Biochemistry Team 435

جامعة الملك سعود
King Saud University

PLASMA PROTEIN.

* Please check out this link to know if there are any changes or additions.

Revised by
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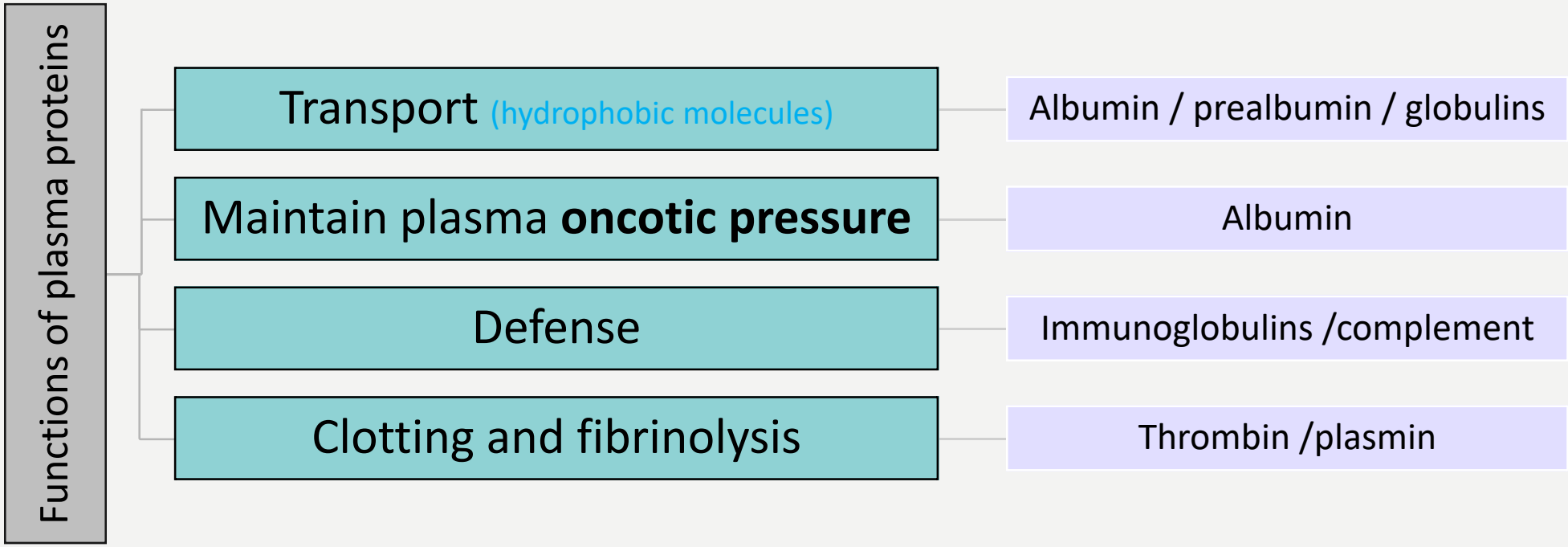
Color index: Important | Doctors notes | Further explanation.

OBJECTIVES:

- Functions and characteristics of plasma proteins
- Measurement of plasma proteins and diagnosis of diseases
- Electrophoretic patterns of plasma proteins
- Acute phase proteins

Plasma proteins (PPS)

- Plasma contains more than 300 different proteins.
- Many pathological conditions affect level of plasma proteins.
- **Mostly synthesized in: the liver.**
- Some are produced in other sites (examples: immunoglobulins are produced from B Lymphocytes)
- A normal adult contains ~70 g/L of pps



Measurement of plasma proteins

Plasma proteins can be measured in 2 ways

Quantitative measurement

- Numerical measurement
- It is obtained by chemical or immunological reactions (antibodies against specific proteins) ELSA IS ONE of the METHOD s

Semi-quantitative measurement

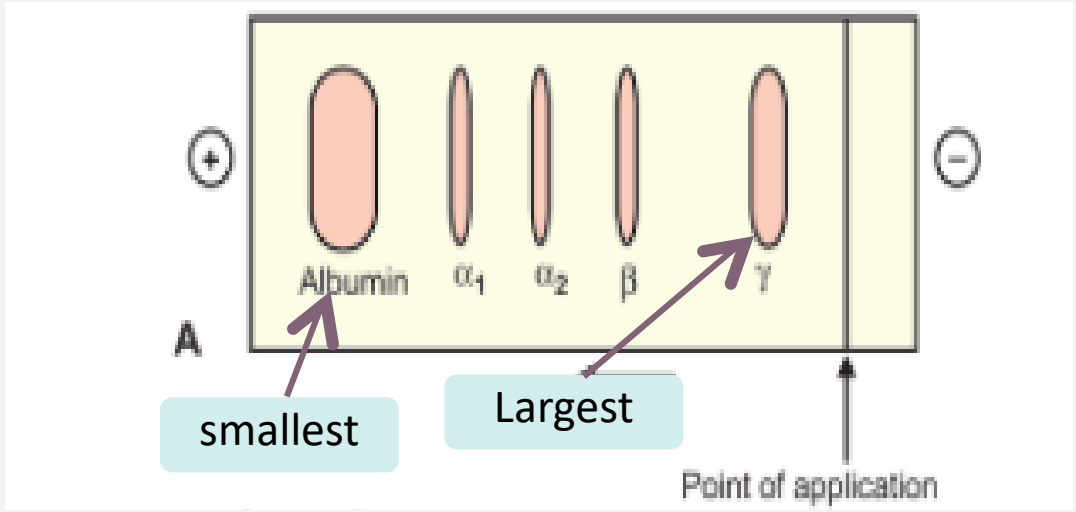
- Proteins are separated by **their electrical charge** in electrophoresis
- Five separate bands of proteins are observed
- These bands change in disease

