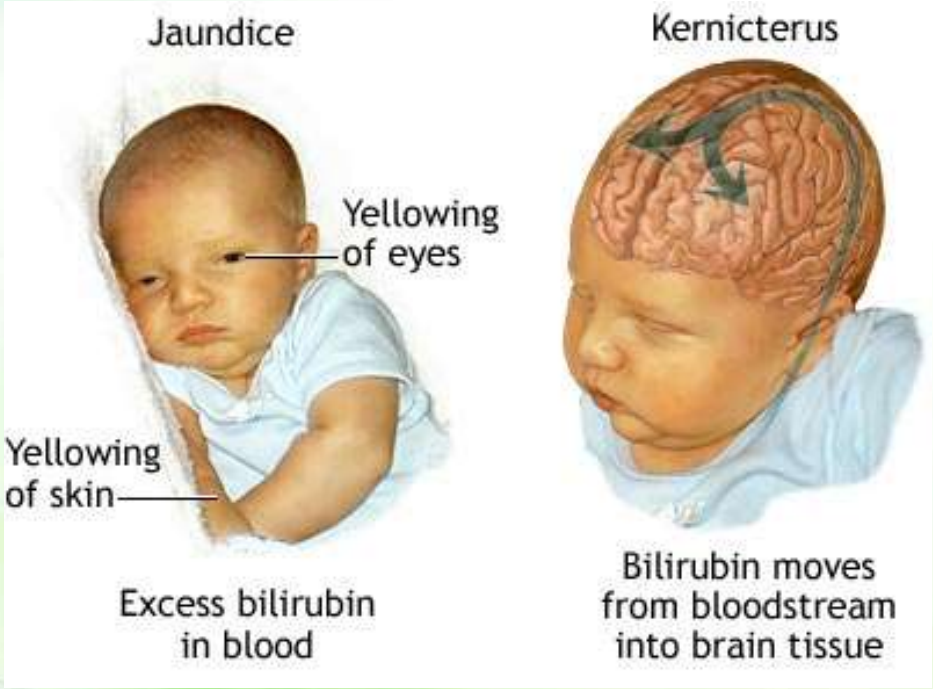


- Hyperalbuminemia: dehydration (relative increase)



