Al-Mustaqbal University College
Department of Pharmacy
General Toxicology
4th stage
Lecture: 3

TOXIC RESPONSE OF THE BLOOD

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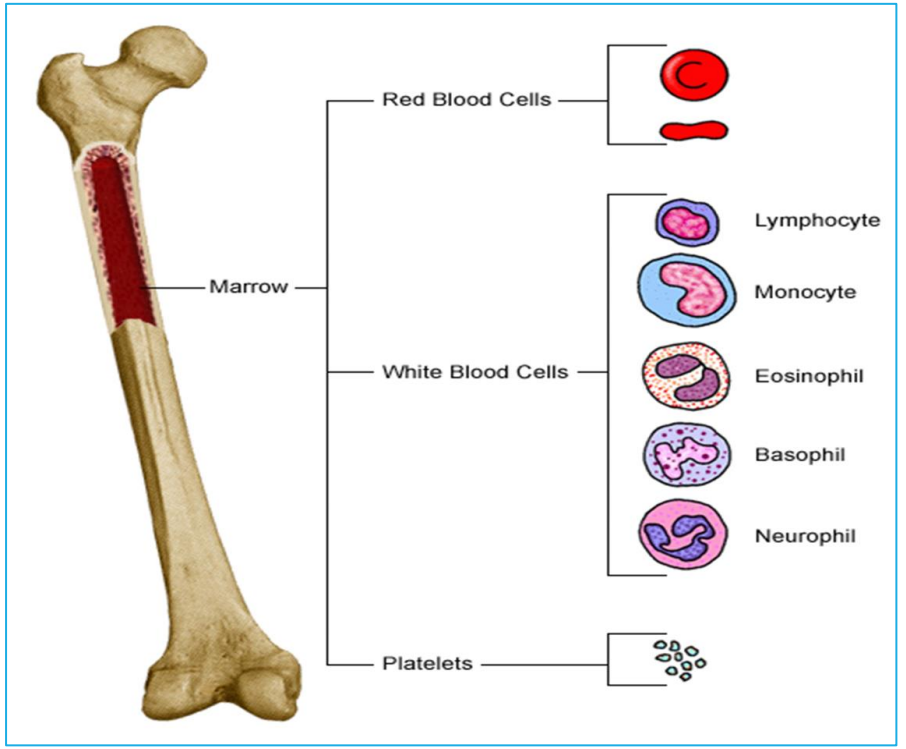
Hematotoxicology

Hematotoxicology is the study of the **adverse effects** of exogenous chemicals on **blood** and **blood-forming** tissues.



Hematotoxicology

✓**Blood or hematopoietic tissue consider as a sensitive target organ for cytoreductive or antimitotic agents because:**

1. **The vital functions that blood cells perform.**
2. **Blood has a high proliferative and regenerative capacity (16 weeks) susceptible to intoxication**

The production rate of blood cells is 1-3 million / second in a healthy adult.