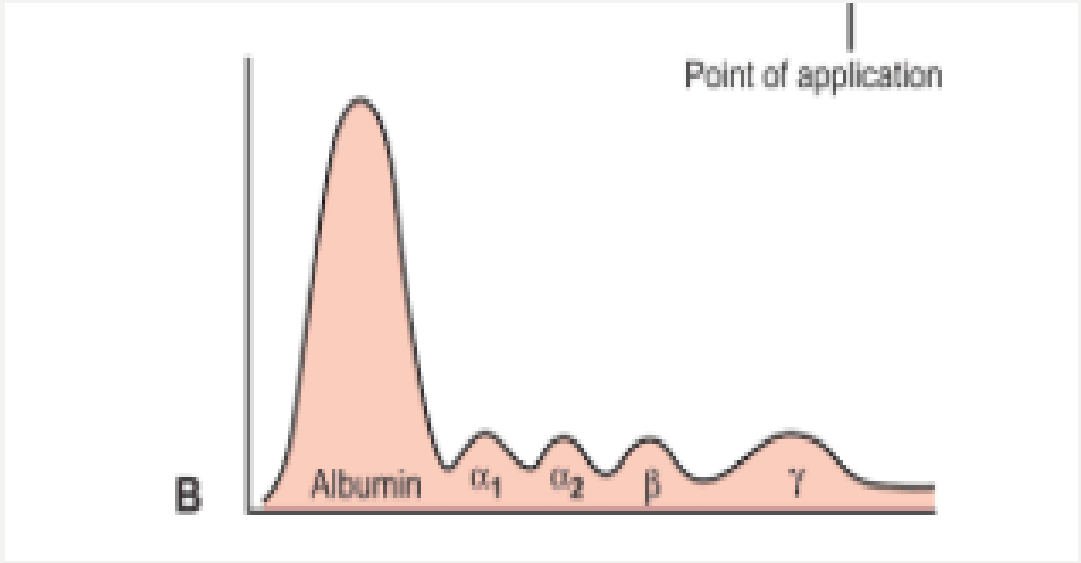
Note: A semi-quantitative test is one that doesn't give you the absolute amount of analytes in a sample. It only gives the amount of analytes relative to the others. For example it will tell that there is 3 times as much aluminium than iron in a sample but it won't tell how much of either is in the sample.

what we do in electrophoresis is that we have plasma which contain mixture of proteins we want to measure.
We add a chemical to it, and the good thing about this chemical is that it goes and bind to all protein molecules, it has a sulfate group that imparts negative charge on proteins, irrespective of what the origin of this protein was! So it kind of make a layer of(-) charge on them.

5 mins video about the electrophoresis

Extra





In normal condition, plasma proteins are separated by electrophoresis into 5 bands

As we all know, proteins are negatively charged. That's why they migrate from the cathode (-ve) to the anode (+ve)

- The smallest protein is going to migrate the furthest because it is so small "albumin"
- Giant protein is going to move for just a little bit "immunoglobulin"

The intensity of the band "thickness & darkness" reflects how many molecules are present. So, we can say that

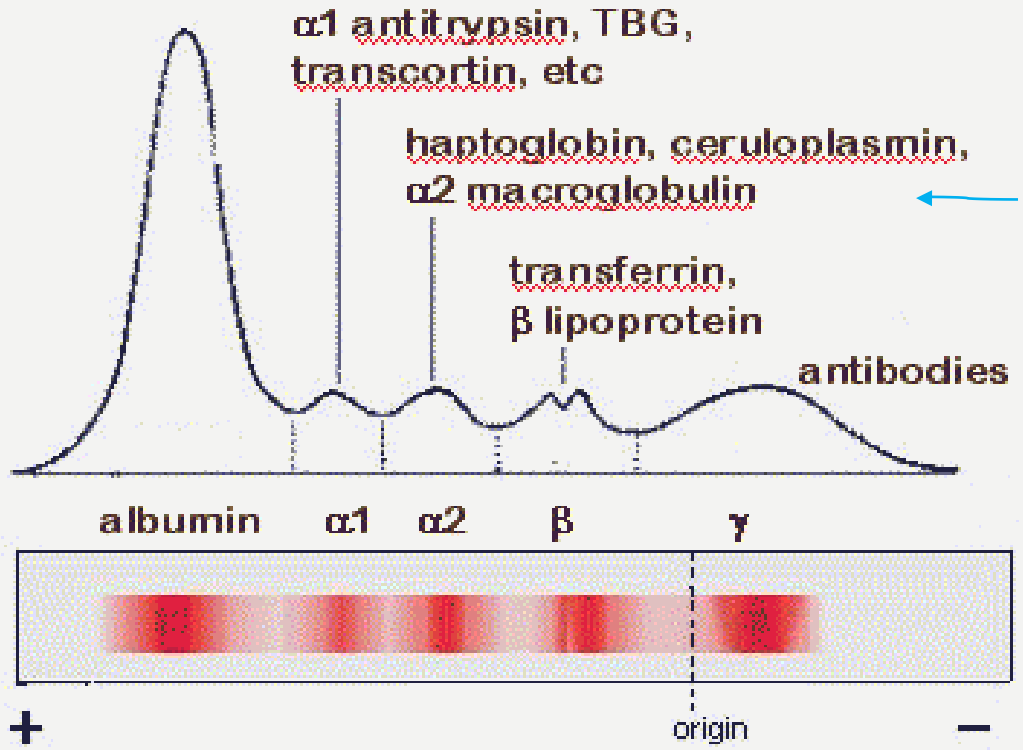
- Albumin "the thickest" is the most abundant plasma protein
- It is followed by immunoglobulin

The 5 bands appear as 5 peaks on the densitometer graph

This will converts the intensity into numbers

Measurement of plasma proteins

Normal Pattern of Plasma Protein Electrophoresis



You Just have to memorize the 5 bands and the patterns explained in the lecture.

