Plasma Proteins

GNT Block

Objectives:

By the end of this lecture, the Second Year students will be able to:

- **Identify types and various functions of plasma proteins**
- **Discuss the role of plasma proteins in the diagnosis of diseases and conditions**
- **Interpret the normal and abnormal electrophoretic patterns of plasma proteins**
- **Identify the role positive and negative acute phase proteins in various diseases**

Overview:

- 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 >300 different proteins
- Many pathological conditions affect level of pps
- Mostly synthesized in the liver
- Some are produced in other sites
- A normal adult contains ~70 g/L of pps

Functions of pps

- **Transport (Albumin, prealbumin, globulins)**
- **Maintain plasma oncotic pressure (Albumin)**
- **Defense (Immunoglobulins and complement)**
- **Clotting and fibrinolysis (Thrombin and plasmin)**

Measurement of Plasma Proteins

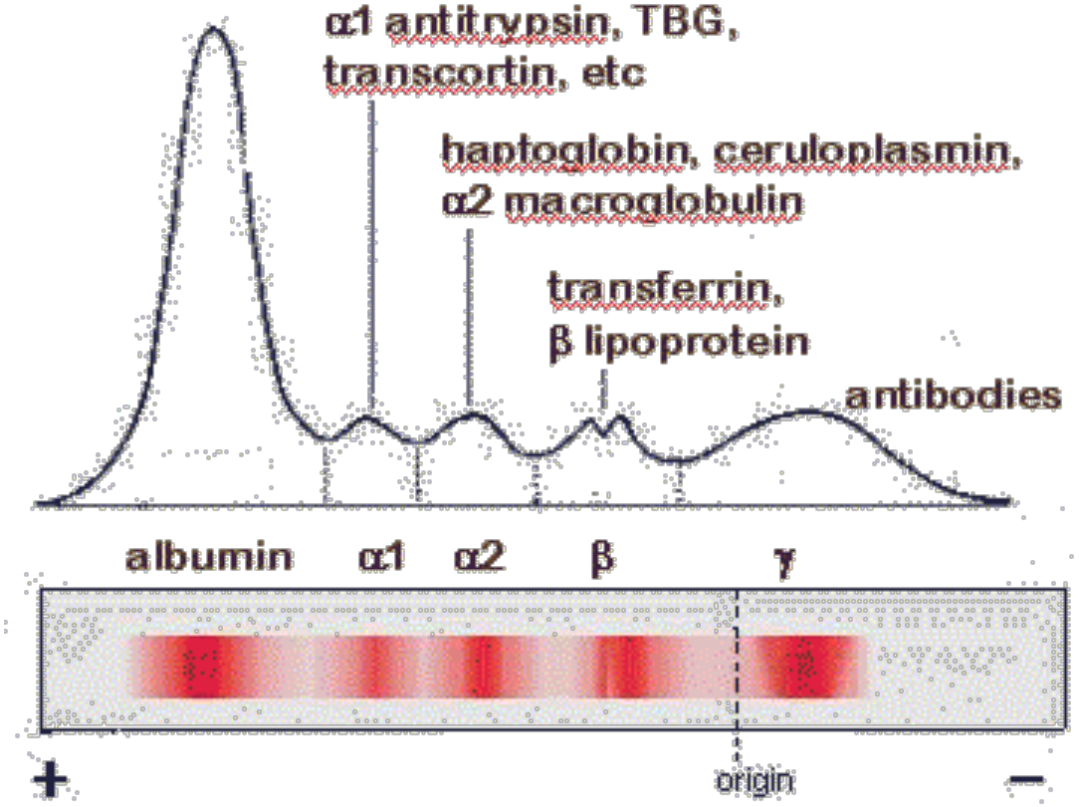
A) Quantitative measurement of a specific protein:

Chemical or immunological reactions

B) Semiquantitative measurement by electrophoresis:

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

Normal Pattern of Plasma Protein Electrophoresis



Types of Plasma Proteins

- Prealbumin
- Albumin
- α_1-Globulins:
  - α_1-Antitrypsin, α-fetoprotein
- α_2-Globulins:
  - Ceruloplasmin, haptoglobin
- β-Globulins:
  - CRP, transferrin, β2-microglobulin
- γ- Globulins

Prealbumin (Transthyretin)

- A transport protein for:
  - Thyroid hormones
  - Retinol (vitamin A)
- Migrates faster than albumin in electrophoresis
- Separated by immunoelectrophoresis
- Lower levels found in:
  - liver disease, nephrotic syndrome, acute phase inflammatory response, malnutrition
- Short half-life (2 days)

Albumin

- **Most abundant plasma protein (~40 g/L) in normal adult**
- **Synthesized in the liver as preproalbumin and secreted as albumin**
- **Half-life in plasma: 20 days**
- **Decreases rapidly in injury, infection and surgery**

Functions

- Maintains oncotic pressure:
  - The osmotic pressure exerted by plasma proteins that pulls water into the circulatory system
  - Maintains plasma volume and fluid distribution in and outside cells

- 80% of plasma oncotic pressure is maintained by albumin

Functions

- **A non-specific carrier of**
  - **hormones, calcium, free fatty acids, drugs, etc.**
- **Tissue cells can take up albumin by pinocytosis where it is hydrolyzed to amino acids**
- **Useful in the treatment of liver diseases, hemorrhage, shock and burns**

Hypoalbuminemia

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

Hypoalbuminemia

Effects

- Edema due to low oncotic pressure
  - Albumin level drops in liver disease causing low oncotic pressure
  - Fluid moves into the interstitial spaces causing edema
- Reduced transport of drugs and other substances in plasma
- Reduced protein-bound calcium
  - Total plasma calcium level drops
  - Ionized calcium level may remain normal

Hyperalbuminemia

- No clinical conditions are known that cause the liver to produce large amounts of albumin
- The only cause of hyperalbuminemia is dehydration

α_1-Antitrypsin

- Synthesized by the liver and macrophages
- An acute-phase protein that inhibits proteases
- Proteases are produced endogenously and from leukocytes and bacteria
  - Digestive enzymes (trypsin, chymotrypsin)
  - Other proteases (elastase, thrombin)
- Infection leads to protease release from bacteria and leukocytes

