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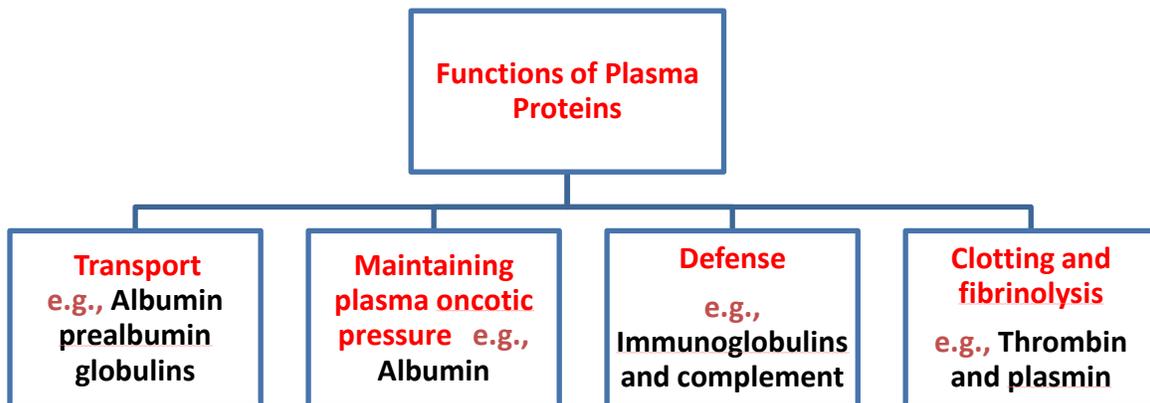
Special thanks to :

Abdullah alaqeel

## Plasma Proteins (PPs)

- & Plasma contains over **300** different proteins.
- & The concentration of many of PPs are affected by pathological processes.
- & Therefore, measurement of PPs is clinically useful.
- & Most plasma proteins are synthesized in the **liver**, although some of them are produced in other sites **e.g. immunoglobulins by lymphocytes.**
- & The total PPs concentration is **~70 g/L** in normal adult males
- & Application of a tourniquet (a strip of cloth which is tied tightly round an injured arm or leg to stop it bleeding) for extended periods leads to fluid loss from the occluded veins; increasing apparently plasma protein concentrations \*

\* إذا حصرنا الدم بواسطة عصابه يضيق مجرى الدم فلا يخرج الا السوائل ولكن البروتينات التي فيه لا تخرج لذلك يزيد تركيزها

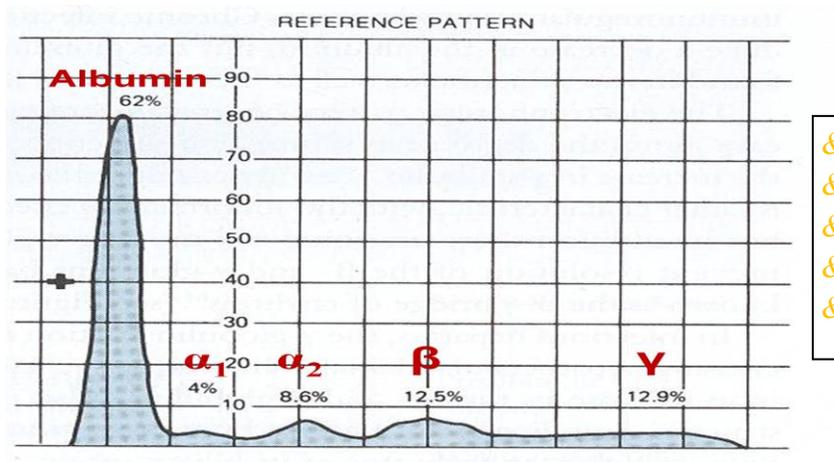


Measurement of Plasma Proteins

1. **Quantitative** measurement of a specific protein :  
( Chemical or immunological reactions )
2. Semiquantitative measurement **by electrophoresis:**

