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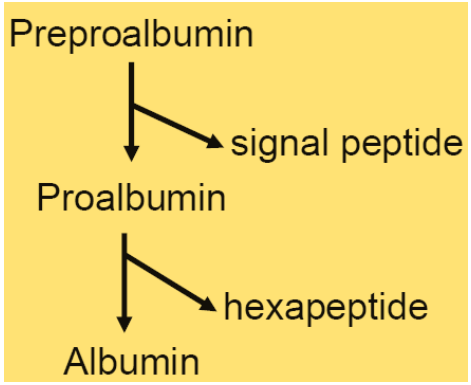
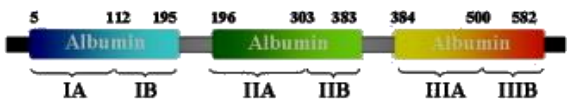
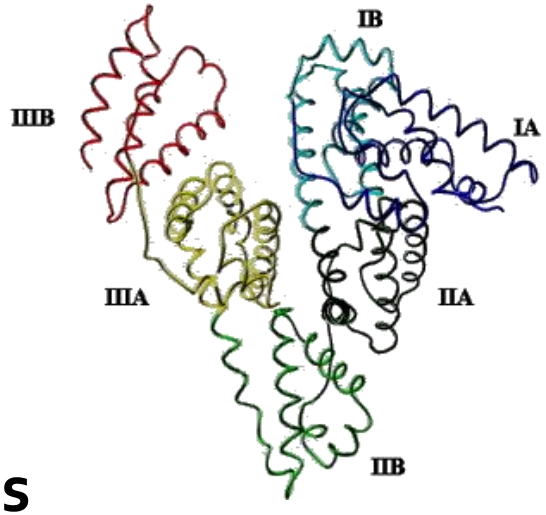
Plasma Proteins