Types of α_1-Antitrypsin

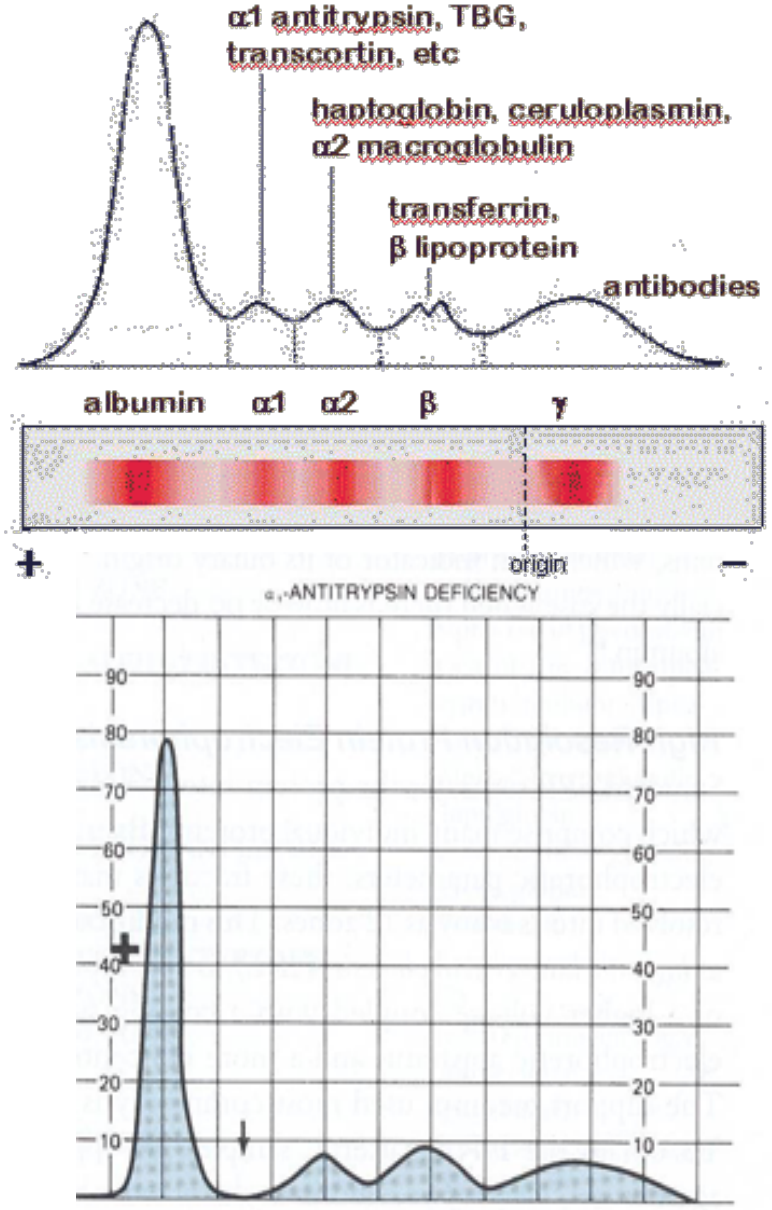
- Over 30 types are known
- The most common is M type
- Genetic deficiency of α_1-antitrypsin
  - Synthesis of the defective α_1-antitrypsin occurs in the liver but it cannot secrete the protein
  - α_1-Antitrypsin accumulates in hepatocytes and is deficient in plasma

Clinical Consequences of α_1-Antitrypsin Deficiency

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

Laboratory Diagnosis

- Lack of α_1-globulin band in protein electrophoresis
- Quantitative measurement of α_1-Antitrypsin by:
  - Radial immunodiffusion, isoelectric focusing or nephelometry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transcortin, etc
haptoglobin, ceruloplasmin,
α2 macroglobulin
transferrin,
β lipoprotein
antibodies
albumin
α1
α2
β
γ
origin
+
−
α1-ANTITRYPSIN DEFICIENCY
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80
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50
40
30
20
10

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

α-Fetoprotein (AFP)

- **Elevated maternal AFP levels are associated with:**
  - **Neural tube defect (spina bifida), anencephaly**
- **Decreased maternal AFP levels are associated with:**
  - **Increased risk of Down syndrome**
- **AFP is a tumor marker for:**

  Hepatoma and testicular cancer

Ceruloplasmin

- Synthesized by the liver
- Contains >90% of serum copper
- An oxidoreductase that inactivates ROS causing tissue damage in acute phase response
- Important for iron absorption from the intestine
- Wilson's disease:
  - Due to low plasma levels of ceruloplasmin
  - Copper is accumulated in the liver and brain

Haptoglobin

- Synthesized by the liver
- Binds to free hemoglobin to form complexes that are metabolized in the RES
- Limits iron losses by preventing Hb loss from kidneys
- Plasma level decreases during hemolysis

Transferrin

- A major iron-transport protein in plasma
  - 30% saturated with iron
- Plasma level drops in:
  - Malnutrition, liver disease, inflammation, malignancy
- Iron deficiency results in increased hepatic synthesis
- A negative acute phase protein

β_2–Microglobulin

- 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
- May be a tumor marker for:
  - Leukemia, lymphomas, multiple myeloma

C-Reactive Protein (CRP)