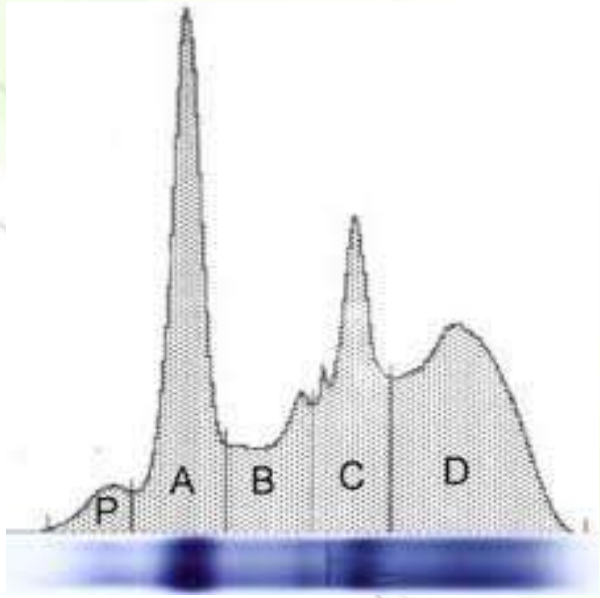
Other clinical disorders

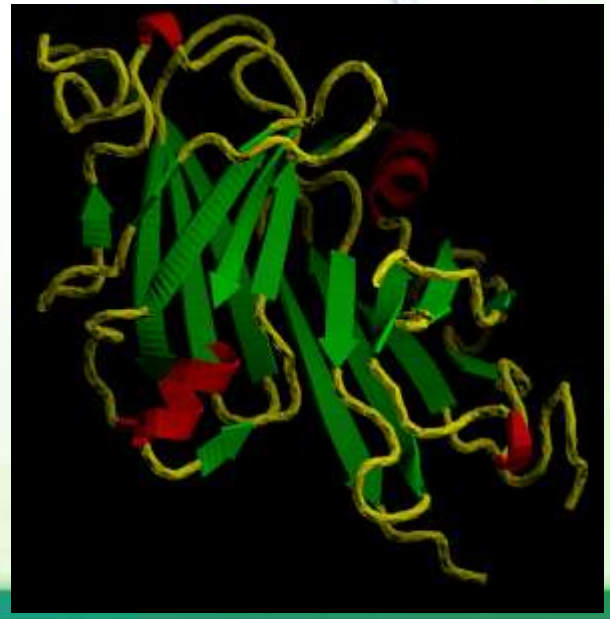
- Drug-drug interaction:
  - Bilirubin toxicity (aspirin is a competitive ligand): kernicterus and mental retardation
  - Phenytoin-dicoumarol interaction (epilepsy vs. anti-coagulant, respectively))



Prealbumin (transthyretin)

- It exists as a 62-kDa glycoprotein.
- It has short half-life (≈2 days).
- It is a sensitive indicator of poor protein nutrition.
- Main function:
  - T4 (Thyroxine) and T3 carrier





Acute-phase proteins

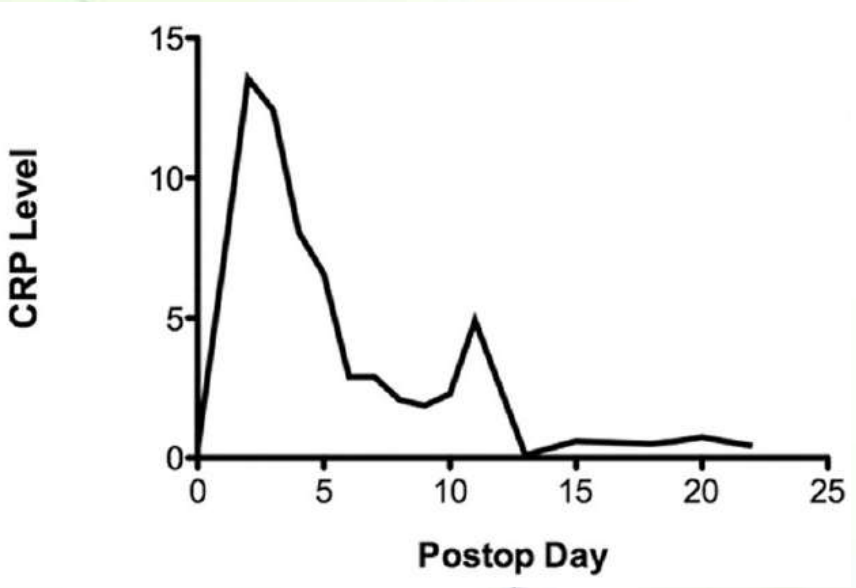
- Plasma proteins whose Levels increase (up to 1000 folds), acute inflammation, tissue damage, chronic inflammation & cancer.
- C-reactive protein (CRP), α1 -antitrypsin, haptoglobin, & fibrinogen
- Interleukin-1 (IL-1) is the main stimulator

Purpose of acute of phase proteins

Protein	Function
C-reactive protein	Stimulates the complement pathway
α1-antitrypsin	neutralizes certain proteases released during acute inflammation
Fibrinogen	Coagulation factor
Transferrin	Iron binding (preventing microbe uptake of iron)
Haptoglobin	Hemoglobin binding (iron protection)
Ceruloplasmin	Iron oxidation (iron binding by ferritin)

C-reactive protein (CRP)

- It is able to bind to a polysaccharide called fraction C in the cell wall of a bacterial species called pneumococci.
- It is undetectable in healthy individuals.
- It helps in the defense against bacteria and foreign substances.
- It is 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).