- Serum protein electrophoretic pattern provides useful diagnostic information
- Different electrophoretic serum protein pattern is associated with various disorders

Extra: (examples of the disorders)

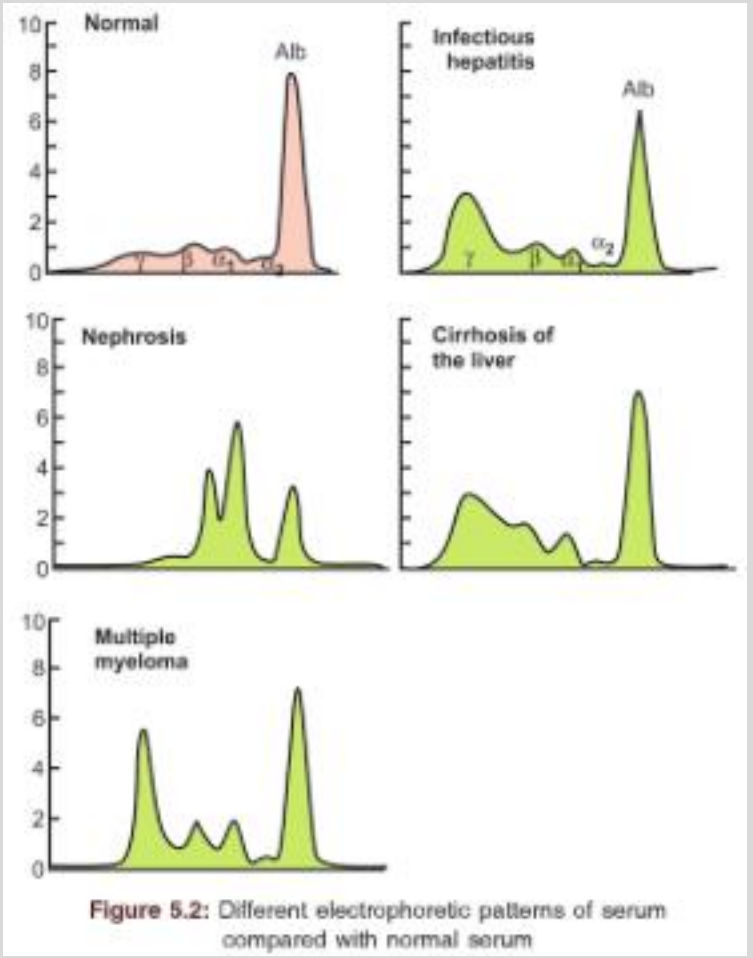


Figure 5.2: Different electrophoretic patterns of serum compared with normal serum

Types of plasma proteins

- **Prealbumin (Transthyretin)**
- **γ- Globulins** (antibodies)
- **α_1-Globulins**: α_1-Antitrypsin, α-fetoprotein
- **α_2-Globulins**: Ceruloplasmin, haptoglobin
- **β-Globulins**: CRP, transferrin, β_2-microglobulin
- **Albumin**

Not related to albumin

- **A transport protein for :**
  1-Thyroid hormones
  2-Retinol (vitamin A). By binding to retinol binding protein.
- **Migrates faster than albumin in electrophoresis** "small molecular weight"
- **Separated by:** immunoelectrophoresis
- **Lower levels found in:** liver disease (because they're mostly synthesized in the liver) , nephrotic syndrome (↑excretion) ,acute phase inflammatory response and malnutrition*
- Short half-life **(2 days)**

Transthyertin : trans = transpot , thy=thyroid , retin = retinol

- Most abundant plasma protein (~40 g/L) in normal adult 50-65%
- Synthesized in the liver (in RER) as **preproalbumin** and secreted as **albumin.**
- Half-life in plasma: **20 days** "more than prealbumin"
- Decreases rapidly in injury, infection and surgery

(surgery is kind of trauma and the body try to repair this trauma so albumin level will decrease)

***Clinical application: 1-** measured to assist the nutritional state. **2-** if a person is being treated for malnutrition, the Dr. can closely follow if he's responding to that treatment or not.

Functions of plasma proteins

- **Maintains oncotic pressure**
  - The osmotic pressure exerted by plasma proteins that pulls water into the circulatory system
  - Maintains fluid distribution in and outside cells and plasma volume
  - 80% of plasma oncotic pressure is maintained by **albumin**
- A **non-specific carrier**
  - Of hormones, calcium, free fatty acids and drugs,etc.
- **Take up tissue cells**
  - By albumin “pinocytosis where it is hydrolyzed to amino acids”
- **Useful in treatment**
  - of liver diseases, hemorrhage, shock and burns

Works by ↑ plasma volume

HYPOALBUMINEMIA

Causes of hypoalbuminemia :

- **Decreased albumin synthesis:**

(liver cirrhosis, malnutrition)