Hematotoxicology

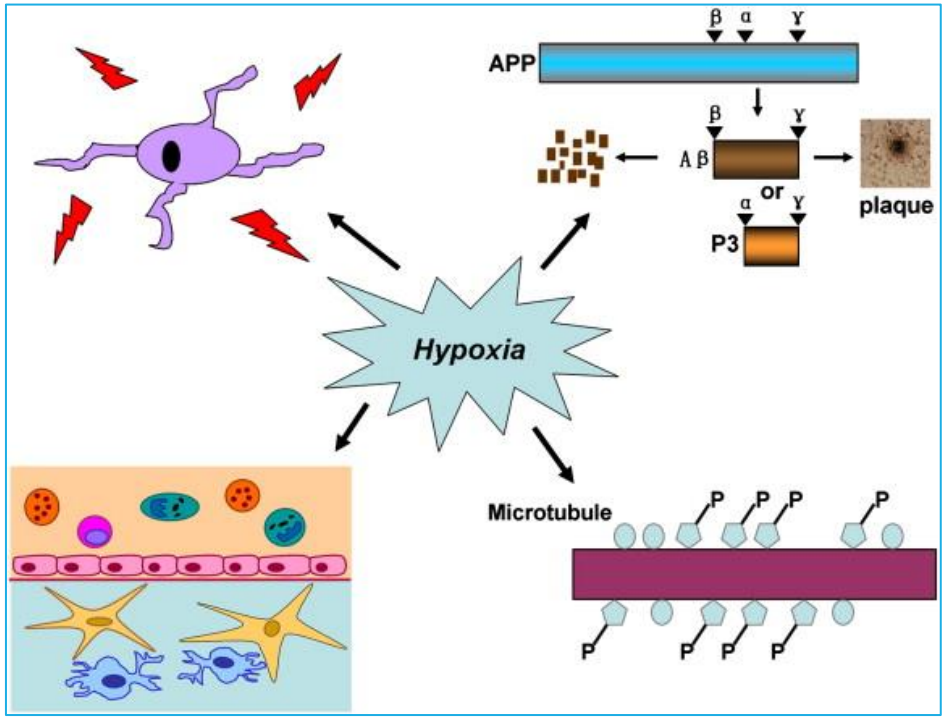
This tissue is also susceptible to secondary effects of toxic agents that affect:

1. **The supply of nutrients such as iron**
2. **The clearance of toxins and metabolites such as urea**
3. **The production of vital growth factors such as erythropoietin.**

Hematotoxicology

The consequences of direct or indirect damage to blood cells may include:

1. **Hypoxia**
2. **Hemorrhage**
3. **Infection**



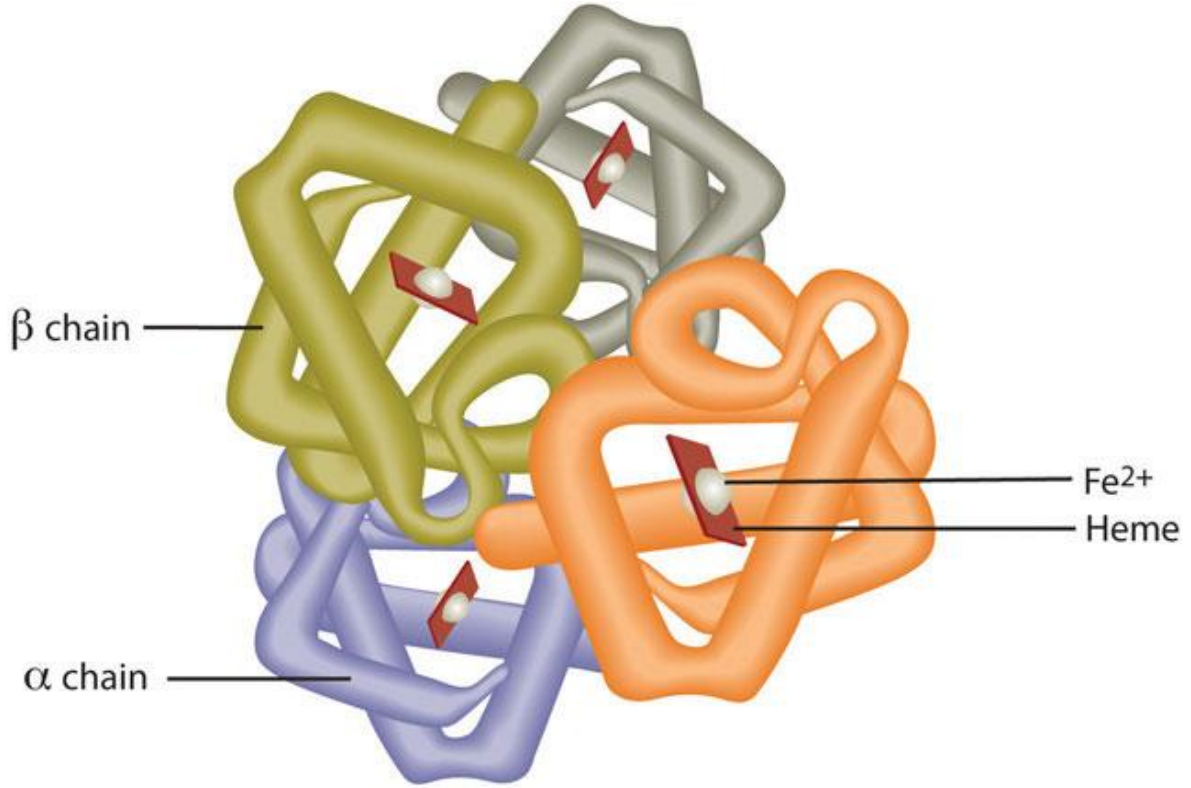
Toxicology of Erythron

Xenobiotics may affect the:

- **1. Production of erythrocytes**
- **2. Function of erythrocytes**
- **3. Survival of erythrocytes**

Erythrocytosis or anemia

Alterations in Red Cell Production:



Adult Hb(HbA)

Mechanisms of alteration in RBCs Production and consequences

1. An **imbalance** between **α- and β-chain** production of **Hb** is the basis of congenital **thalassemia** syndromes and results in **decreased** haemoglobin production and microcytosis.
2. **Xenobiotics** can affect the globin-chain **synthesis** and **alter** the composition of haemoglobin within erythrocytes e.g **hydroxyurea**, which has been found to increase the synthesis of γ-globin chains.

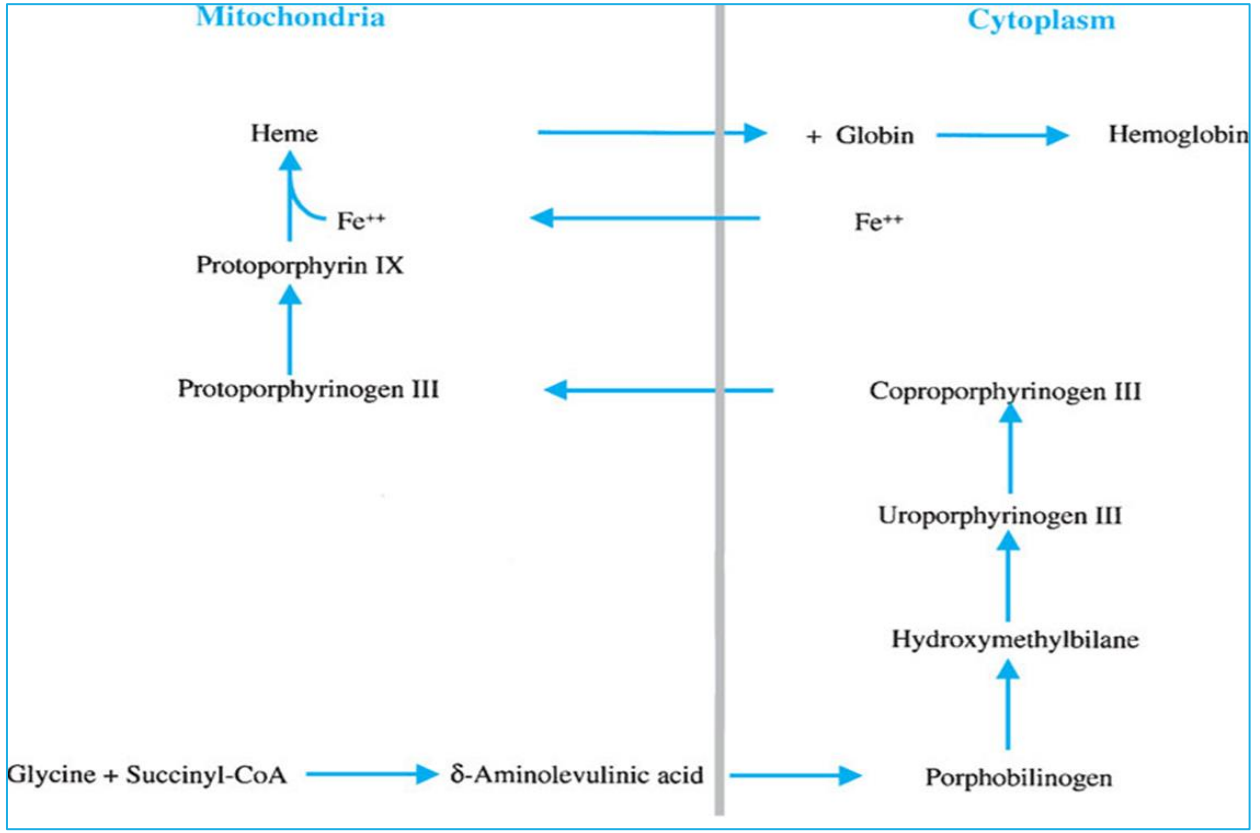
Mechanisms of alteration in RBCs Production and consequences

