بسم الله الرحمن الرحيم

BioChemistry | FINAL 7

Plasma Proteins pt.2

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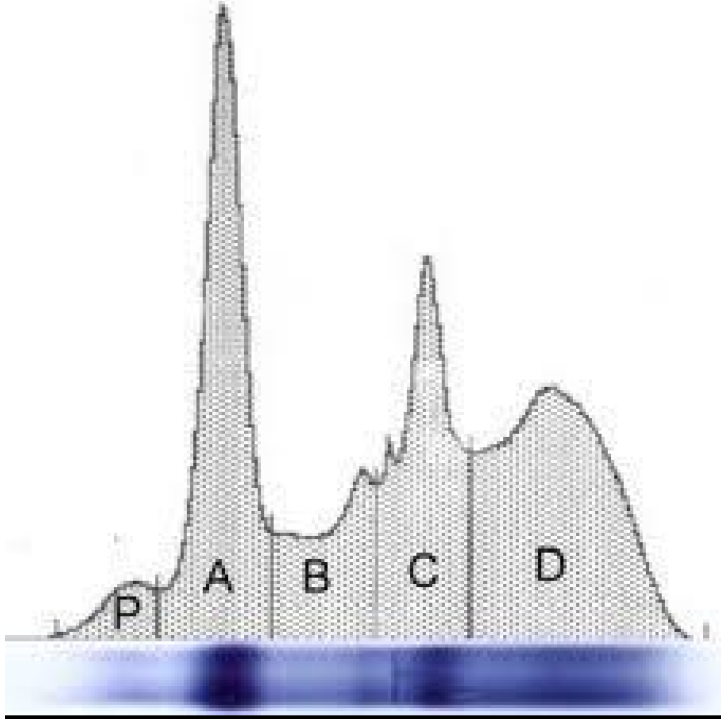
PREALBUMIN (TRANSTHYRETIN)

- 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

- Globulins are divided into many classes :

✓ 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 γ -globulins will be explained in he next Lectures.

We are going to study the globulins colored with red

α1- ANTITRYPSIN

- α1-Antiproteinase (52 kDa).
  -Antiproteinase and Antitrypsin are synonyms to each other.
  -Antiproteinases are globulins that antagonise the action of proteinases (enzymes that broke up proteins into small sequence of amino acids).
- Neutralizes trypsin & trypsin-like enzymes (<u>elastase</u> :breaks up elastin).
- It constitute 90% of α1- globulin band.
- Many polymorphic forms (at least 75).
- Its expressed at the gene with Alleles **Pi^M, Pi^S, Pi^Z, Pi^F** any copy(allele other than M is less functional than it) ,MM is the most common, M is the most functional copy).
- Deficiency (genetic): emphysema (ZZ, SZ). MS, MZ usually not affected (there should at least be one M copy to be normally functional).

α1- ANTITRYPSIN

- Increased level of α1- antitrypsin (acute phase response --> increases in cases of acute inflammation, chronic inflammation, cancer, truma).
- Inflammation --> increases antitrypsin --> increases the antagonist of elastase --> stopping the damages that occur to normall tissues (elastic).
- If antitrypsin is modified (polymorphic) it will less active --> increases elastase's activity --> normal tissue will be damaged more.

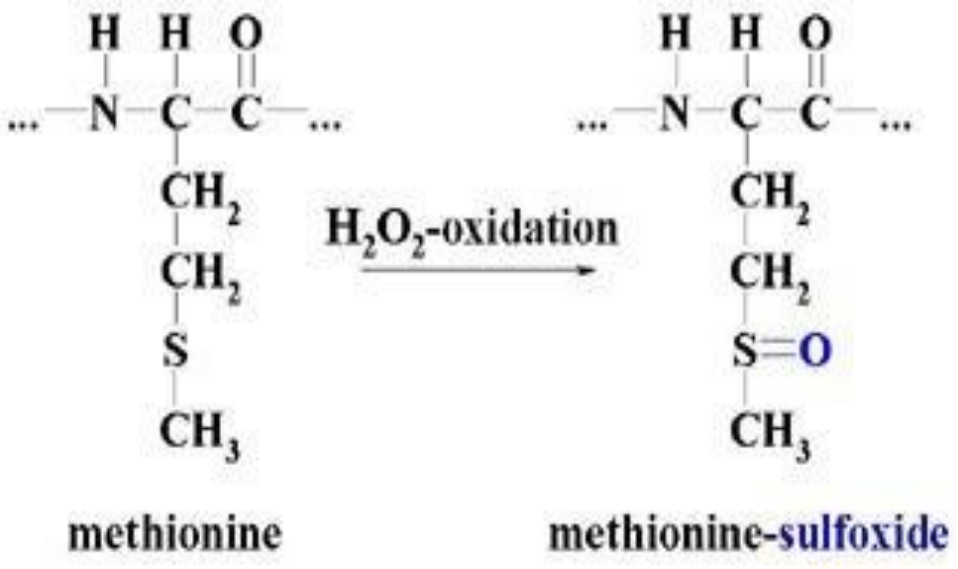
Active elastase + α_1–AT → Inactive elastase: α_1–AT complex → No proteolysis of lung → No tissue damage