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

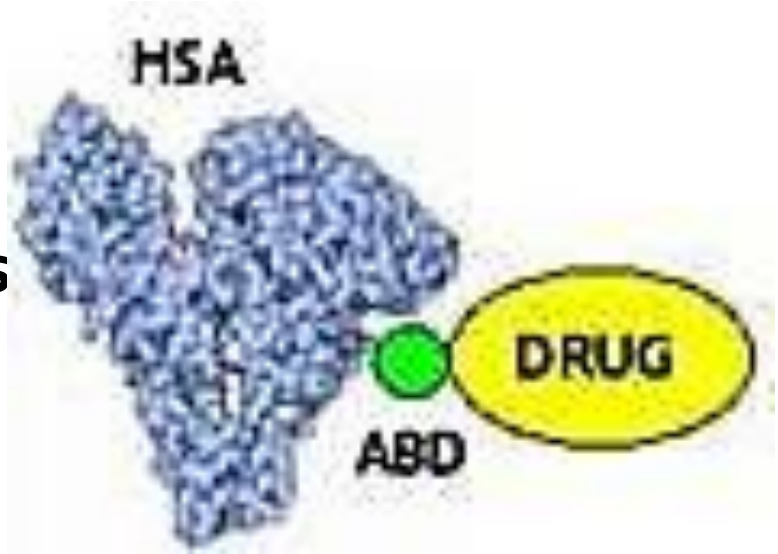






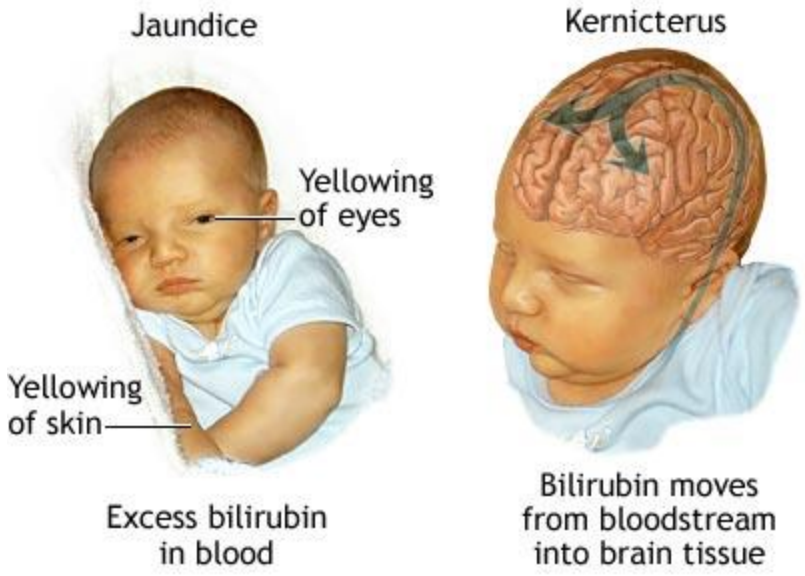
Albumin binding capacity

- **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)**



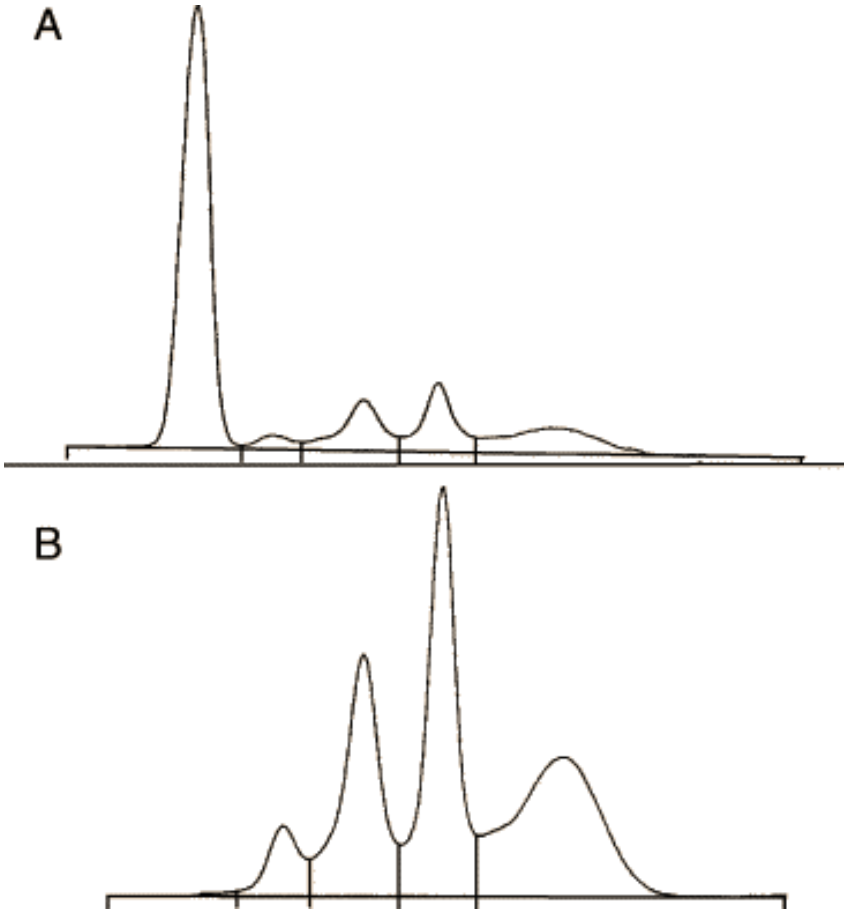
Drug-Drug Interactions

- **Drug-drug interaction:**
  - ✓ **Bilirubin toxicity (aspirin is a competitive ligand): kernicterus and mental retardation**
  - ✓ **Phenytoin-dicoumarol interaction**