- **Increased losses of albumin:**

- Increased catabolism in infections

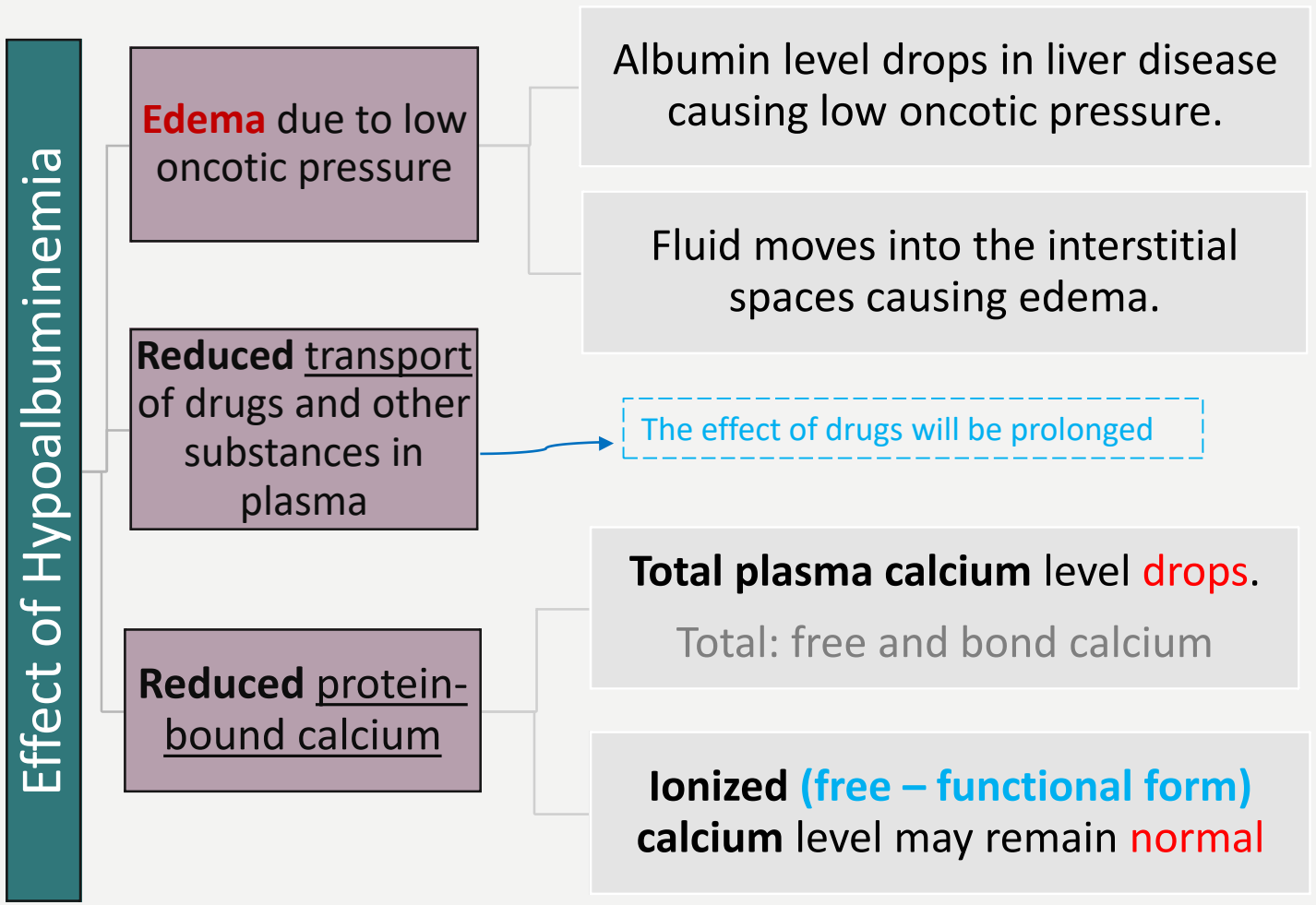
- Excessive excretion by the kidneys

(nephrotic syndrome)

- Excessive loss in bowel (bleeding)

- Severe burns (plasma loss in the absence of skin barrier)

Normal albumin excretion is 30 mg/day. So excretion above that level is pathologic



HYPOALBUMINEMIA

No clinical conditions are known that cause the liver to produce large amounts of albumin

The only cause of hyperalbuminemia is Dehydration

- Dehydration decreases plasma volume which increases albumin concentrations.
-Treated by giving the patient more solution.

Another condition which may cause an increase in albumin & all the majority of proteins is the process of drawing blood from a patient. Because when tying the tourniquet (compressing band) to take blood, some Tie it very tight and for a long time, leading to false (+)results; due to occlusion of vessels

A1-ANTITRYPSIN

❖ Synthesized by the liver and macrophages.
❖ An acute-phase that **inhibits proteases**.

Acute-phase protein?
When the protein level changes (↑or↓)
In the initial hours of an inflammation (first 24hrs.)

Proteases are produced **endogenously** and from **leukocytes** and **bacteria**

Such as:

-Digestive enzymes (Trypsin, chymotrypsin)

-Other proteases (Elastase, Thrombin)

Infection leads to: **protease release** from bacteria and from leukocytes

Types of α_1-Antitrypsin

- **Over 30 types are known**
- **The most common is M type**

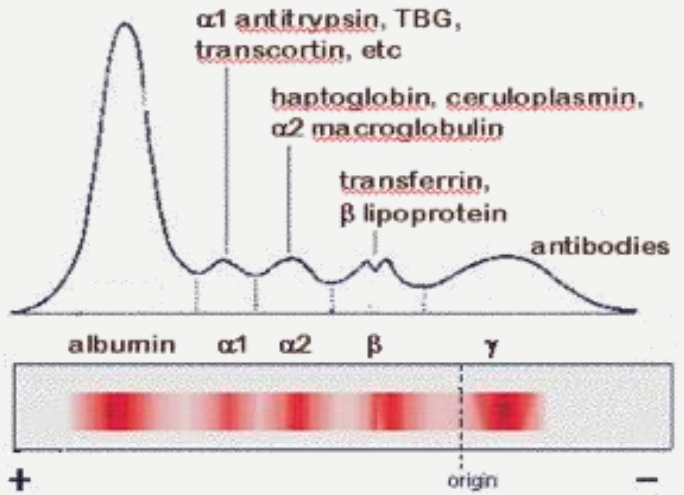
Even though leukocytes release proteases to kill the bacteria yet antitrypsin work on it, why ?
Because sometimes leukocytes fight the infection so aggressively that they release more proteases and damage the normal cells. So antitrypsin keeps balance.