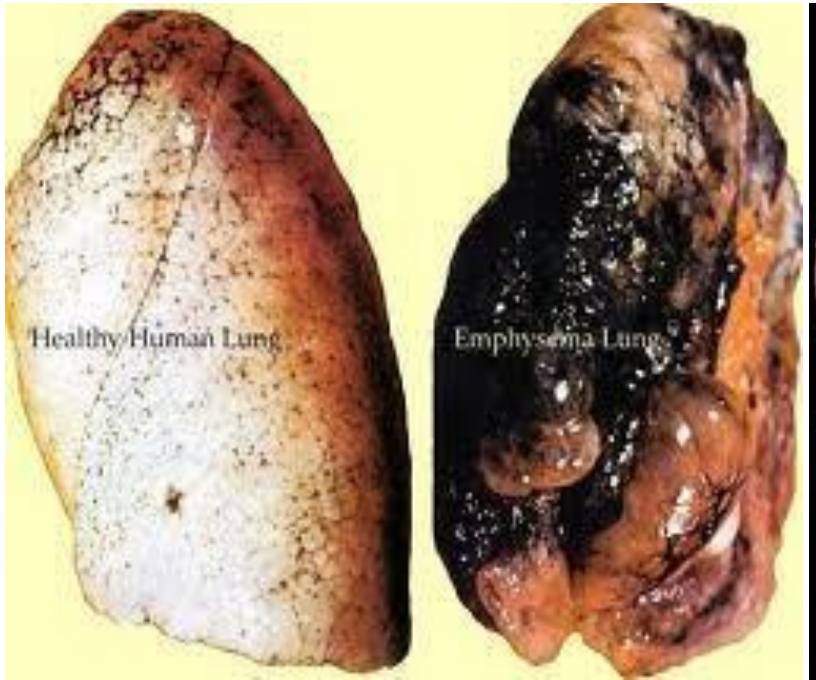
Active elastase + ↓ or no α_1–AT → Active elastase → Proteolysis of lung → Tissue damage

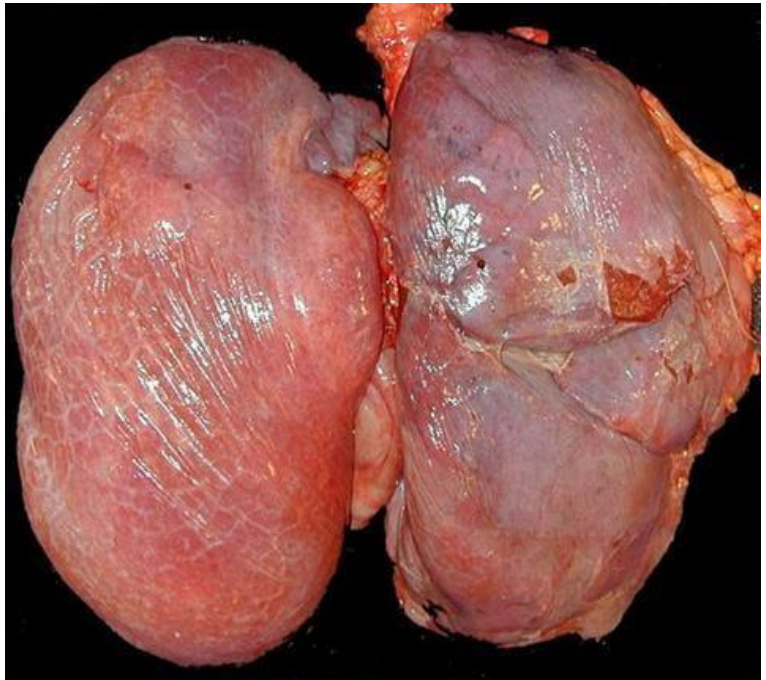
SMOKING & α1- ANTITRYPSIN DEFICIENCY

- Chronic inflammation (neutrophil elastase) → Inflammation effect has been explained in previous slides.
- Oxidation of Met^{358}
- Devastating in patients with PiZZ

→ Explained in the next 2 slides.







SMOKING & α1- ANTITRYPSIN DEFICIENCY

- The tissue is composed of a **alveoli** to **increase the surface area for gas exchange.**
- Alveoli are made of elastic fibers which alow them to **streach** and **expand** to **hold more air,** but these **elastic walls** are **occupying space** so, when they are damged and degarded more **we will have more space which means lungs can hold more air**, but the beneficial effect that we get from gas exchange through elastin wall is much higher than getting more space which was occupied by alveoli walls.