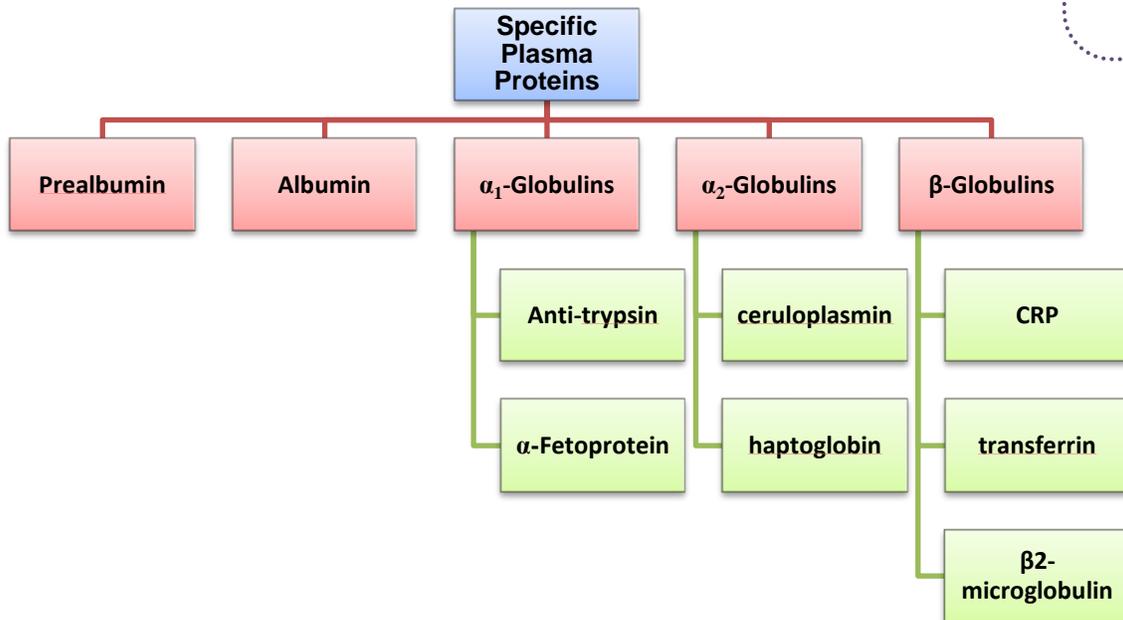
- & Proteins are separated on the basis of their electrical charge.
- & Serum or plasma is applied to a support medium, cellulose acetate or a gel, and an electrical current applied. The, the gel is stained with a dye that visualizes the proteins.
- & In **normal** subjects **5 discrete bands of proteins** are seen and altered patterns occur in various diseases.

Normal Pattern of Plasma Protein Electrophoresis



- & Albumin
- &  $\alpha_1$ -Globulins
- &  $\alpha_2$ -Globulins
- &  $\beta$ -Globulins
- &  $\gamma$ -Globulins

**Electrophoresis :**  
هي طريقه تعتمد على صفات البروتين الكهربائيه ( سرعه تحرك البروتين من الشحنة السالبه للشحنه الموجبه - مهمه ) الطبيعي يظهر فيه 4 ارتفاعات كما يلي : اسرع البروتينات هو : الالبومين وفي نفس الوقت هو اكثرها لذلك يظهر على شكل عمود طويل قريب للشحنه الموجبه .



	function	Plasma level	Synthesis	Others
<b>Prealbumin</b>	<ul style="list-style-type: none"> <li>■ It is the transport protein for:                             <ul style="list-style-type: none"> <li>○ Thyroid hormones and</li> <li>○ Retinol (vitamin A)</li> </ul>                             (As a complex with retinol-binding protein)                         </li> </ul>	↓ in liver disease , nephrotic syndrome, acute phase inflammatory response and malnutrition	_____	<ul style="list-style-type: none"> <li>◆ Prealbumin migrates faster than albumin in the classic electrophoresis</li> <li>◆ It can also be separated by immunoelectrophoresis.</li> <li>◆ It has a short half-life of approximately 2 days</li> </ul>
<b>Albumin</b>	_____	Rapid ↓ in response to injury, infection and surgery.	in the liver and has a half-life of 20 days.	<ul style="list-style-type: none"> <li>◆ is present in higher concentrations than other plasma proteins ( ~40 g/L in normal adults).</li> <li>◆ has a molecular weight of ~66 kDa. Very small amounts cross the glomerular capillary wall.</li> </ul>
<b>α<sub>1</sub>-Antitrypsin</b>	It inhibits proteases	_____	by the liver and macrophages	It is acute-phase protein
<b>α-Fetoprotein (AFT)</b>	protects the fetus from immunologic attack by the mother.	↓ Gradually during intrauterine life and reach adult levels at birth.	in the developing embryo and fetus by the parenchymal cells of the liver	◆ has no known physiological function in adults
<b>ceruloplasmin</b>	It is an oxidoreductas and this property is important in <b>acute phase response</b> as it is able to inactivate reactive O <sub>2</sub> species (ROS) that produce tissue damage. It is important for iron absorption from the intestine. (so when ↓ → <b>Iron deficiency anemia</b> )	↓ in Wilson's disease in which copper is accumulated in the liver leading to cirrhosis , and in the basal ganglia of the brain leading to choreoathetosis  ↑ during pregnancy and in response to oral estrogens.	by the liver	◆ Contains over 90% of serum copper – the metal is tightly bound and does not exchange readily.