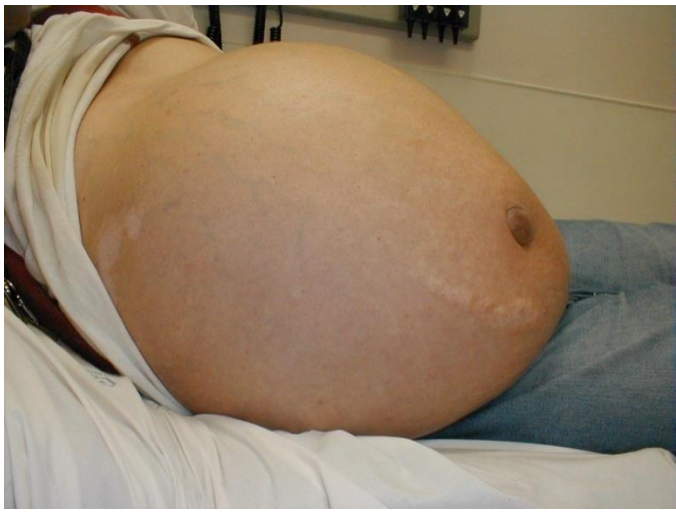
Analbuminemia

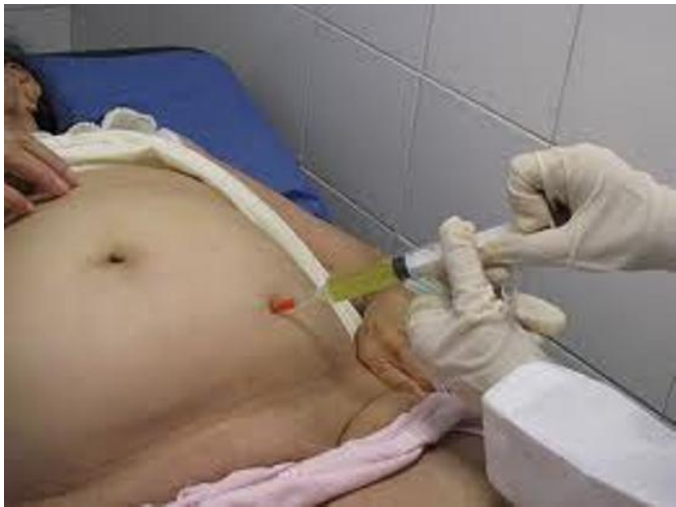
- There are human cases of analbuminemia (rare)
- Autosomal recessive inheritance
- One of the causes: a mutation that affects splicing
- Patients show moderate edema!!!



Other clinical disorders

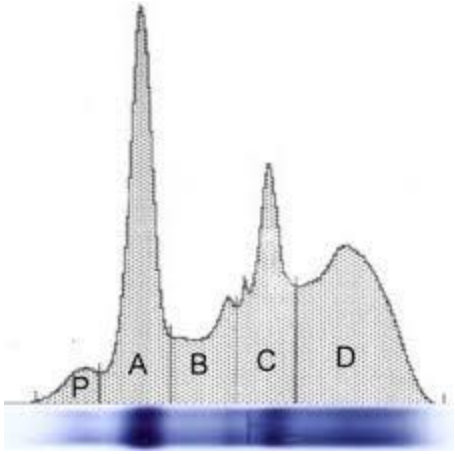
- Hypoalbiminemia: edema seen in conditions where albumin level in blood is less than 2 g/dl
  - ✓Malnutrition (generalised edema)
  - ✓Nephrotic syndrome
  - ✓Cirrhosis (mainly ascites)
  - ✓Gastrointestinal loss
- Hyperalbuminemia: dehydration (relative increase)





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:
  - ✓ T_4 (Thyroxine) and T_3 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

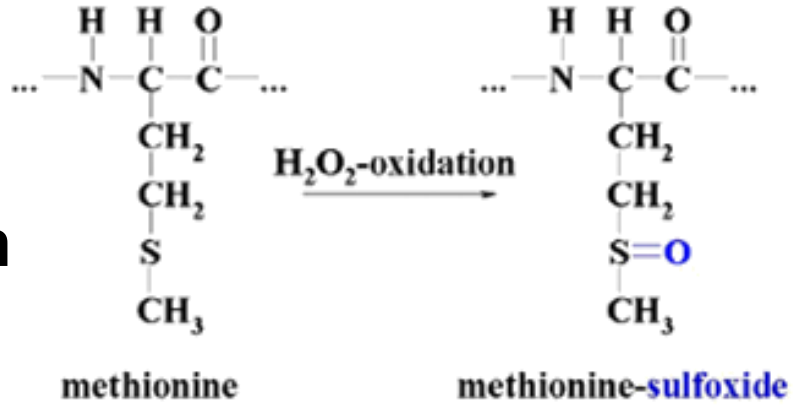
- α1-Antiproteinase (52 kDa)
- Neutralizes trypsin & trypsin-like enzymes (elastase)
- 90% of α1- globulin band
- Many polymorphic forms
- Alleles Pi^M, Pi^S, Pi^Z, Pi^F (MM is the most common)
- Deficiency (genetic): emphysema (ZZ, SZ). MS, MZ usually not affected
- Increased level of α1- antitrypsin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