- When alveoli walls is broken (by elastase --> caused by deficiency in **α1-antitrypsin**) leading for more air inside the lungs which will cause barrel chest (انتفاخ الصدر) but also less area for gas exchange. ---> this case is called Emphysema.
- Emphysema is characterized by **more air inside the lungs** and **less area for gas exchange.**
- **People who had a genetic deficiency in α1-antitrypsin will have higher chance to suffer from emphysema.**

SMOKING & α1- ANTITRYPSIN DEFICIENCY

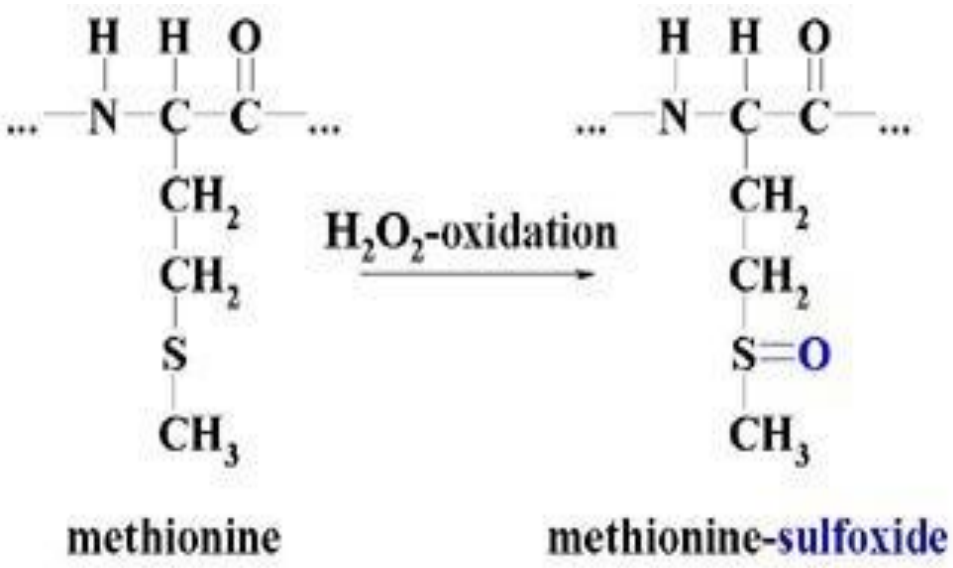
- Chronic inflammation (neutrophil elastase)
- Oxidation of Met^{358} (Caused by smoking material)

– Methionine is non-polar but it can be oxidized (becomes methionine sulfoxide which is polar).

– Methionine (358) Is very important for the binding of antitrypsin with proteinases, as a result oxidizing it will affect this binding, increasing the effect of elastase and increasing the possibility of having emphysema (or increase its effect).