<p><b>haptoglobin</b></p>	<p>It limits iron losses which may occur as Hb is small enough to be filtered by the glomeruloi</p>	<p>↓ during hemolysis ↑ in acute inflammatory conditions (acute phase reactant).</p>	<p>by the liver • It binds free hemoglobin to form complexes that are metabolized in the RES.</p>	<p>_____</p>
<p><b>CRP</b></p>	<p>It is important for phagocytosis .</p>	<p>↑ in many inflammatory conditions e.g., rheumatoid arthritis.</p>	<p>by liver</p>	<ul style="list-style-type: none"> <li>◆ It precipitates the polysaccharide (fraction C) of pneumococcal cell walls.</li> <li>◆ It is an acute-phase protein</li> <li>◆ CRP measurement with a sensitive assay (Ultra-sensitive CRP) is used for risk assessment of patients with ischemic heart disease</li> </ul>
<p><b>transferrin</b></p>	<p>The major iron-tansport protein in the plasma.</p>	<p>↓ malnutrition, liver disease, inflammatory conditions and malignancy</p>	<p>_____</p>	<ul style="list-style-type: none"> <li>◆ It binds up to 2 atoms of iron per molecule of protein</li> <li>◆ Normally, it is 30% saturated with iron</li> <li>◆ Iron deficiency results in increased hepatic synthesis.</li> <li>◆ It is a negative acute phase protein.</li> </ul>
<p><b>β2-microglobulin</b></p>	<p>_____</p>	<p>↑ impaired clearance by the kidney or overproduction of the protein that occurs in a number of inflammatory diseases such as rheumatoid arthritis and systemic lupus erythrematosus (SLE).</p>	<p>_____</p>	<ul style="list-style-type: none"> <li>◆ It is a component of human leukocyte Antigen (HLA).</li> <li>◆ Found on the surface of most nucleated cells and present in high concentration on lymphocytes</li> <li>◆ Because of its small size, it is filtered by the renal glomeruli but most (&gt;99%) is reabsorbed</li> </ul>

## $\alpha_1$ -Antitrypsin :

It inhibits proteases :

- Proteases arise from: endogenous production, leukocytes and bacteria.

e.g., Digestive enzymes such as trypsin & chymotrypsin Other endogenous proteases: elastase and thrombin

- Infection leads to protease release from bacteria and from leucocytes

### Genetic Polymorphisms of $\alpha_1$ -Antitrypsin:

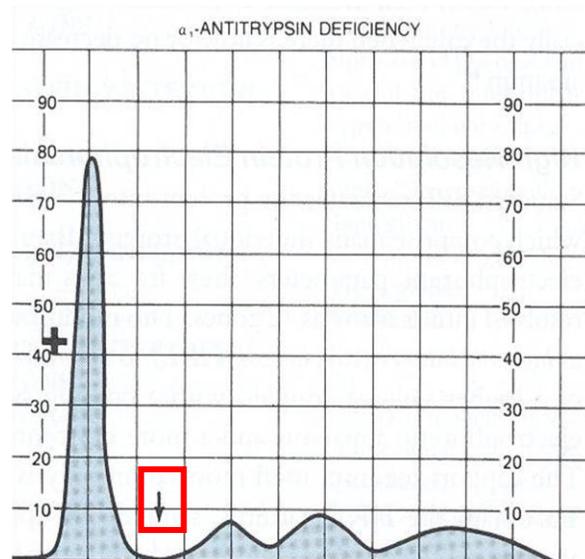
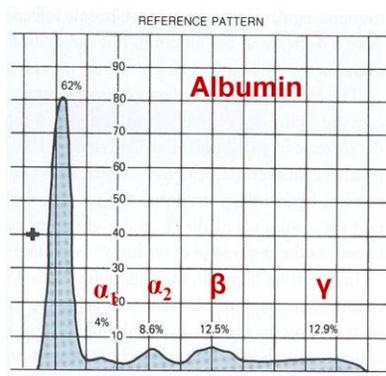
- ⊙ Several variants of  $\alpha_1$ -Antitrypsin alleles occur, the phenotypes being designed by the prefix Pi (Protease inhibitor) and over 30 alleles have been described, these being designed by a letter. The most common type is M.