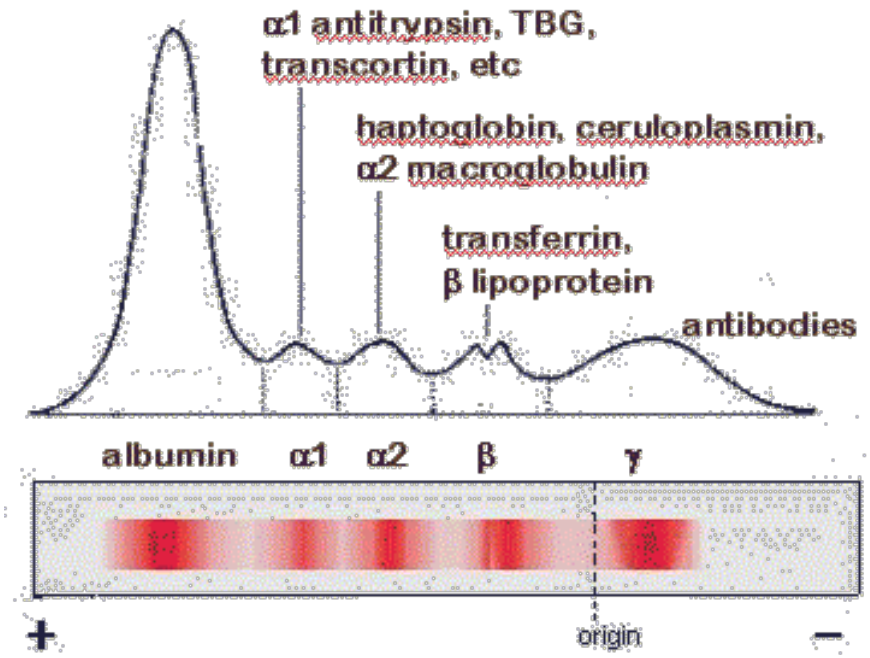
- An acute-phase protein synthesized by the liver
- Important for phagocytosis
- High plasma levels are found in many inflammatory conditions such as rheumatoid arthritis
- A marker for ischemic heart disease

Hypergammaglobulinemia

- **May result from stimulation of**
  - **B cells (Polyclonal hypergammaglobulinemia)**
  - **Monoclonal proliferation (Paraproteinemia)**

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**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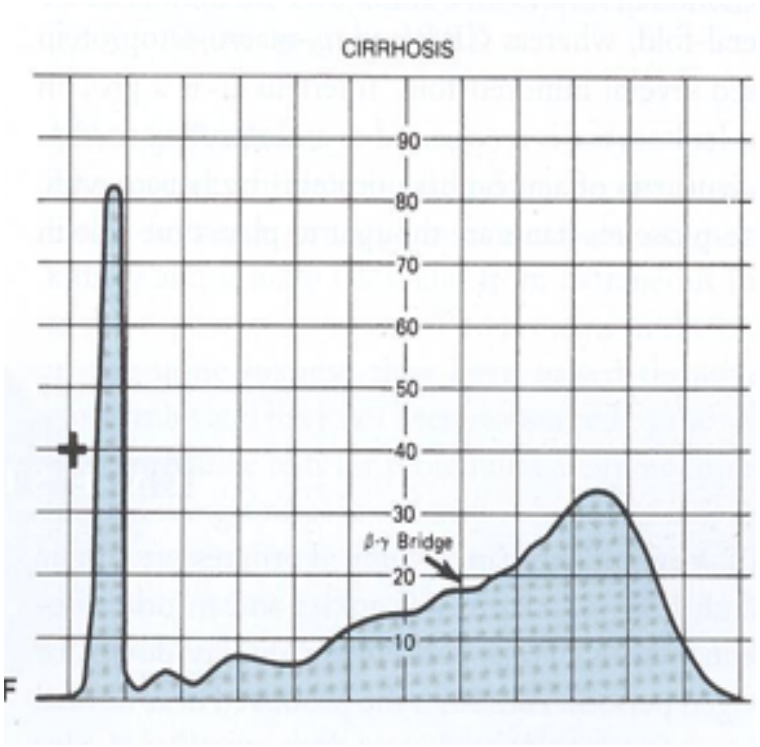
CIRRHOSIS
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β-γ Bridge
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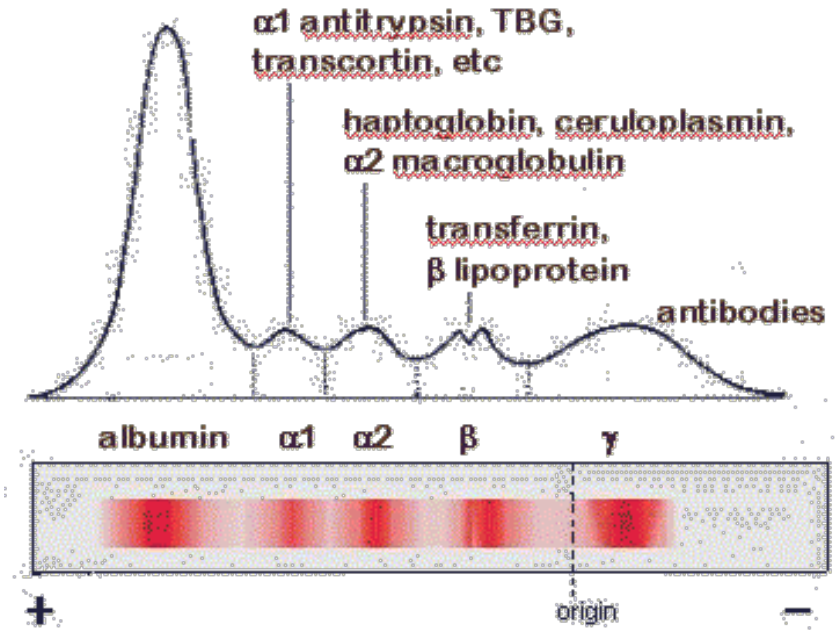
Monoclonal Hypergammaglobulinemia