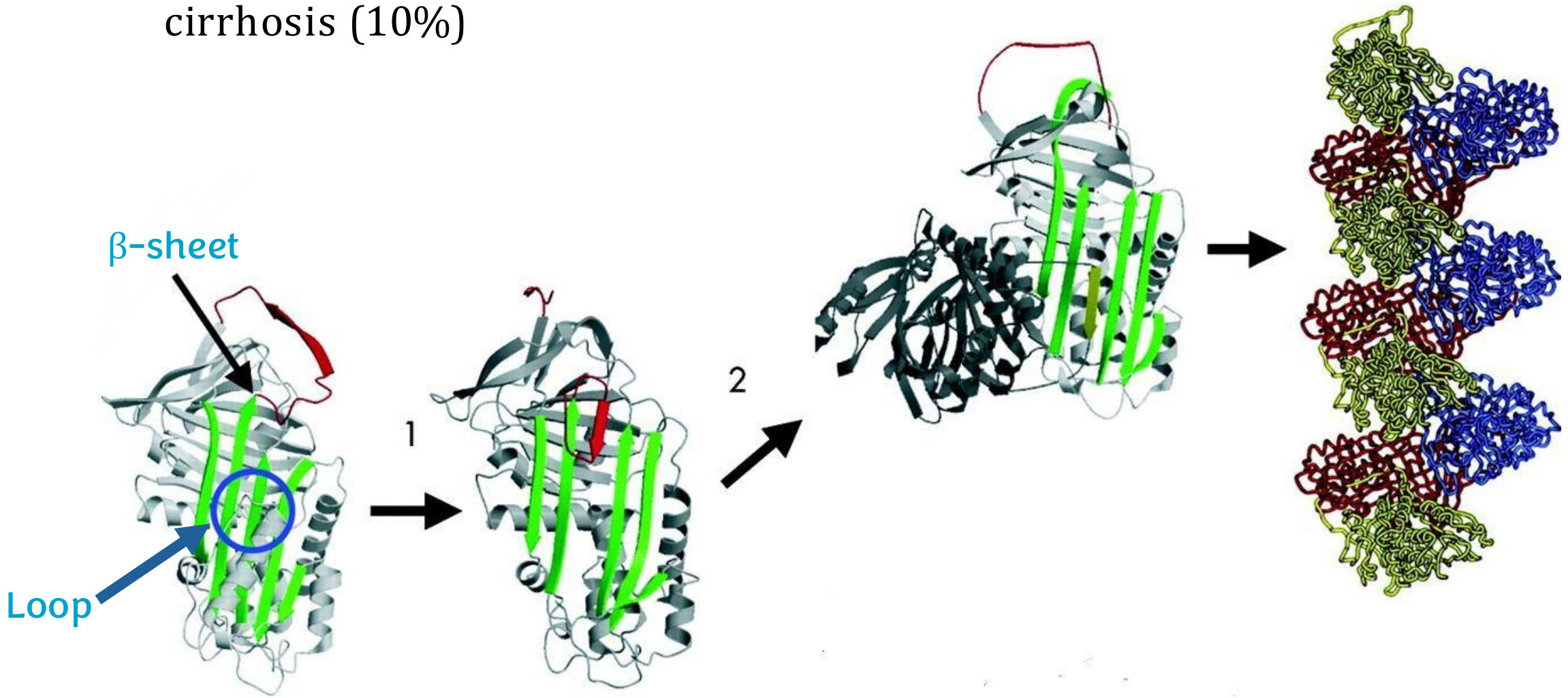
- Devastating in patients with PiZZ

– PiZZ is the least functional antitrypsin, in this case Smoking effect will be devastating leading to much advanced emphysema.



LIVER DISEASE & α1- ANTITRYPSIN DEFICIENCY

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

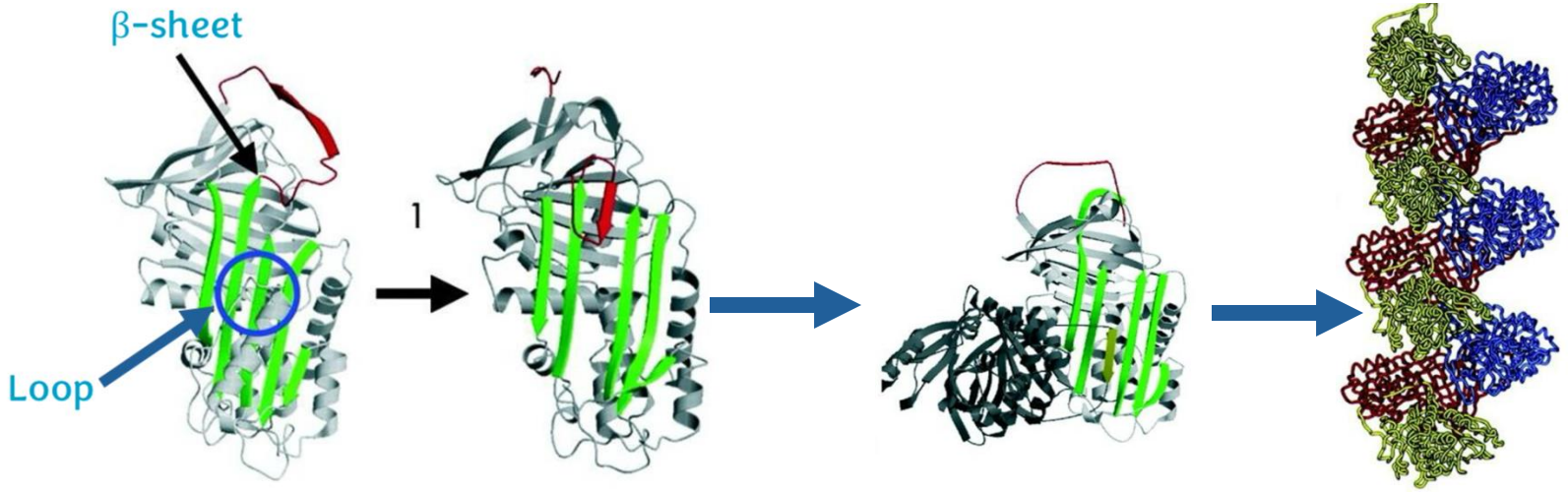


LIVER DISEASE & α1- ANTITRYPSIN DEFICIENCY

- Antitrypsin like other plasma proteins (except for Immunoglobulins) are produced in the liver, so it may affect the liver.

- In ZZ phenotype (less functional type of antitrypsin) there will be a modification in the tertiary structure by having a loop and β-sheet.

- The β-sheet and the loop have high affinity towards each other, which will cause either binding of β-sheet to the loop (not energetically favourable), or binding between β-sheet of antitrypsin and loop of other antitrypsin and this will form aggregation s of antitrypsin.



aggregations of antitrypsin.

α1- FETOPROTEIN

- Synthesized primarily by the **fetal yolk sac** and then by **liver parenchymal cells** in fetus.
- Very low levels in adult (Undetectable in normal situations).
- Functions of α1-fetoprotein:

➢ **Protect** the fetus from **immunolytic attacks.**

➢ **Modulates** the **growth** of the fetus.

➢ Transport compounds e.g. steroids.

➢ **Low** level: could increase the risk of having Down's syndrome.