- ⊙ Inherited deficiency of  $\alpha_1$ -Antitrypsin is most commonly found in the Pi<sup>ZZ</sup> phenotype.

- ⊙ Synthesis of the defective  $\alpha_1$ -Antitrypsin occurs in the liver but there is a failure to secrete the protein .

$\alpha_1$ -Antitrypsin accumulates in hepatocytes and is deficient in plasma.

## $\alpha_1$ -Antitrypsin Pattern of PPs Electrophoresis



all alpha 1 disappears ... because these protein consist 90 % from these group

***Clinical Consequences of  $\alpha_1$ -Antitrypsin Deficiency:***

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

***Laboratory Diagnosis:***

Lack of  $\alpha_1$ -globulin band on protein electrophoresis

Quantitative measurement of  $\alpha_1$ -Antitrypsin by:

Radial immunodiffusion, isoelectric focusing or nephelometry

 **$\alpha$ -Fetoprotein (AFT):**

Conditions associated with	an <b>elevated</b> maternal (الأم الحامل)	a <b>decreased</b> maternal
The disease	Neural tube defects Spina bifida Anencephaly	Down syndrome

**Some PPs may be used as a tumor marker:**

$\beta_2$ -Microglobulin	$\alpha$ -Fetoprotein (AFT)
for leukemia, lymphomas and multiple myeloma.	Hepatoma and testicular cancer

## Hypergammaglobulinemia

Increases Ig levels may result from stimulation of

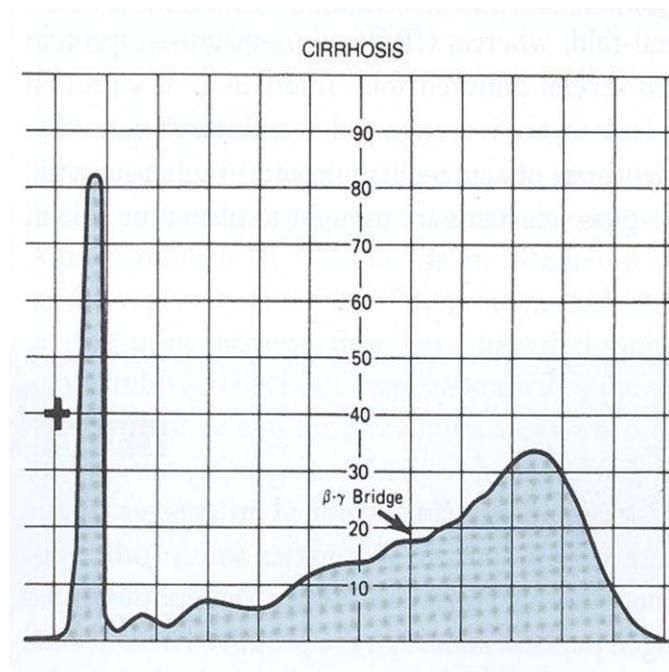
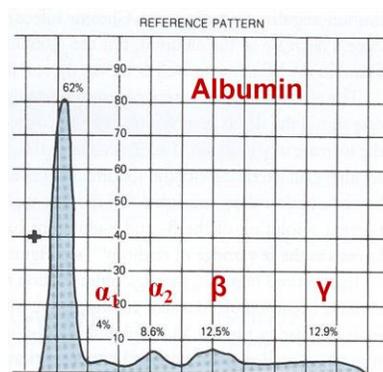
1. many clones of B cells (Polyclonal hypergammaglobulinemia)
2. monoclonal proliferation (Paraproteinemia).