A1-ANTITRYPSIN

Genetic deficiency of α_1-Antitrypsin

Synthesis of the defective α_1-Antitrypsin occurs **in the liver** but it cannot secrete the protein

α_1-Antitrypsin accumulates in: **hepatocytes** and is deficient in plasma



Clinical Consequences of α1-Antitrypsin Deficiency

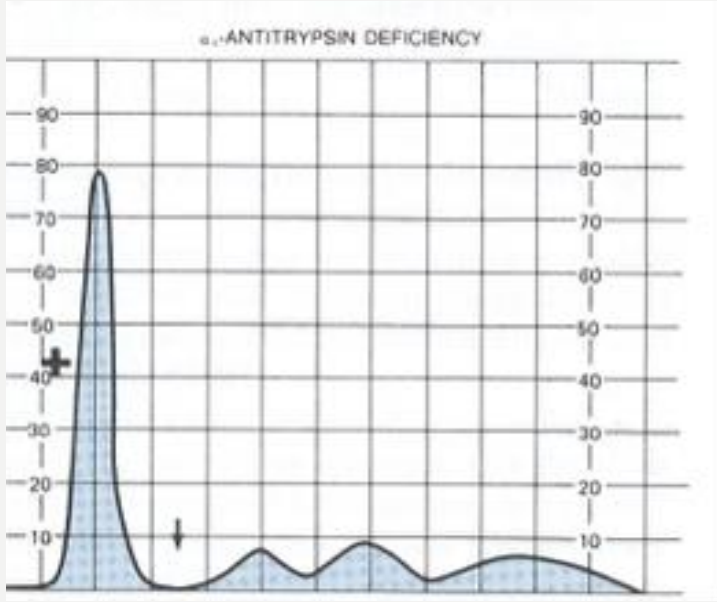
- Neonatal **jaundice** with evidence of **cholestasis**
- Childhood **liver cirrhosis**
- **Pulmonary emphysema** in young adults

Laboratory Diagnosis

1.Lack of α_1-globulin band in protein electrophoresis

2.Quantitative measurement of α_1-Antitrypsin by:

Radial immunodiffusion, isoelectric focusing or nephelometry



α-FETOPROTEIN (AFP)

- Synthesized in the **developing embryo** and **fetus** by the **parenchymal cells of the liver**
- AFP levels **decrease** gradually during intra-uterine life and **reach adult levels** at birth.
- **Function:** is unknown but it **may protect fetus** from immunologic attack by the mother
- No known physiological function in **adults**
- Has oxygen transport function in fetus

Abnormalities

- **Elevated** maternal AFP levels associated with : → Neural tube defect (spina bifida), anecephaly
- **Decreased** maternal AFP levels associated with: → Increased risk of **Down syndrome**
- AFP tumor marked for :**in adults** → **Hepatoma** and testicular cancer

CERULOPLASMIN

Its called apoceruloplasmin. But When it binds to copper it's referred to ceruloplasmin.

An oxidoreductase that **inactivates ROS** causing tissue damage in acute phase response.

Contains >90% of serum **copper**

(facilitate its transportation)

Important for:

iron absorption from the intestine

Ceruloplasmin converts ferrous to ferric, making it available to bound to transferrin .

Synthesized by:

the **liver**

ceruloplasmin

Wilson's disease:

* Due to **low** plasma levels of ceruloplasmin
* Copper is accumulated in **the liver** and **brain**

Depending on which area the brain is affected, it can cause memory loss or movement disorder

A2-GLOBULINS

CERULOPLASMIN	HAPTOGLOBIN
Synthesized by: the **liver**	**Synthesized by:** the **liver**
Contains >90% of serum **copper** (binds to copper to facilitate its transportation)	Binds to **free hemoglobin** to form complexes that are metabolized in the RES . (hemoglobin doesn't occur in kidney if present that indicate of renal failure)
• An oxidoreductase that **inactivates ROS** causing tissue damage in acute phase response. • **Important for iron absorption from the intestine**	**Limits iron losses** by preventing Hb loss from kidneys.
Wilson's disease: • Due to **low** plasma levels of ceruloplasmin • Copper is accumulated in **the liver** and **brain.** Depending on which area the brain is affected, it can cause memory loss or movement disorder	**Plasma level decreases during hemolysis** Can be measured for the diagnosis of hemolytic disease

Ceruloplasmin converts ferrous to ferric, making it available to bound to transferrin .

Haptoglobin is involved in the degradation of hemoglobin. When hemolysis takes place, it binds to hemoglobin and takes it to RES (reticulo-endothelial system) where the hemoglobin is degraded → it prevents the loss of Hemoglobin and iron from the body. Also it prevents kidney damage because hemoglobin damages kidney

β-Globulins

Transferrin

- **A major iron-transport protein in plasma**

30% saturated with iron

- **Plasma level drops in: (low level of transferrin)**

Malnutrition, liver disease, inflammation, malignancy

(all these condition will affect transferrin)

- **Iron deficiency results in increased hepatic synthesis** why? Because the liver receives it as not enough transferrin are present to carry iron. So it starts to make more transferrin
- **A negative acute phase protein**

C-Reactive Protein (CRP)

β2–Microglobulin

Lets imagine that the transferrin are taxis & iron are the passengers. When iron level becomes low, the taxi service company thinks that maybe they have less taxis, so they get more taxis on the road.☺

β-Globulins

Transferrin

- An acute-phase protein synthesized by the liver
- Important for phagocytosis
- High plasma levels are found in many inflammatory conditions such as rheumatoid arthritis
- ultra-sensitive CPR
- IT is a marker for ischemic heart disease

(a very good marker for ischemic heart disease and myocardial infarction)

C-Reactive Protein (CRP)

- **A component of human leukocyte antigen (HLA)**
- **Present on the surface of lymphocytes and most nucleated cells**
- **Filtered by the renal glomeruli due to its small size but most (>99%) is reabsorbed**
- **Elevated serum levels are found in:**

  Overproduction in disease ↑in Rheumatoid Arthritis & SLE
- **Maybe a tumor marker for:(plasma level will)**

  Leukemia, lymphomas, multiple myeloma

  Not for diagnosis. Just indicate the size of it (the higher protein level the larger the tumor.