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

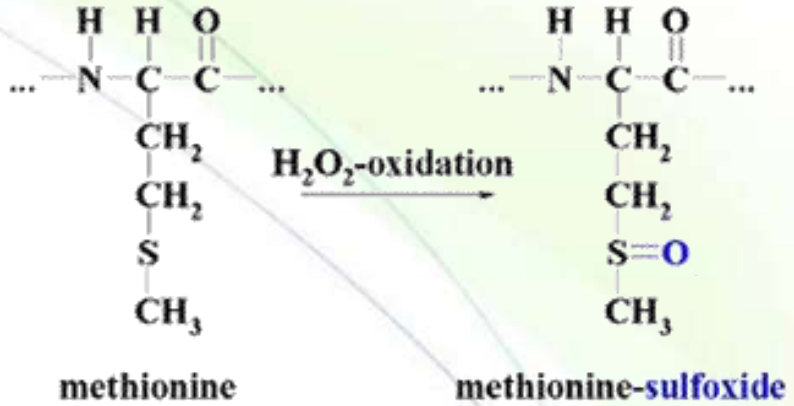
- Also known as (AKA) α1-antiproteinase (52 kDa)
- It neutralizes the trypsin & trypsin-like enzymes (such as elastase).
- 90% of α1- globulin band
- Polymorphic (75)
  - Alleles Pi^M, Pi^S, Pi^Z, Pi^F (MM is the most common)
- Deficiency (genetic): Emphysema is found in people with ZZ or SZ.
  - MS and MZ usually not affected
- It is ncreased level of α1- antitrypsin (acute phase response)

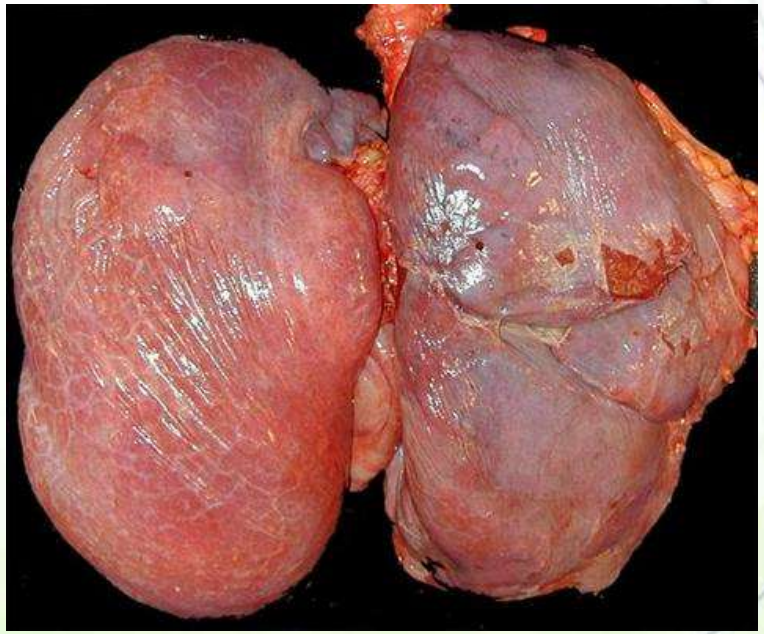
Active elastase + α_1–AT → Inactive elastase: α_1–AT complex → No proteolysis of lung → No tissue damage