- 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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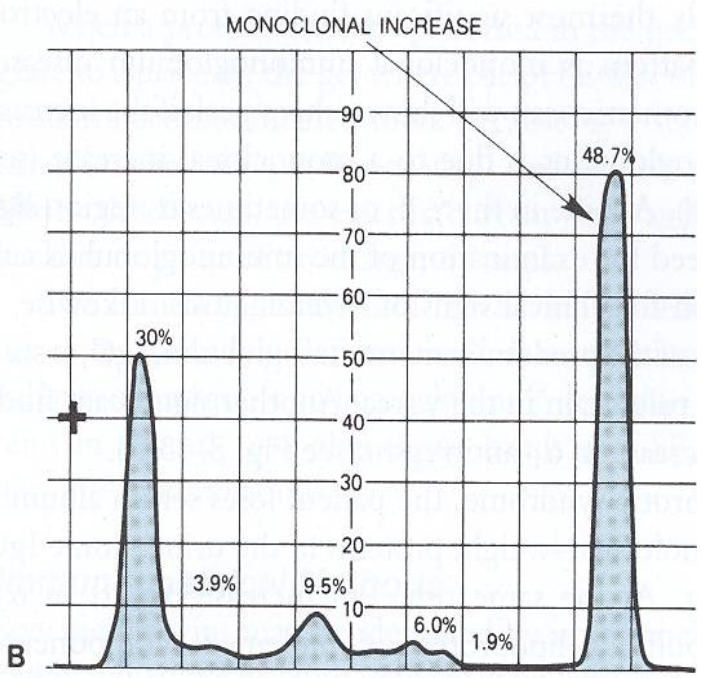
MONOCLONAL INCREASE
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48.7%
30%
3.9%
9.5%
6.0%
1.9%
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B

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: α_1-Antitypsin, haptoglobin, ceruloplasmin, fibrinogen, c-reactive protein**