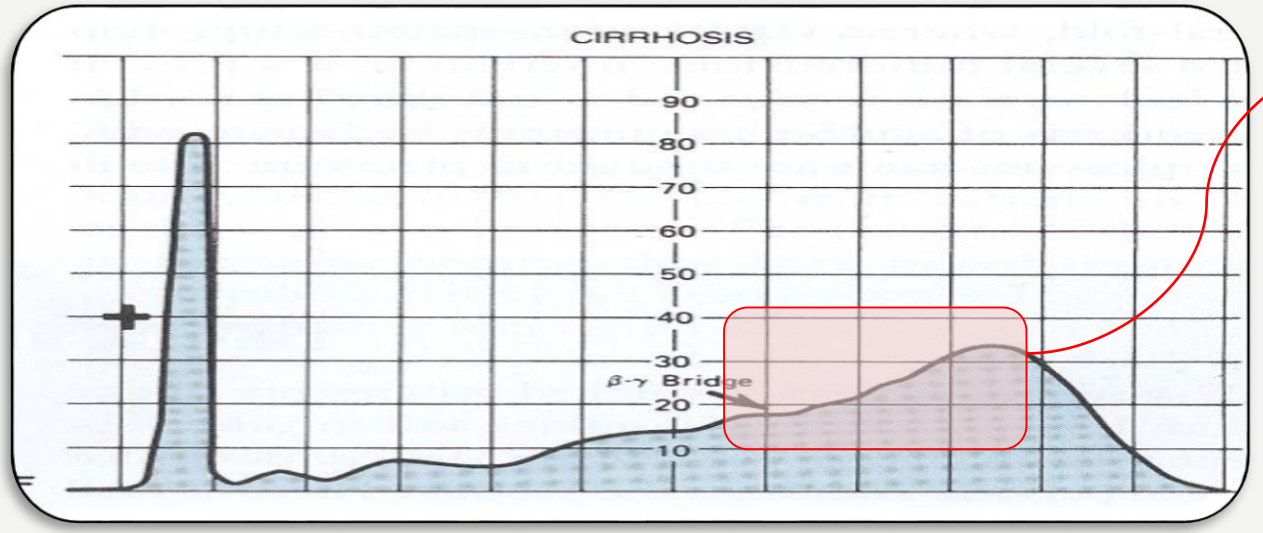
β2–Microglobulin

Hypergammaglobulinemia

May result from stimulation of:

- **B cells** (Polyclonal hypergammaglobulinemia)
- **Monoclonal proliferation** (Paraproteinemia)

(there are 2 types of antibodies mono and poly)
(Polyclonal antibodies are antibodies that are secreted by different B cell lineages within the body.
whereas monoclonal antibodies come from a single cell lineage)



Polyclonal hypergammaglobulinemia
Stimulation of many clones of B cells produce a wide range of antibodies
γ-globulin band appears large in electophoresis
Clinical conditions: acute and chronic infections, autoimmune diseases, chronic liver diseases

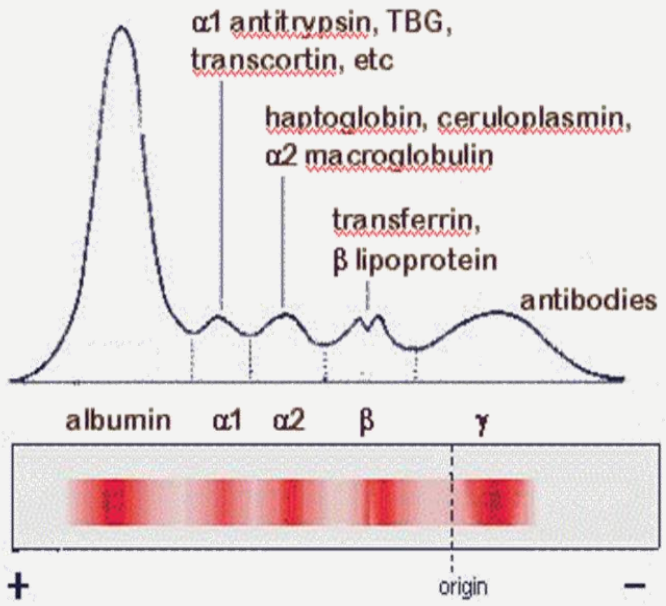
Monoclonal Hypergammaglobulinemia

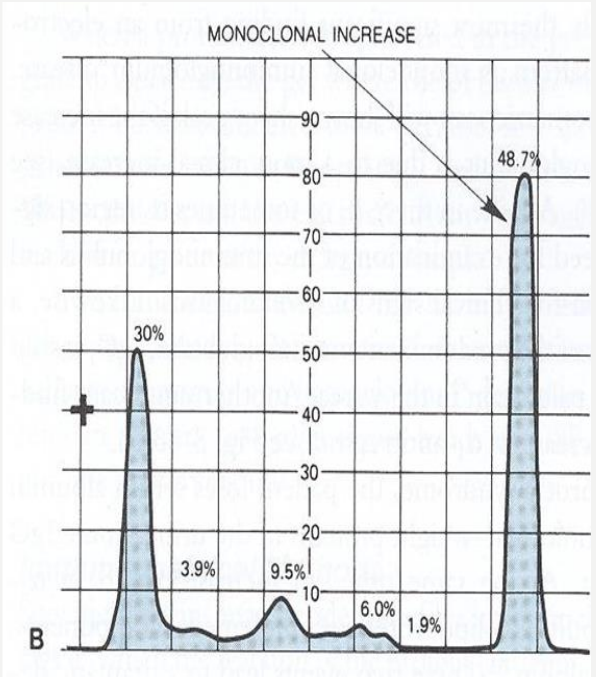
Proliferation of a single B-cell clone produces a single type of Ig