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

Smoking & α1- antitrypsin deficiency

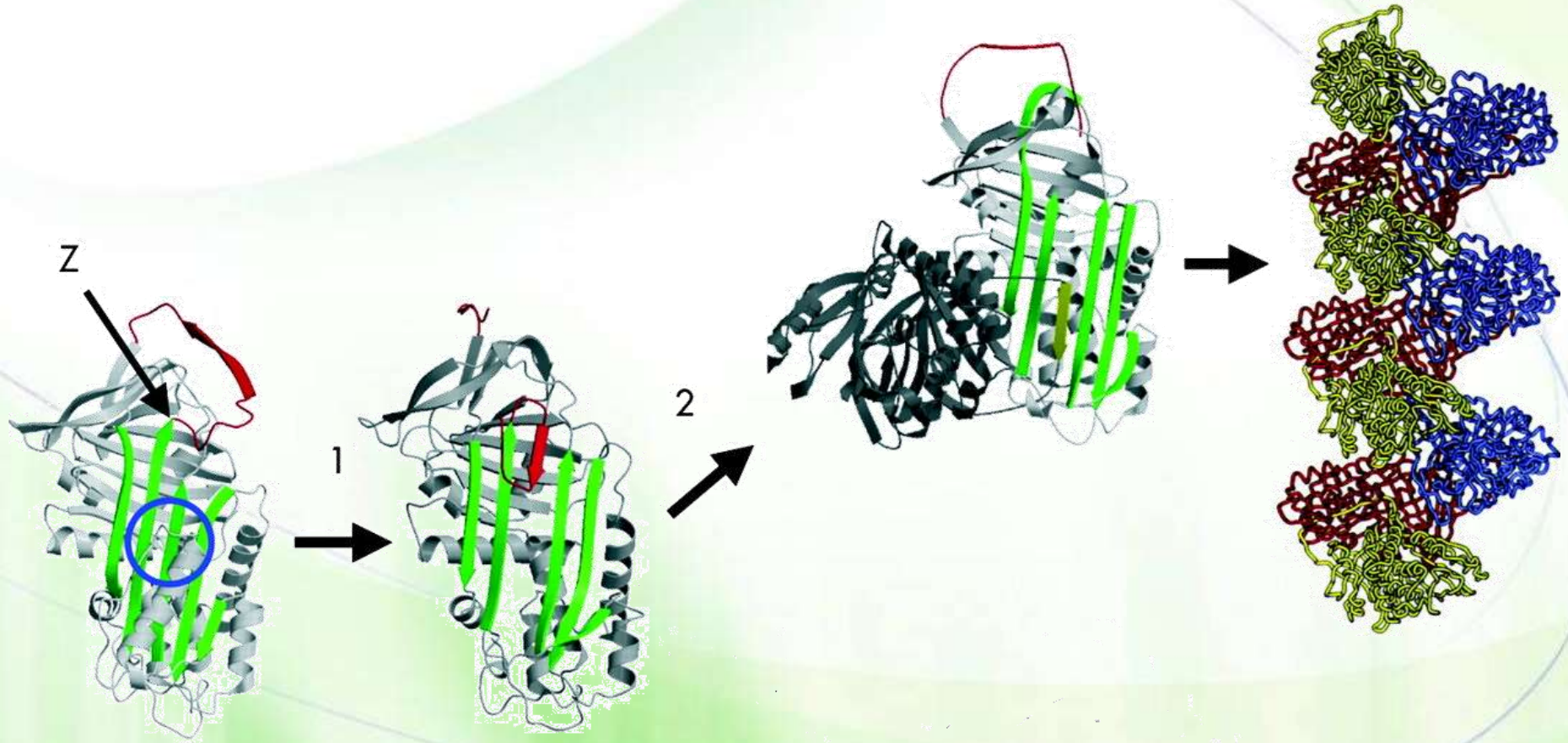
- Chronic inflammation
- Oxidation of Met358
- devastating in patients





Liver disease & α1- antitrypsin deficiency

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



Haptoglobin (Hp)

- It is an acute phase protein.
- α2 glycoprotein (90kDa)
- A tetramer (2α, 2β)
- Two genes, designated Hp1 and Hp23, producing 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

Heme-binding proteins

- Certain other plasma proteins bind heme, but not hemoglobin, such as
  - Hemopexin (β1-globulin), which binds free heme,
  - Albumin, which binds metheme (ferric heme) to form methemalbumin.
    - Methemalbumin subsequently transfers metheme to hemopexin.