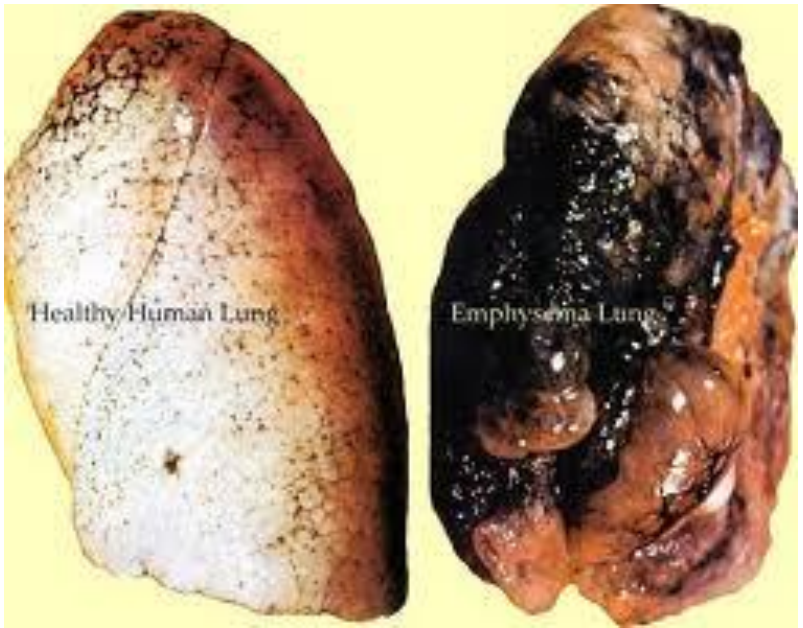
Active elastase + α_1–AT → Inactive elastase: α_1–AT complex → No proteolysis of lung → No tissue damage

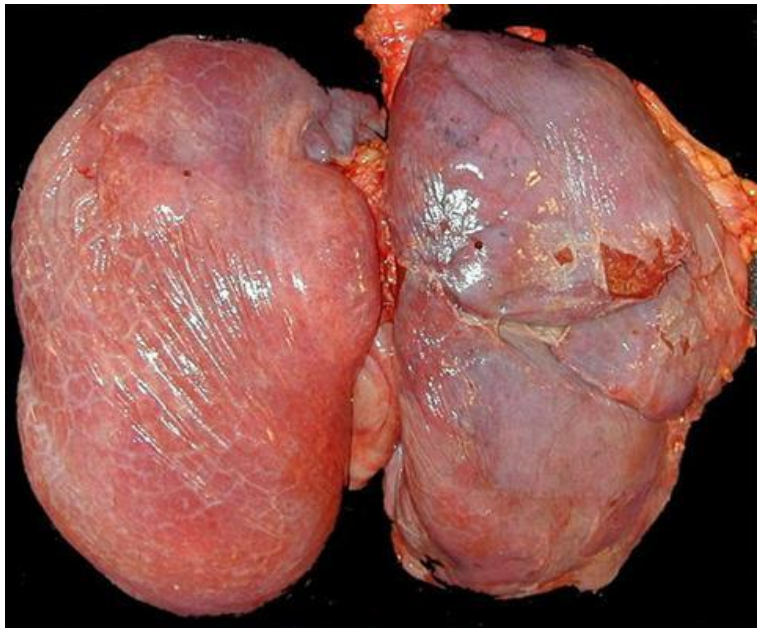
Active elastase + ↓ or no α_1–AT → Active elastase → Proteolysis of lung → Tissue damage