Appears as a separate dense band **(paraprotein or M band) in** electrophoresis

Paraproteins are characteristic of **malignant B-cell proliferation**

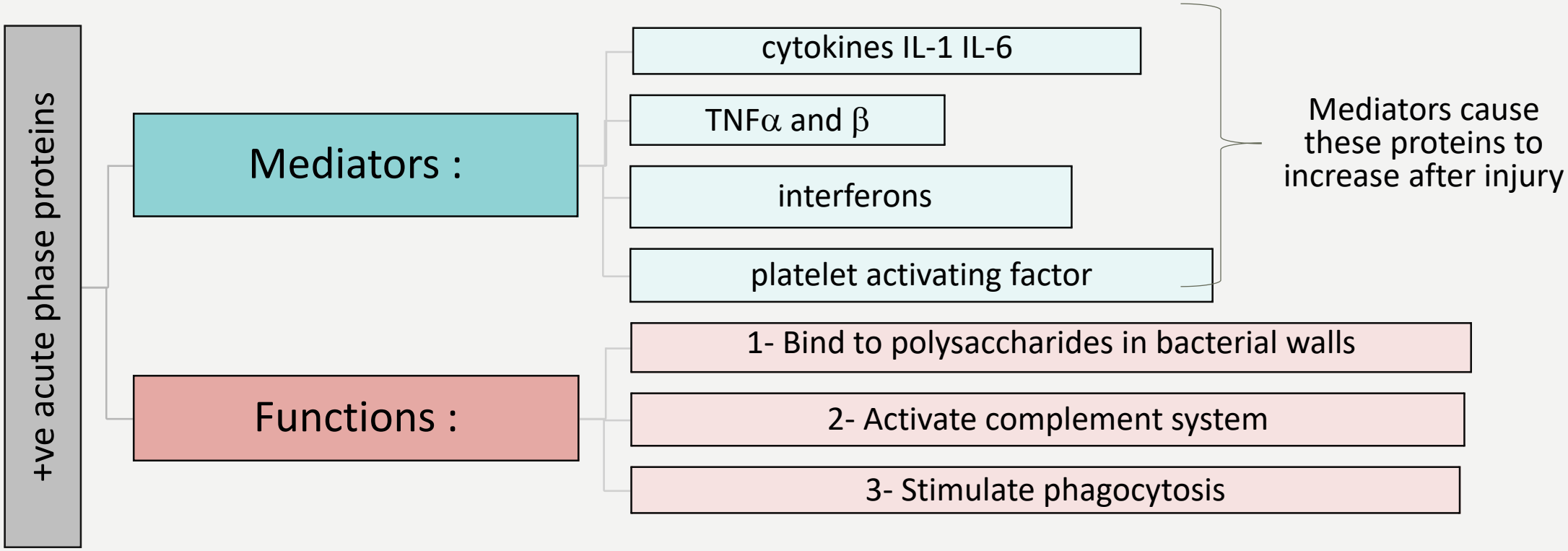
Clinical condition: multiple myeloma





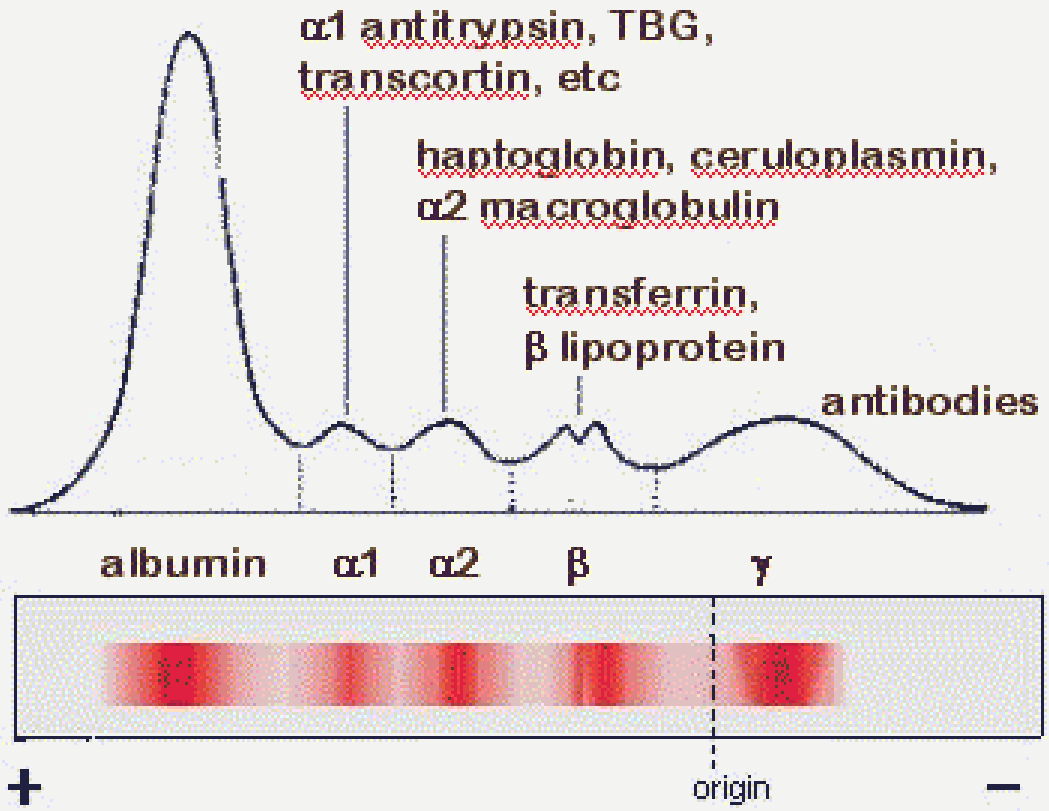
POSITIVE ACUTE PHASE PROTEINS

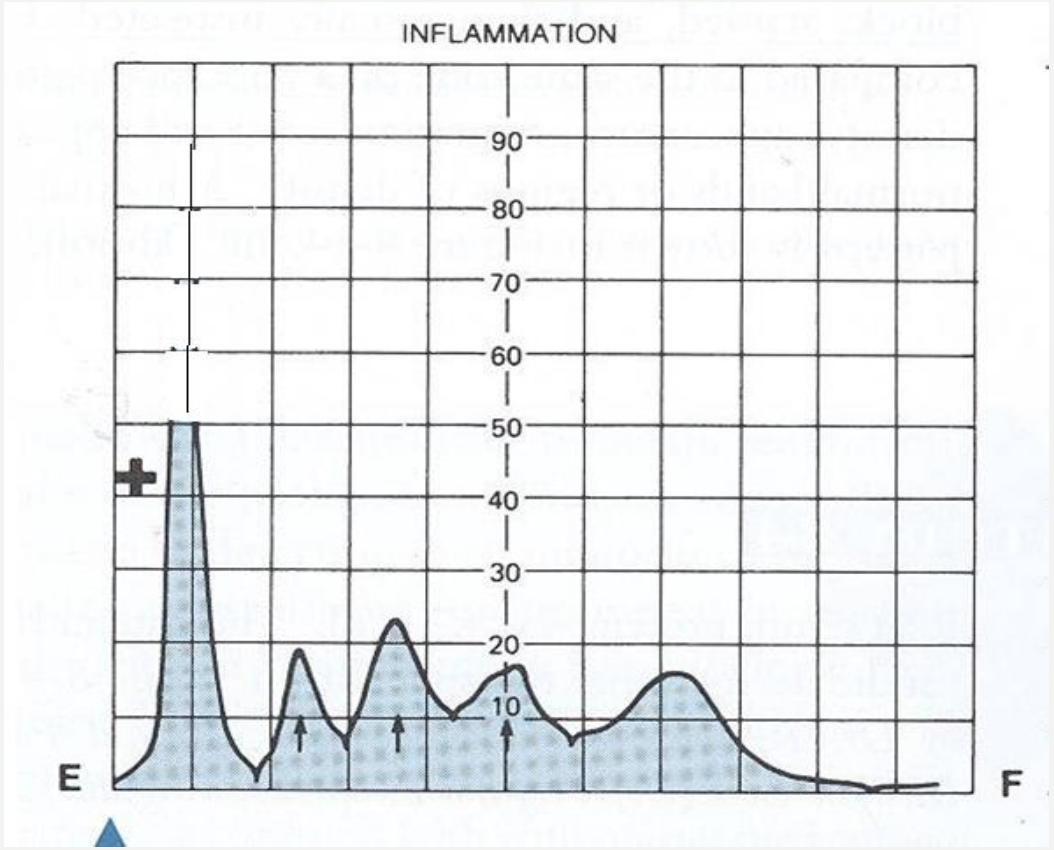
- **Plasma protein levels increase in:**
  * Infection, inflammation , malignancy, trauma, surgery
- **These proteins are called: acute phase reactants.**
- **Synthesized due to:** body's response to injury
- **Examples:** α1-Antitypsin, haptoglobin, ceruloplasmin, fibrinogen, c-reactive protein



POSITIVE ACUTE PHASE PROTEINS

When the tissue is damage , the tissue will send signals to cytokines so , the cytokines will send signals to increase the level of these positive acute phase proteins . When these proteins reach to the site of infection it will fight .





NEGATIVE ACUTE PHASE PROTEINS

Negative acute phase proteins

These proteins decrease in inflammation

Albumin, prealbumin, transferrin

Mediated by inflammatory response via **cytokines** and **hormones**

Synthesis of these proteins decrease to save amino acids for positive acute phase proteins

Check your understanding!

Q1: Which one of the following plasma proteins maintain the oncotic pressure:

A. Albumin.
B. Globulins.
C. Thrombin.
D. Plasmin.

Q2: Which one of the following acts as a transport protein for thyroid hormone:

A. Albumin.
B. Prealbumin.
C. Ceruloplasmin.
D. Plasmin.

Q3: The only cause of hyperalbuminemia is:

A. Liver disease.
B. Burns.
C. Dehydration.
D. None of the above.

Q4: α_1-Antitrypsin is synthesized by:

A. Liver.
B. Macrophages.
C. A&B.
D. None of the above.

Q5: Increased risk of spina bifida is associated with which of the following:

A. Decreased maternal AFP.
B. Polyclonal hypergammaglobulinemia.
C. Monoclonal hypergammaglobulinemia.
D. Elevated maternal AFP.

Q6: Which protein is important in preventing Hb loss from kidney:

A. Haptoglobin.
B. Albumin.
C. Transferrin.
D. Ceruloplasmin.

Q7: Monoclonal proliferation is a marker for:

A. Multiple sclerosis.
B. Multiple myeloma.
C. Spina bifida.
D. Hepatoma

1.A 2.B 3.C 4.C 5.D 6.A 7.B

Check your understanding!

Q8: Which one of the following is a negative acute phase protein:

A. Haptoglobin.
B. Fibrinogen.
C. Transferrin.
D. C-reactive protein.

Q9: Which one of the following is a marker for ischemic heart disease:

A. C-reactive protein.
B. Haptoglobin.
C. Transferrin.
D. None of the above.

Q10: A patient has Wilsons disease which one of the following will decrease:

A. Haptoglobin.
B. Fibrinogen.
C. Ceruloplasmin.
D. C-reactive protein.

Q11: A patient has testicular cancer, which one of the following will increase:

A. Gamma globulin.
B. α-Fetoprotein.
C. Albumin.
D. Prealbumin.

Q12: A patient has nephrotic syndrome, which one of the following will decrease:

A. Ceruloplasmin.
B. α-Fetoprotein.
C. Transferrin.
D. Prealbumin.

8.C 9.A 10.C 11.B 12.D

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Resource:

- 435's slides notes.

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