Ceruloplasmin

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

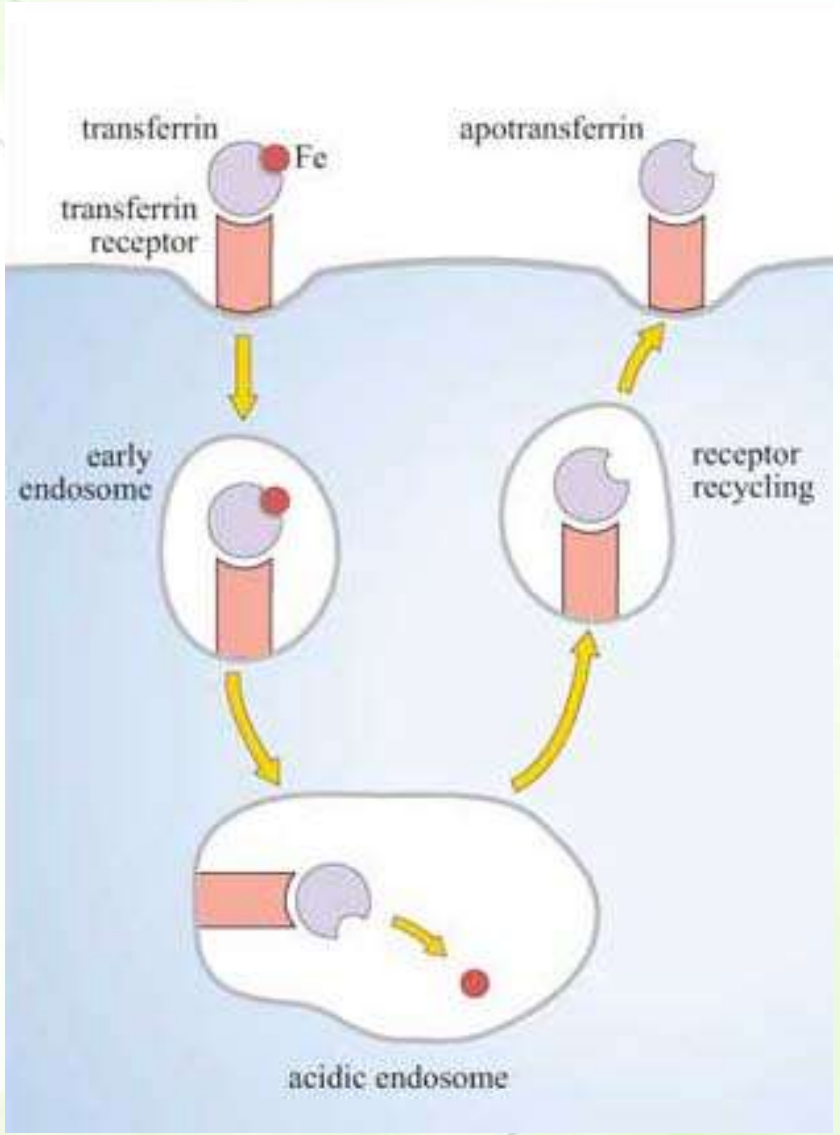
- A copper-containing glycoprotein (160 kDa)
  - It contains 6 atoms of copper
- Metallothioneins (regulate tissue level of Cu)
- It regulates copper level: contains 90% of serum Cu.
- A ferroxidase: oxidizes ferrous to ferric
  - Important for transferrin binding
- Albumin (10%) is more important in transport

Pathological conditions related to ceruloplasmin

- Ceruloplasmin deficiency can arise from genetic causes or lack of dietary copper.
- Hypoceruloplasmenia
  - Ceruloplasmin levels are ~50% of normal
  - No clinical abnormalities
- Aceruloplasminemia
  - No ferroxidase activity of ceruloplasmin
  - If left untreated, accumulation of iron in tissues and organ failure
- Wilson’s disease
  - Defective transporter (copper-binding P-type ATPase or ATP7B protein) leading to excess liver copper, increased apoceruloplasmin, and copper toxicosis.