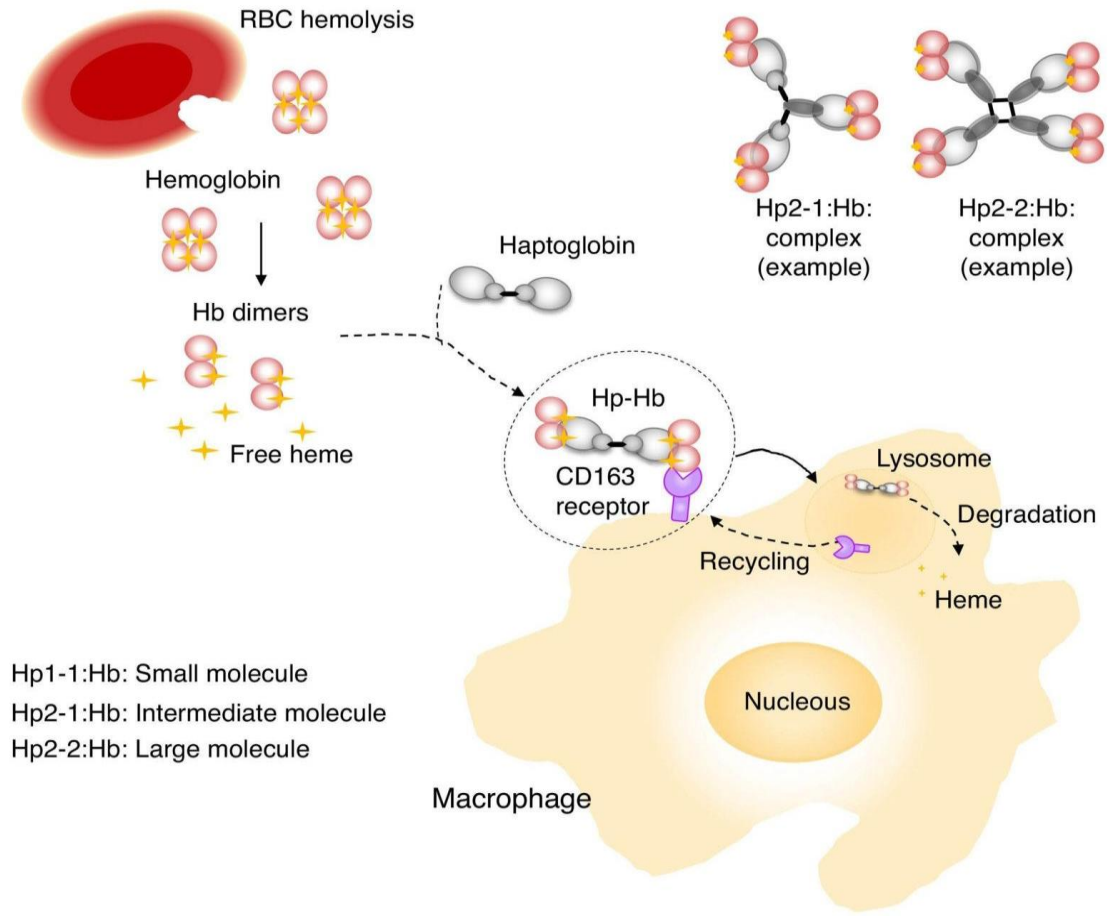
➢ Level of α1-fetoprotein **increases** in:

1)Fetus and pregnant women **Normally** (The only plasma globulin that it's expression can be increased normally).

2)Hepatoma & acute hepatitis Cancer, acute phase inflammation (increase number of cell).

HAPTOGLOBIN (HP)

- It is an **acute phase reactant protein**
- α2 glycoprotein (90kDa)
- A tetramer (2α, 2β) Composed of 4 subunits.
- 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.



- **Heptaglobin** function is to bind to free **hemoglobin** but, hemoglobin is present inside RBCs and Heptaglobin is at the plasma, **how can you explain that?**

Answer -> **RBCs** are being **degraded** all the time which results in having **hemoglobin** in the **plasma**, **Heptaglobin binds** them **preventing their loss into urine** (the important is not at preventing hemoglobin loss, it is at preventing the loss of iron bound to it since iron is essential while hemoglobin can be reformed).

HAPTOGLOBIN (HP)

Hb= hemoglobin
Hp= heptaglobin

- Hb-Hp complex has shorter half-life (90 min) than that of Hp (5 days).
  - Hemoglobin molecular weight is 65 KDa.
  - Heptaglobin molecular weight is 90 KDa.

  - When Heptaglobin bind to hemoglobin it results in a complex with molecular weight equals 155 KDa, and this molecule is to large to be filtered out (excreted) by the kidneys, and as a result of all of that :

  - ✓ Having iron bounded to hemoglobin back.
  - ✓ The degradation of this complex will be very fast to catch the iron since the half life of this complex is (90 minutes).