3. **Synthesis of heme requires the incorporation of iron into a porphyrin ring.**

✓**Iron deficiency is usually the result of dietary deficiency or increased blood loss.**

✓**Any drug that contributes to blood loss, such as NSAIDs, with their increased risk of gastrointestinal ulceration and bleeding, may potentiate the risk of developing iron-deficiency anaemia.**

Mechanisms of alteration in RBCs Production and consequences



Hb synthesis

Mechanisms of alteration in RBCs Production and consequences

4. **Defects in the synthesis of the porphyrin ring of heme can lead to sideroblastic anaemia, with its characteristic accumulation of iron in bone marrow erythroblasts.**

✓**Lead can result in such a condition via inhibiting two enzymes in the heme synthesis pathway, aminolevulinic acid dehydratase (ALAD) and ferrochelatase.**

✓**Others include Ethanol, Chloramphenicol, Isoniazid, Copper chelation/deficiency, Pyrazinamide, and Zinc intoxication.**

Mechanisms of alteration in RBCs Production and consequences

5. **Hematopoiesis requires active DNA synthesis and frequent mitoses.**

✓**Folate and vitamin B12 are necessary to maintain the synthesis of thymidine for incorporation into DNA.**

✓**Deficiency of folate and/or vitamin B12 results in megaloblastic anaemia.**

Mechanisms of alteration in RBCs Production and consequences

- ✓A number of **xenobiotics** may contribute to a deficiency of vitamin B12 and/or folate.
- ✓**B12 deficiency** is caused by Colchicine, Cycloserine, Ethanol, and Isoniazid.
- ✓**Folate deficiency** is caused by Ampicillin, Antimetabolites, Chloramphenicol, and Cholestyramine .

Mechanisms of alteration in RBCs Production and consequences

6. **Many of the antiproliferative drugs used in the treatment of malignancy predictably inhibit hematopoiesis, including erythropoiesis.**

✓**Although new chemicals, such as amifostine, are being developed that may help protect against the marrow toxicity of these agents.**

Mechanisms of alteration in RBCs Production and consequences

7. **Drug-induced aplastic anaemia may represent either a predictable or idiosyncratic reaction to a xenobiotic.**

✓**This life-threatening disorder is characterized by :**

1. **Peripheral blood pancytopenia**
2. **Reticulocytopenia**
3. **Bone marrow hypoplasia**

Pure red cell aplasia

- ✓Is a syndrome in which the decrease in marrow production is limited to the erythroid lineage.
- ✓Pure red cell aplasia is an uncommon disorder that may be due to genetic defects, infection, immune-mediated injury, myelodysplasia, drugs or other toxicants.