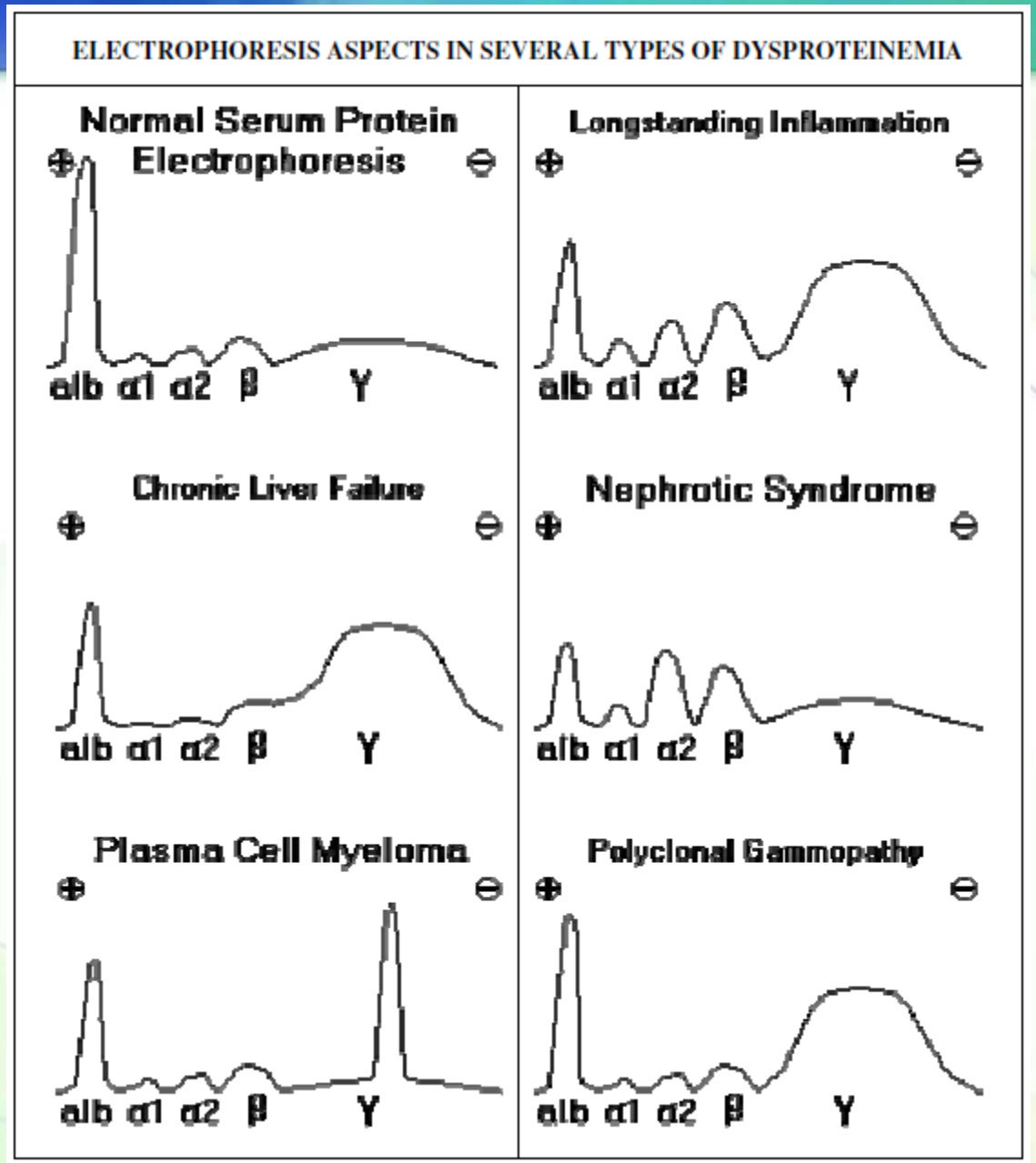
Transferrin

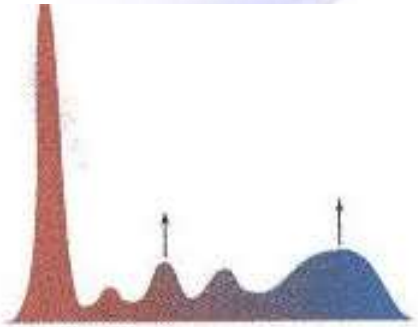
- A β1-globulin that functions as iron transporter
- A glycoprotein synthesized by the liver.