  - ❖ **The higher the half life the higher the chance of losing what you are looking for (iron bound to Hp in this case).**

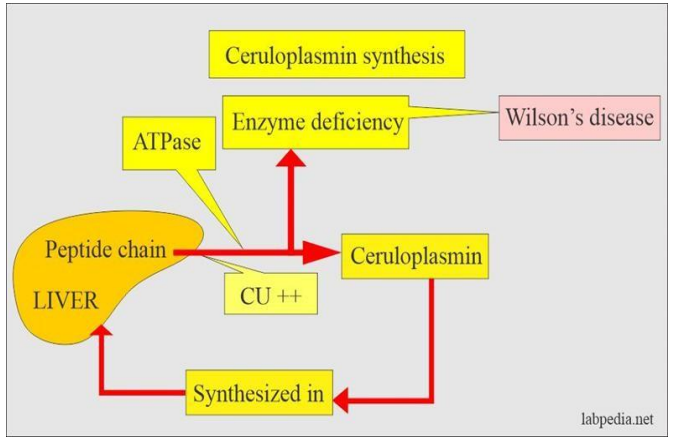
- Decreased level in hemolytic anemia A pathological condition of RBCs degradation which will result in more binding of Hb and Hp and decrease in Hb since it is bounded to Hp.

Cu-containing enzymes

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

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)



CERULOPLASMIN

Ceruloplasmin it's a Copper containing glycoprotein with 160 kilo dalton in molecular weight, This protein has **six** copper binding sites very high affinity for them.

- if you have a protein with very high affinity for something, Do you think its function in transport?

No, it can transfer but this is not the main function, so the main function of ceruloplasmine is to store copper inside the plasma and its with reversible and equilibrium with three copper inside the plasma .

- Whatever that copper inside the plasma get decreasing in its concentration the ceruloplasmine can get free some of its copper to the plasma to keep copper level normal, which is responsible for regulating on copper levels .

The other protein which can regulate copper levels inside tissue called Metallothioneines

What transfer copper to the tissue? Is it ceruloplasmine?

No , copper get bound to albumin , so albumin transfer 10% of copper to the tissue .While 90% is retained with ceruloplasmine proteine.

Do we need copper in our bodies?

Yes, copper is essential for the human body for several reasons:

Copper is a key component in important enzymes such as:

Amine oxidas

Superoxide dismutase (antioxidant enzyme)

Tyrosinase

Cytochrome C oxidase

➢Why is cytochrome c oxidase important?

It's part of the electron transport chain in cells

It takes oxygen from hemoglobin

It converts oxygen to water in the final step of cellular respiration

Without copper, this enzyme cannot function

Therefore energy (ATP) production in the body would be severely impaired

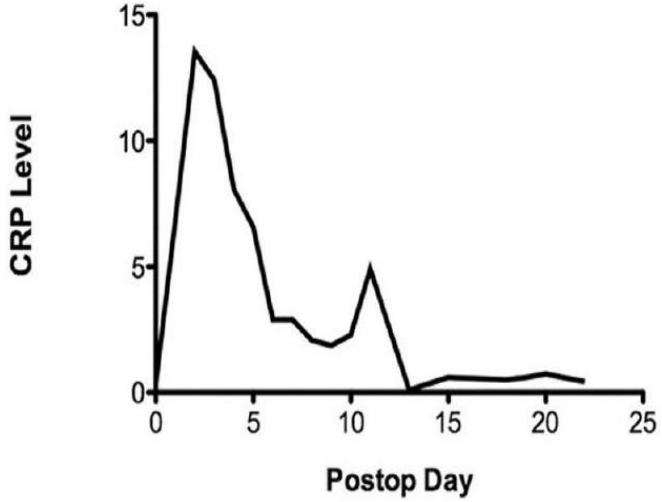
CERULOPLASMIN

- ceruloplasmine function like **ferroxidase** it oxidizes ferrou to ferric and you need iron to be in the oxidized form so you can transfer because the protein which called transferrin it bind the oxidised iron.
- Ceruloplasmine it's level get decreased in liver disease like(fibrosis and roses)or any thing affect liver cells because it produced from liver.

- Also the ceruloplasmine it affected by autosomal recessive genetic disease which called Wilson's disease , the ability to bind copper from ceruloplasmine protein affected so either the ceruloplasmine protein level in blood is less or normal but the activity in binding copper is less so will have much more free copper inside blood , For example have a lot of copper inside eyes to filter your tissue including eyes.
- One of the diagnostic Marked of Wilson's disease ls REM Which your skin looks like golden/copper..