Pure red cell aplasia

✓**The drugs most clearly implicated include:**

1. **Isoniazid**
2. **Phenytoin**
3. **Azathioprine**

✓**The mechanism of drug-induced pure red cell aplasia is unknown, but some evidence suggests that it may be immune-mediated**

Megaloblastic Anemia

Xenobiotics Associated with Megaloblastic Anemia

B_{12} DEFICIENCY	FOLATE DEFICIENCY
Paraminosalicylic acid	Phenytoin
Colchicine	Primidone
Neomycin	Carbamazepine
Ethanol	Phenobarbital
Omeprazole	Sulfasalazine
Hemodialysis	Cholestyramine
Zidovudine	Triamterine
Fish tapeworm	Malabsorption syndromes
	Antimetabolites

Alterations in the Respiratory Function of Hemoglobin

✓**Hemoglobin transports** oxygen and carbon dioxide between the lungs and tissues.

✓The **ability** of haemoglobin is **dependent** on:

1. **Intrinsic** (homotropic)
2. **Extrinsic** (heterotropic)

Alterations in the Respiratory Function of Hemoglobin

1. Homotropic Effect (Intrinsic)

- ✓ **Consistent oxidation of heme iron to the ferric state to form methemoglobin.**
- ✓ **Methemoglobin is not capable of binding and transporting oxygen correctly.**

Alterations in the Respiratory Function of Hemoglobin

2. Heterotropic Effects (Extrinsic):

There are 3 major heterotropic (extrinsic) effectors of haemoglobin function:

A. A decrease in pH

- ✓**As an example, lactic acid, carbon dioxide lower the affinity of hemoglobin for oxygen; facilitating the delivery of oxygen to tissues**
- ✓**Clofibric acid and bezafibrate are capable of lowering the oxygen affinity of hemoglobin**

Alterations in the Respiratory Function of Hemoglobin

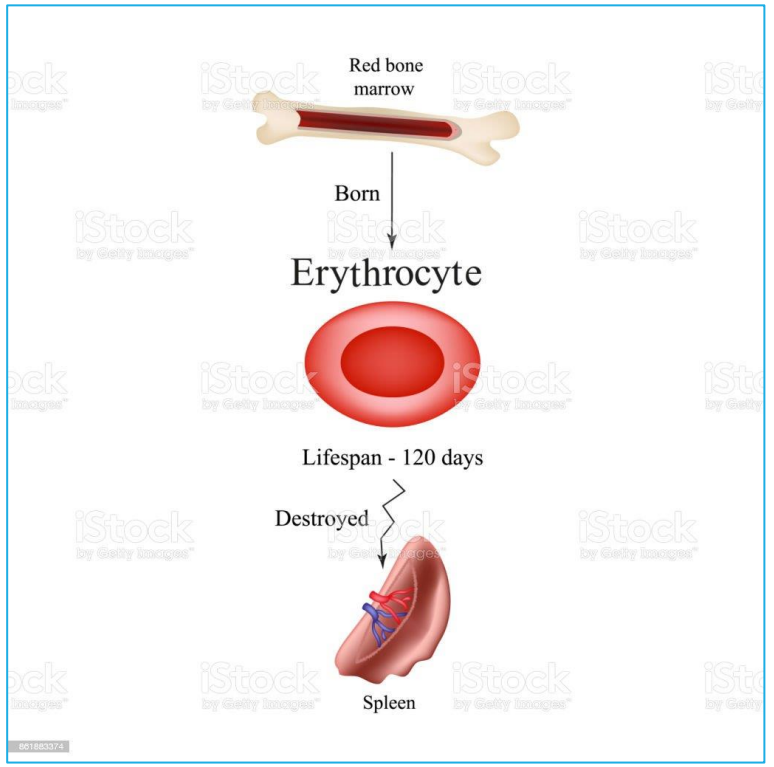
B. Erythrocyte 2,3-bisphosphoglycerate (2,3-BPG)concentration decreases the affinity of haemoglobin for oxygen.