Smoking & α1- antitrypsin deficiency

- Chronic inflammation
- Oxidation of Met^{358}
- devastating in patients with Pi^{ZZ}

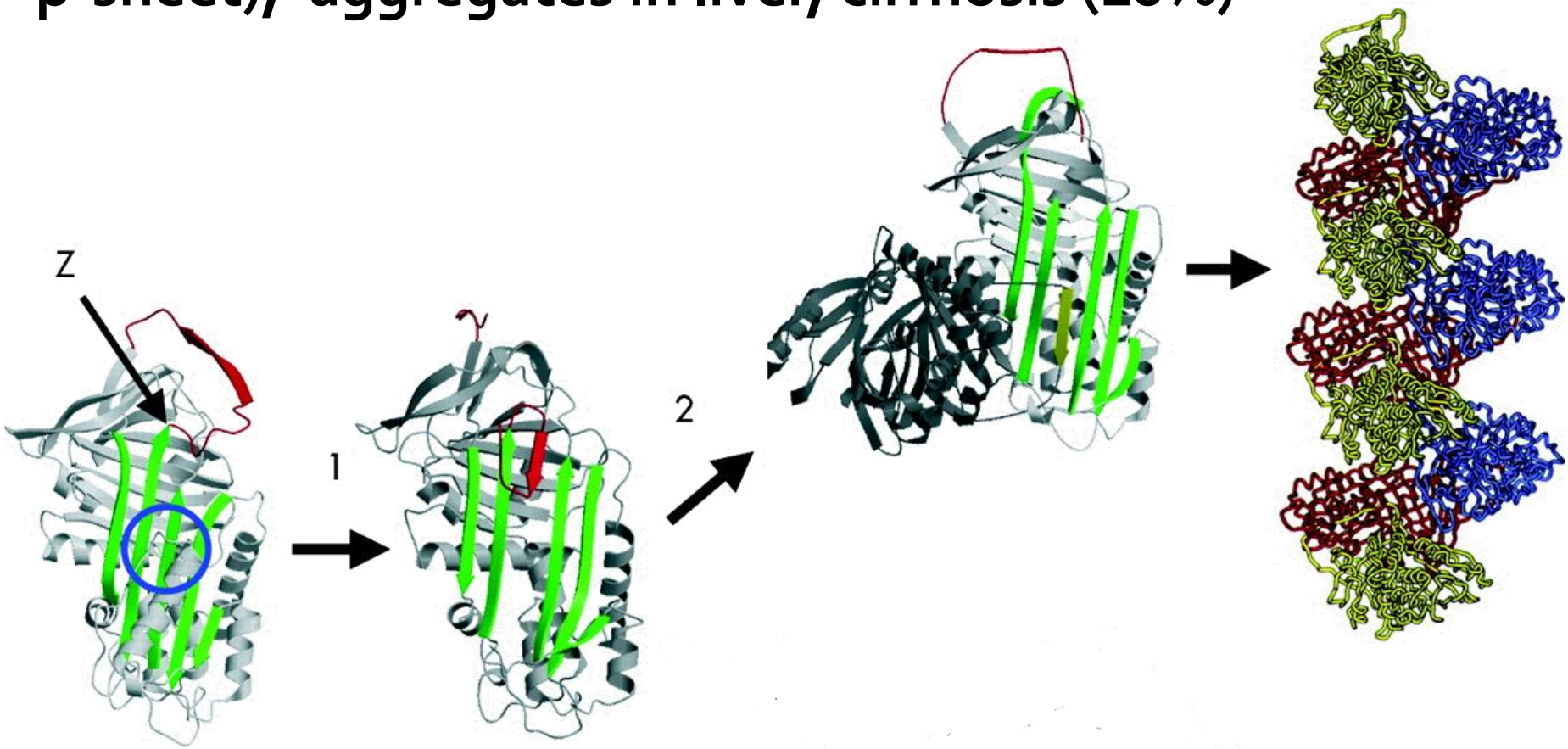






Liver disease & α1- antitrypsin deficiency

- 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)