### 1- Polyclonal Hypergammaglobulinemia:

Stimulation of **many clones of B cells** produce a wide range of **antibodies** that appear as **diffuse increase in  $\gamma$ -globulin** on E/P.

e.g., Acute and chronic infections, autoimmune diseases and chronic liver diseases

**Polyclonal Pattern of PPs Electrophoresis**

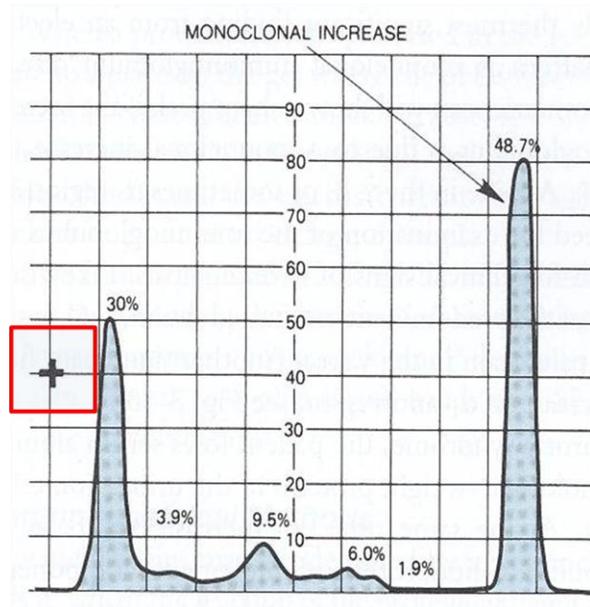
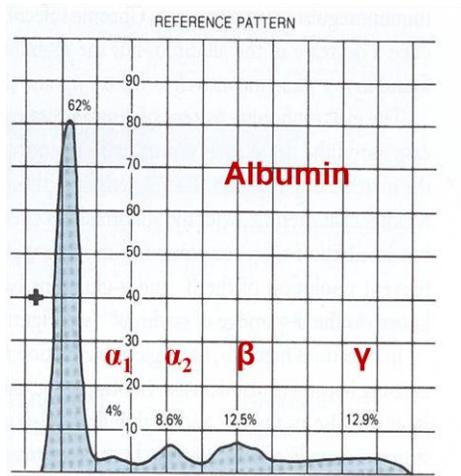


### 2- Monoclonal Hypergammaglobulinemia:

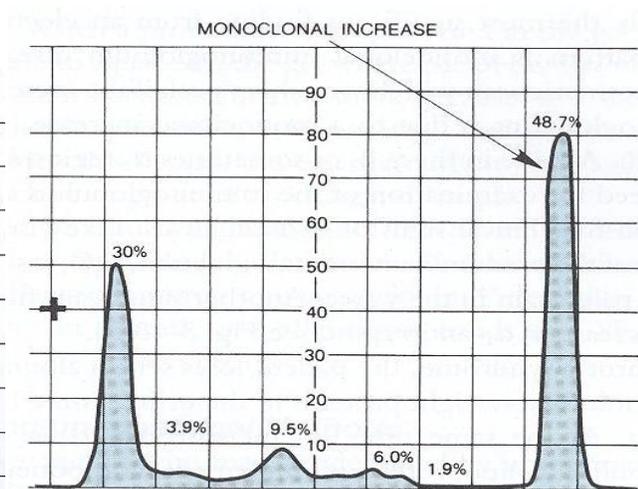
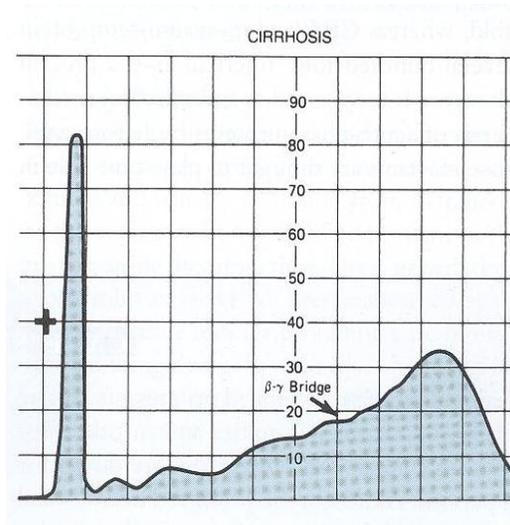
- ⊙ Proliferation of a **single B-cell clone** produces a single Ig which appears as a **discrete densely stained band** (Paraprotein or M band) on E/P.
- ⊙ Paraproteins are characteristic of malignant B-cell proliferation.
- ⊙ Multiple myeloma is the commonest cause of paraproteinemia
- ⊙ **Paraproteinemia**: is rare in chronic lymphatic leukemia and lymphomas.