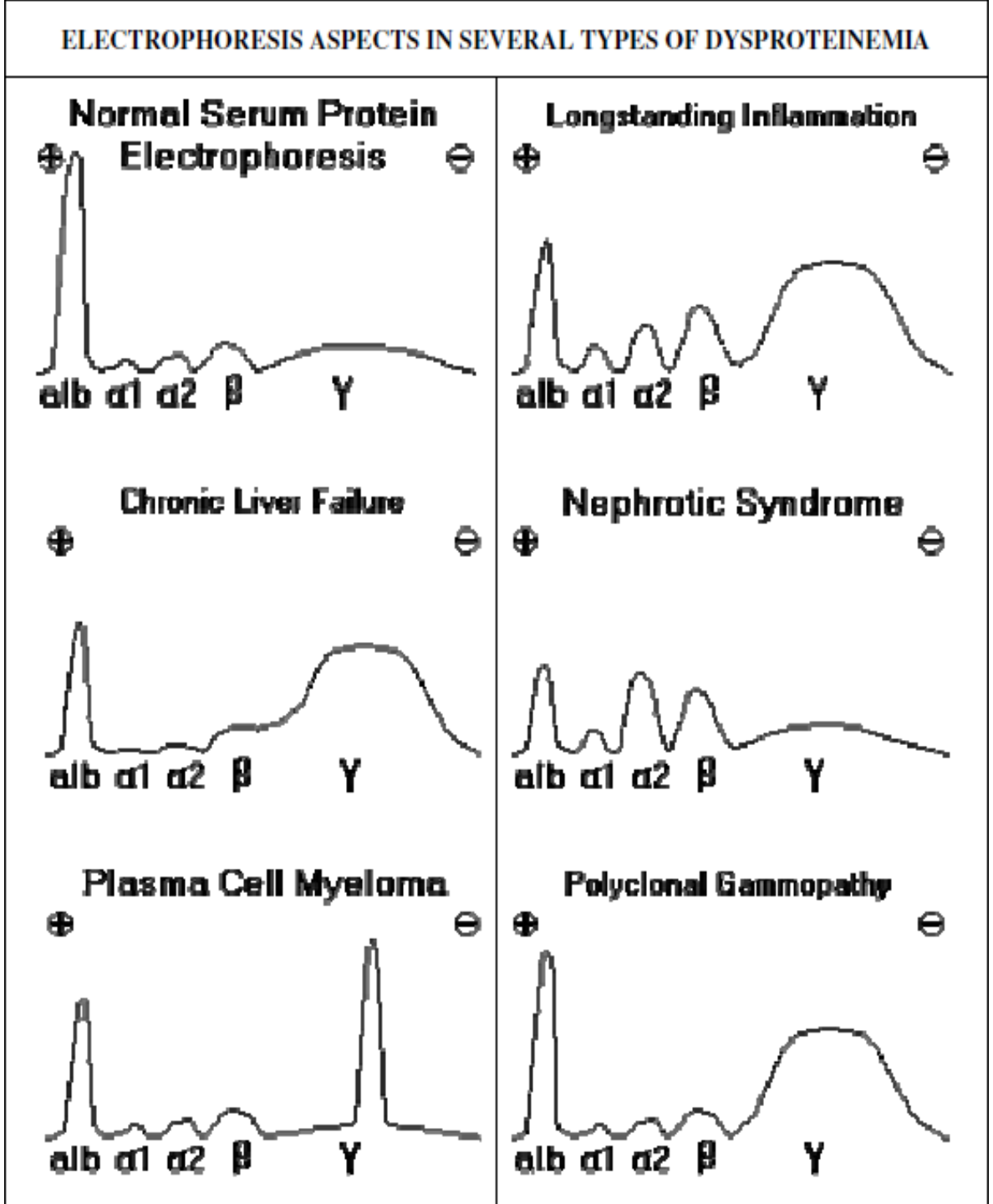
C- REACTIVE PROTEIN (CRP)

- A **homo-pentameric** acute-phase inflammatory protein it's a daily practice for the physicians inside the hospital, tell you there is a problem in patients but not specific, you should be aware when test for that protein and what to test for it.
- **Why it name in that way?**
- Able to bind to a polysaccharide (fraction C) in the cell wall of pneumococci bacteria
- Help in the defense against bacteria and foreign substances
- Undetectable in healthy individuals, detectable or very low levels should below 5 it's level but when any problem happen with patient it will gets high in its concentration for example after surgery or injuries (can't let patient go out of hospital)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

Many diseases can be expressed by electrophoresis



acute phase protein raised in its concentration, that why alpha ½ and beta and gamma become high

albumin +alpha1+alpha2+beta become synthesis in liver, so here liver failed won't get synthesize good protein **all** them will get decrease in concentration with **exception** the gamma globulin because not synthesis in liver