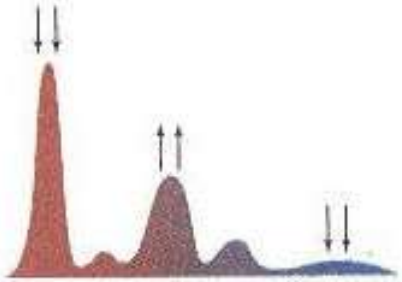
Alpha-2 macroglobulin

- It is a large plasma protein.
- It is responsible for the transport of 10% of zinc and cytokines in blood.
- α2-macroglobulin binds to and inactivates diverse type of proteases.
  - Blood coagulation

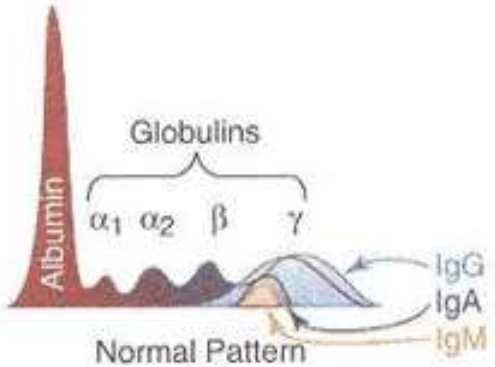

ELECTROPHORESIS ASPECTS IN SEVERAL TYPES OF DYSPROTEINEMIA
Normal Serum Protein Electrophoresis
alb α1 α2 β γ
Longstanding Inflammation
alb α1 α2 β γ
Chronic Liver Failure
alb α1 α2 β γ
Nephrotic Syndrome
alb α1 α2 β γ
Plasma Cell Myeloma
alb α1 α2 β γ
Polyclonal Gammopathy
alb α1 α2 β γ



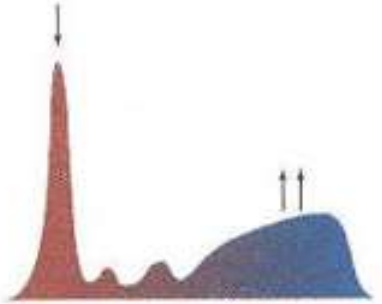
"Delayed Response Pattern"
(c)



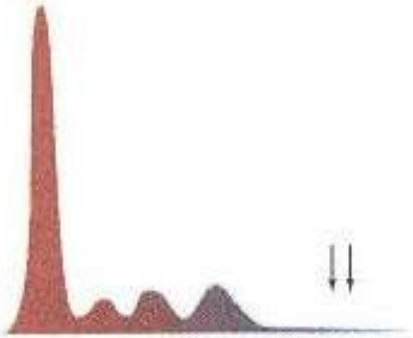
Nephrotic Syndrome
(g)



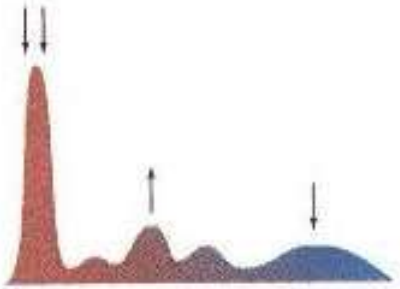
Normal Pattern
(a)



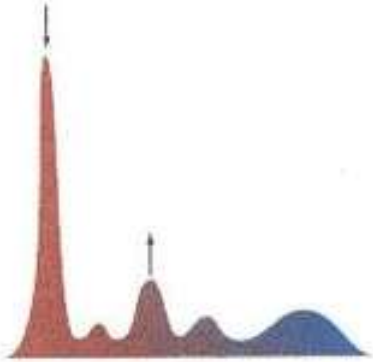
Hepatic Cirrhosis
("Polyclonal Gammopathy")
(e)



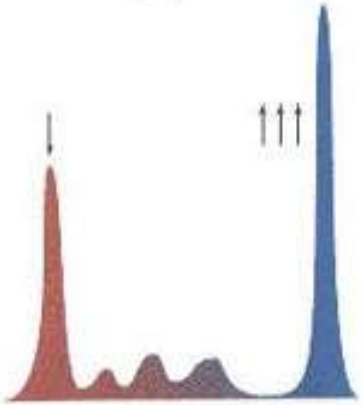
Hypogammaglobulinemia
(d)



Protein-losing Enteropathy
(h)



"Immediate Response Pattern"
(b)



Paraprotein
("Monoclonal Gammopathy")
(f)