C. Temperature: The oxygen affinity of haemoglobin decrease as the body temperature increases.

- ✓**This facilitates delivery of oxygen to tissues during periods of extreme exercise, and febrile illnesses associated with increased temperature.**

Alterations in Erythrocyte Survival

- ✓The **normal** survival of RBC is about **120 days**.
- ✓Then erythrocytes are **removed** by the **spleen**, where the **iron** is recovered for **reutilization** in heme synthesis.
- ✓Red cell **destruction** leads to **anaemia**



The acquired hemolytic anemias

The acquired hemolytic anemias are often divided into:

- **Nonimmune Hemolytic Anemia**
- **Immune Hemolytic Anemia**

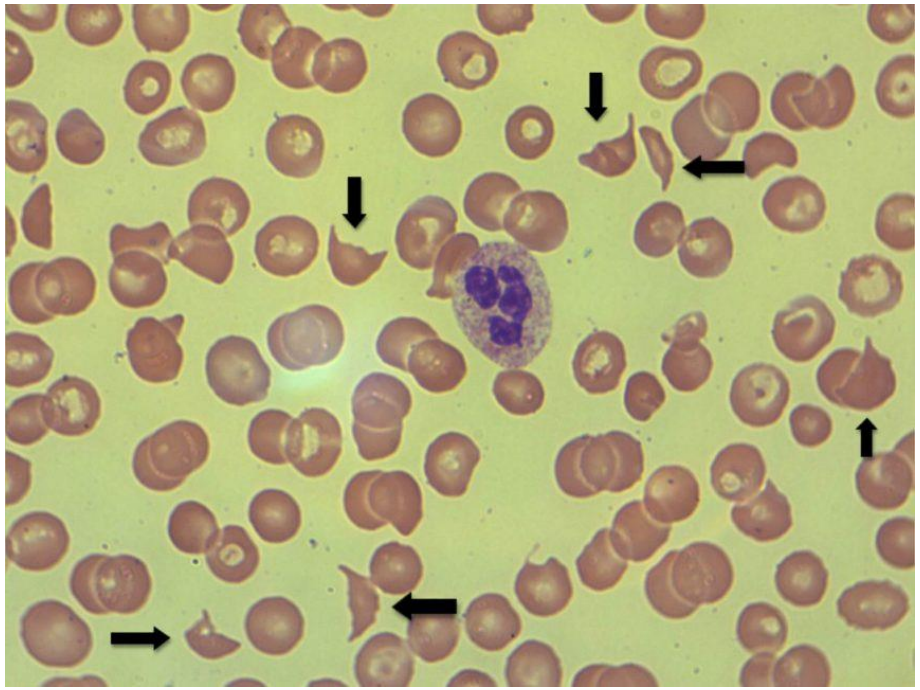
1. Nonimmune Hemolytic Anemia

- ✓**Microangiopathic Anemias**: The formation of **fibrin** strands in the **microcirculation** is a common mechanism for RBC **fragmentation**.
- ✓**Mechanical Injuries:** The erythrocytes appear to be destroyed by mechanical trauma, major thermal burns are also associated with a hemolytic process.
- ✓**Infectious Diseases**: malaria, babesiosis, clostridial infections
- ✓**Oxidative Hemolysis**: the normal respiratory function of erythrocytes generates oxidative stress on a continuous basis.

1. Nonimmune Hemolytic Anemia

Microangiopathic Anemias:

✓The formation of fibrin strands in the microcirculation is a common mechanism for RBC fragmentation.