- 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)

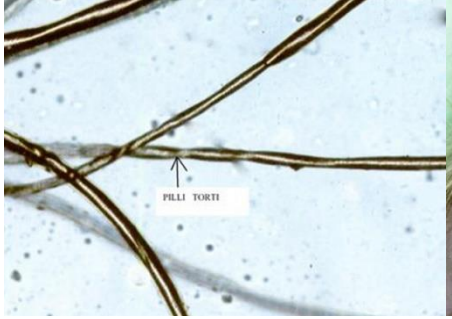
- Decreased level in hemolytic anemia

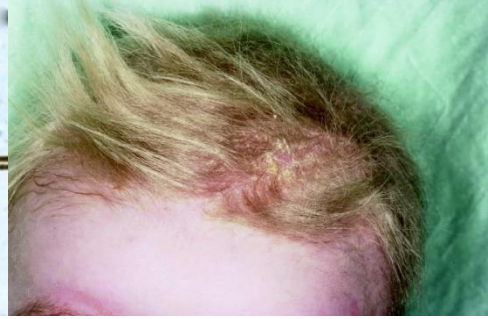
Ceruloplasmin

- 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)
- Regulates copper level: contains 90% of serum Cu
- A ferroxidase: oxidizes ferrous to ferric (transferrin)
- Albumin (10%) is more important in transport
- May decrease in liver disease (ex. Wilson's, autosomal recessive genetic disease)

Menke’s disease



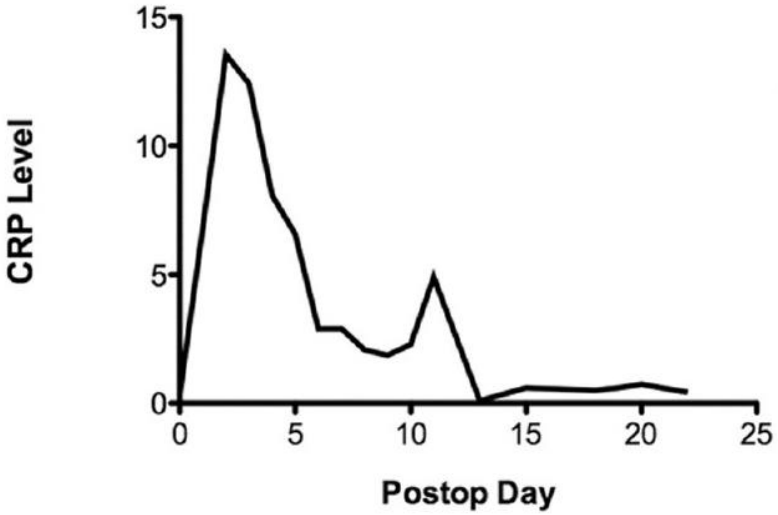


- **Menke’s disease** (also called the **kinky hair disease** or Menke's kinky hair syndrome) is a disorder that affects copper levels in the body.
- Characterized by **sparse and coarse hair, growth failure, and deterioration of the nervous system**
- **Mutations in the ATP7A gene** cause copper to be poorly distributed to cells in the body
- **Copper accumulates in some tissues** reducing the activity of numerous copper-containing enzymes

Wilson's disease

- Copper accumulates in tissues causing copper toxicosis
- Caused by defective copper-binding P-type ATPase (ATP7B), which is expressed primarily in the liver, kidney, brain, and RBCs
- The protein transports copper into bile and incorporates it into ceruloplasmin
- The mutant form of ATP7B expressed in people with Wilson's disease inhibits the release of copper into bile and decrease the coupling to ceruloplasmin

C- reactive protein (CRP)



- Able to bind to a polysaccharide (fraction C) in the cell wall of pneumococci
- Help in defense against bacteria & foreign substances
- Undetectable in healthy individuals, detectable in many inflammatory diseases (Acute rheumatic fever, bacterial infection, gout, etc.) & Tissue damage
- A CRP level greater than 10 mg/L
- Its level reaches a peak after 48 hours of incident (monitoring marker)