Positive Acute Phase Proteins

- **Mediators cause these proteins to increase after injury**

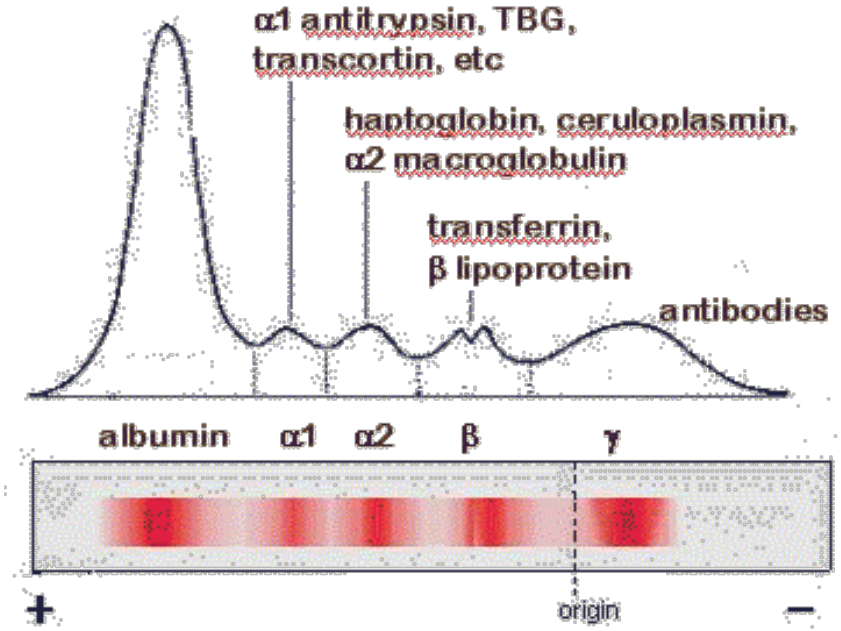
- **Mediators: Cytokines (IL-1, IL-6), tumor necrosis factors α and β , interferons, platelet activating factor**

Functions:

1. Bind to polysaccharides in bacterial walls

2. Activate complement system

3. Stimulate phagocytosis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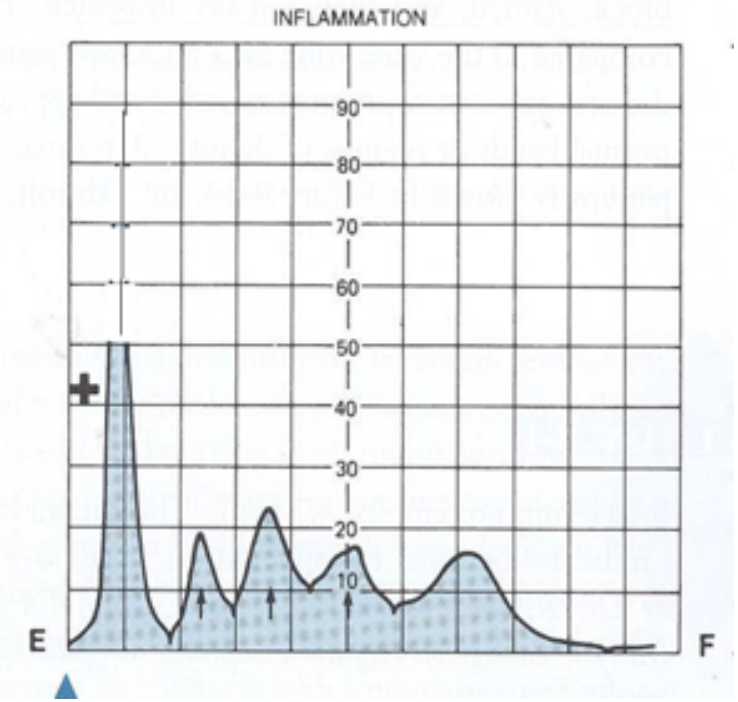
INFLAMMATION
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E
F

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

Take Home Message

- **Plasma proteins play essential roles in a number of cellular functions**
- **They possess diagnostic significance in identifying various pathological conditions**

References

- **Lecture Notes in Clinical Biochemistry, 9th Edition, AF Smith, pp. 86-97, Blackwell Publishing, UK**

- **Clinical Diagnosis and Management by Laboratory Methods, 19th Edition, John Bernard Henry, Saunders, USA**