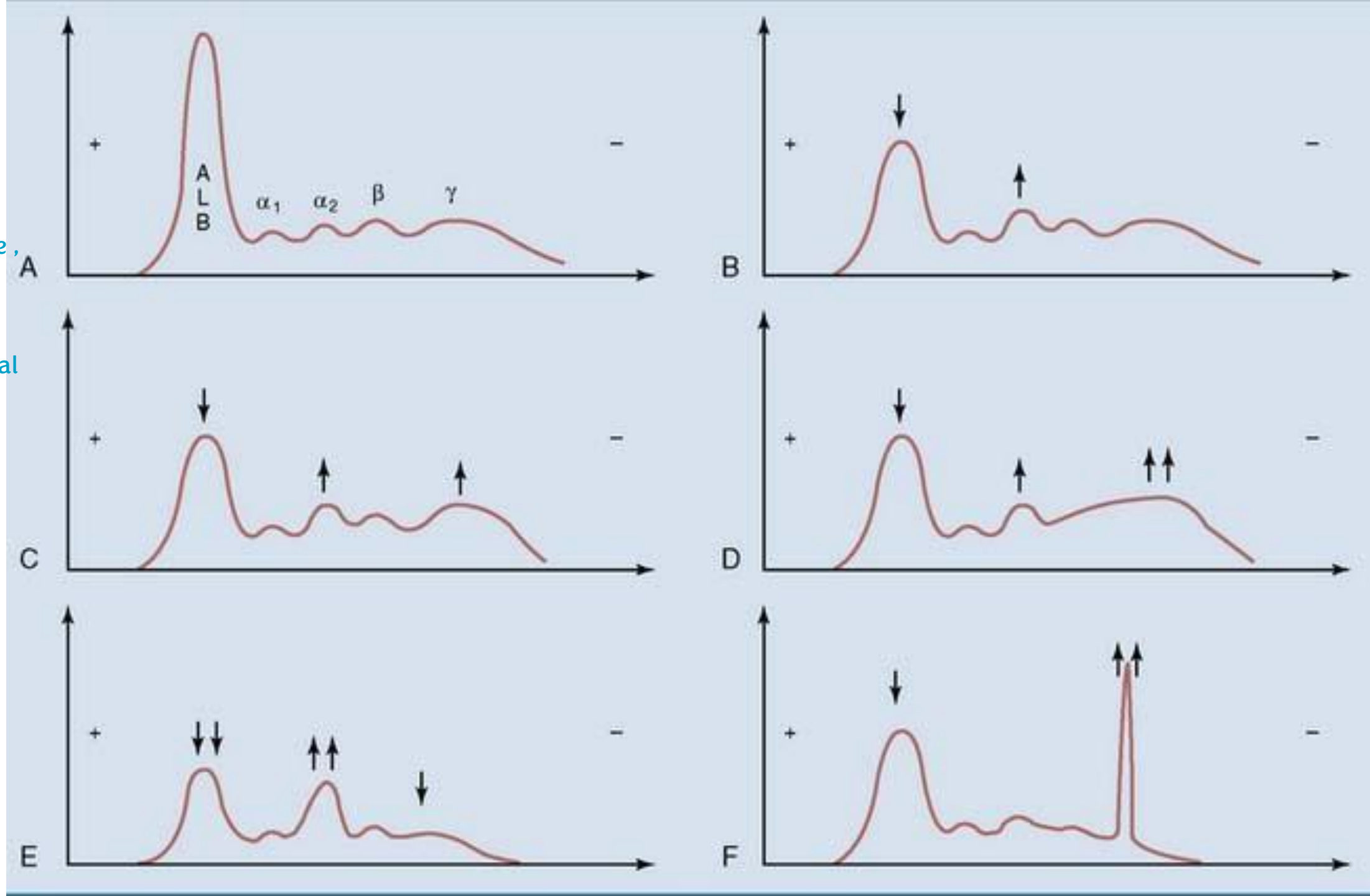
Renal failure kidneys(non functional)won't filter well so **all proteins** will appear inside urine so **all them get decrease in its concentration**

Cancer affecting the gamma globulins (will have very high **sharp peak**)affecting plasma cell can that produces antibodies , this represents where a single plasma cell producing one type of antibody

Also cancer affect on Gamma become high and **wide** because it affect more than one type of plasma cell so more than one antibodies get increasing in its concentration

DISEASES

Be discussed in the previous slide , you should focusing on how to differentiate them as in general



For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	Slide 3; 2nd note Slide 14; right upper corner	Proteinases are globulins that antagonise the action of proteinases Hp= hemoglobin Hb= heptaglobin	Antiproteinases are globulins that antagonise the action of proteinases Hb= hemoglobin Hp= heptaglobin
V1 → V2			

رسالة من الفريق العلمي:

نِعَالُهُم عَلى العِدَى مُسْتَعلِيَة

قِسِ المسافاتِ وقُلْ لي كَمْ هِيَهْ

وَكَم عَلَتْ عَلَى الخَبِيثِ نَعلِيَهْ

يُعْجِبُنِي إِذْ يَرْفَعُ الدِّرْعَ لِيَهْ

وَيَنْحَنِي بِرَأْسِهِ كي يَحمِيَهْ

ذِي وَحْدَهَا قَصِيدَةٌ مُسْتَوْفِيَةْ

أُنْظُرْ إِلَيَّ وَانْظُرَنْ عَدُوِّيَهْ

مَن بَينَنَا هَامَتُهُ مُنْحَنِيَةْ