Monoclonal Pattern of PPs Electrophoresis

Albumin decreases in this case because this case come with renal failure which lead to lose of albumin in urine



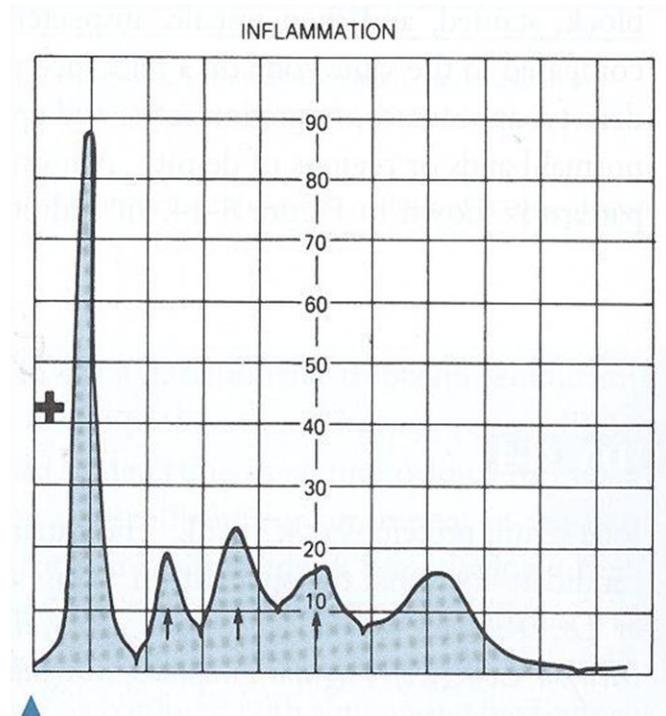
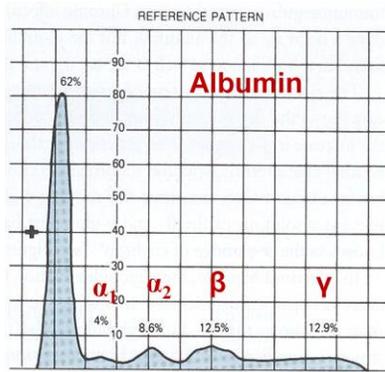
Polyclonal Vs Monoclonal PPs Electrophoresis



### Positive Acute Phase Proteins ( increase conc.) :

- **Stresses** increases the levels of some of plasma proteins as occur in **infection, inflammation , malignancy, trauma or major surgery.**
  - These proteins are termed acute phase reactants and their synthesis is **a part of body's response to injury.**
1.  **$\alpha_1$ -Antitypsin**
  2. **Haptoglobin**
  3. **Ceruloplasmin**
  4. **Fibrinogen**
  5. **C-reactive protein**

### Inflammation Pattern of PPs Electrophoresis



- These acute phase reactants are increased within 24 h of injury in response to humoral mediators (Cytokines – IL-1, IL-6, tumor necrosis factors  $\alpha$  and  $\beta$ , the interferons, and platelet activating factors) which are produced by tissue macrophages, monocytes and endothelial cells.

- Functionions:

1. Binding to polysaccharides in bacterial walls
2. Activating complement
3. Stimulating phagocytosis
4. Protease inhibitors probably inactivate enzymes released from lysosomes and minimize damage that may occur.

### Negative Acute Phase Proteins

- Humoral effects of IL-1 and IL-6 include increased production of ACTH and hence cortisol and inhibition of hepatic synthesis of proteins such as :

1. albumin,
2. prealbumin
3. transferrin



(negative acute phase proteins)

*Good Luck*