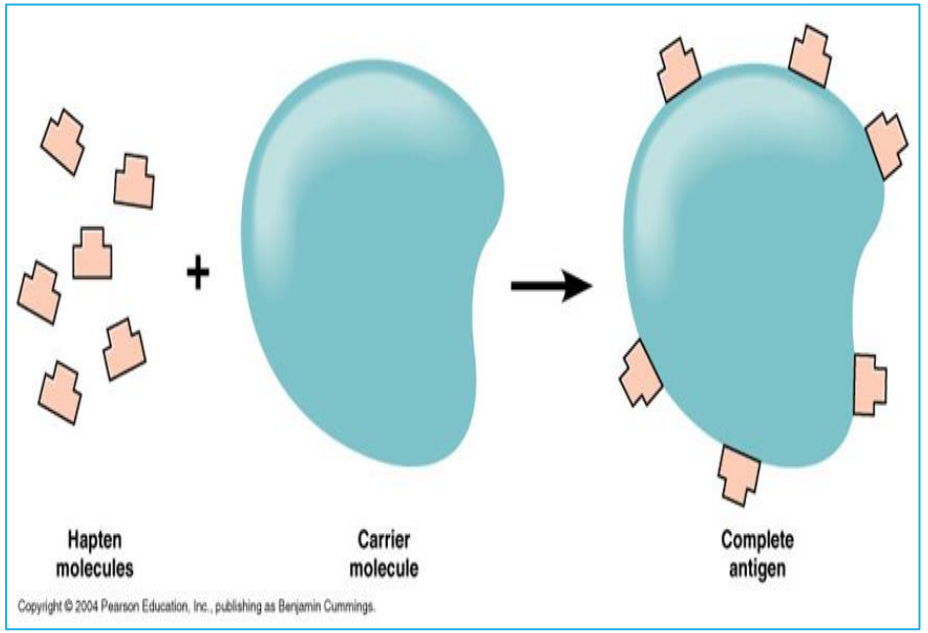


Mechanical Injuries:

✓The erythrocytes appear to be destroyed by mechanical trauma, major thermal burns are also associated with a hemolytic process.

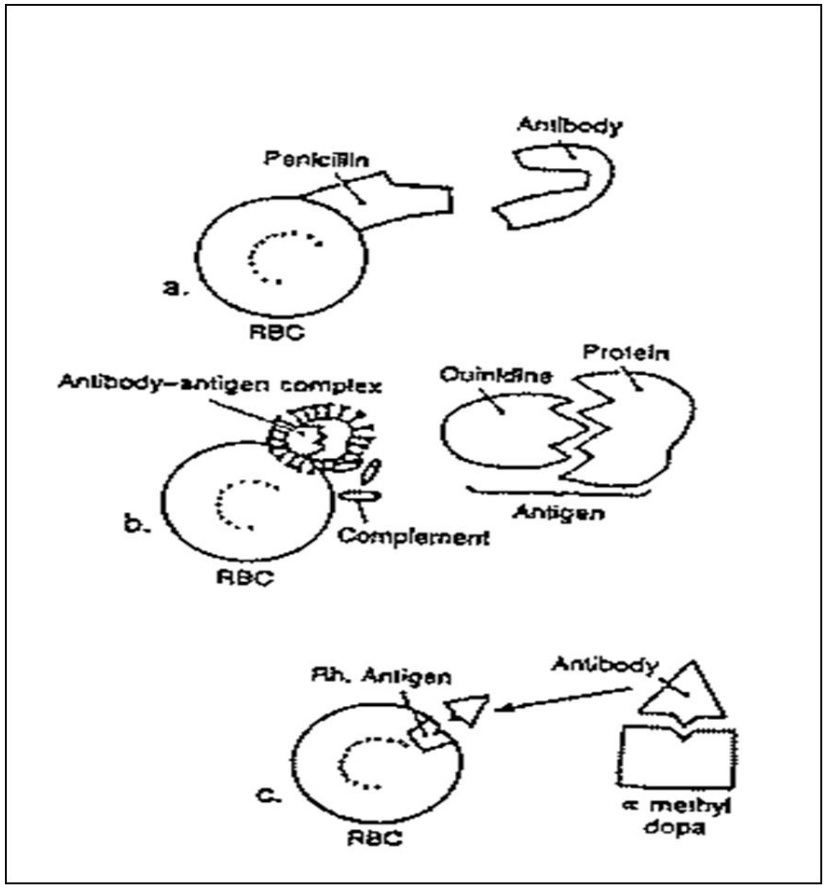
2. Immune mediated hemolytic anemia

- ✓ **Immunologic destruction of RBC is mediated by the interaction of IgG or IgM antibodies with antigens expressed on the surface of the erythrocyte,**
- ✓ **In the case of autoimmune hemolytic anaemia, the antigens are intrinsic components of the patient's own erythrocytes.**



2. Immune mediated hemolytic anemia

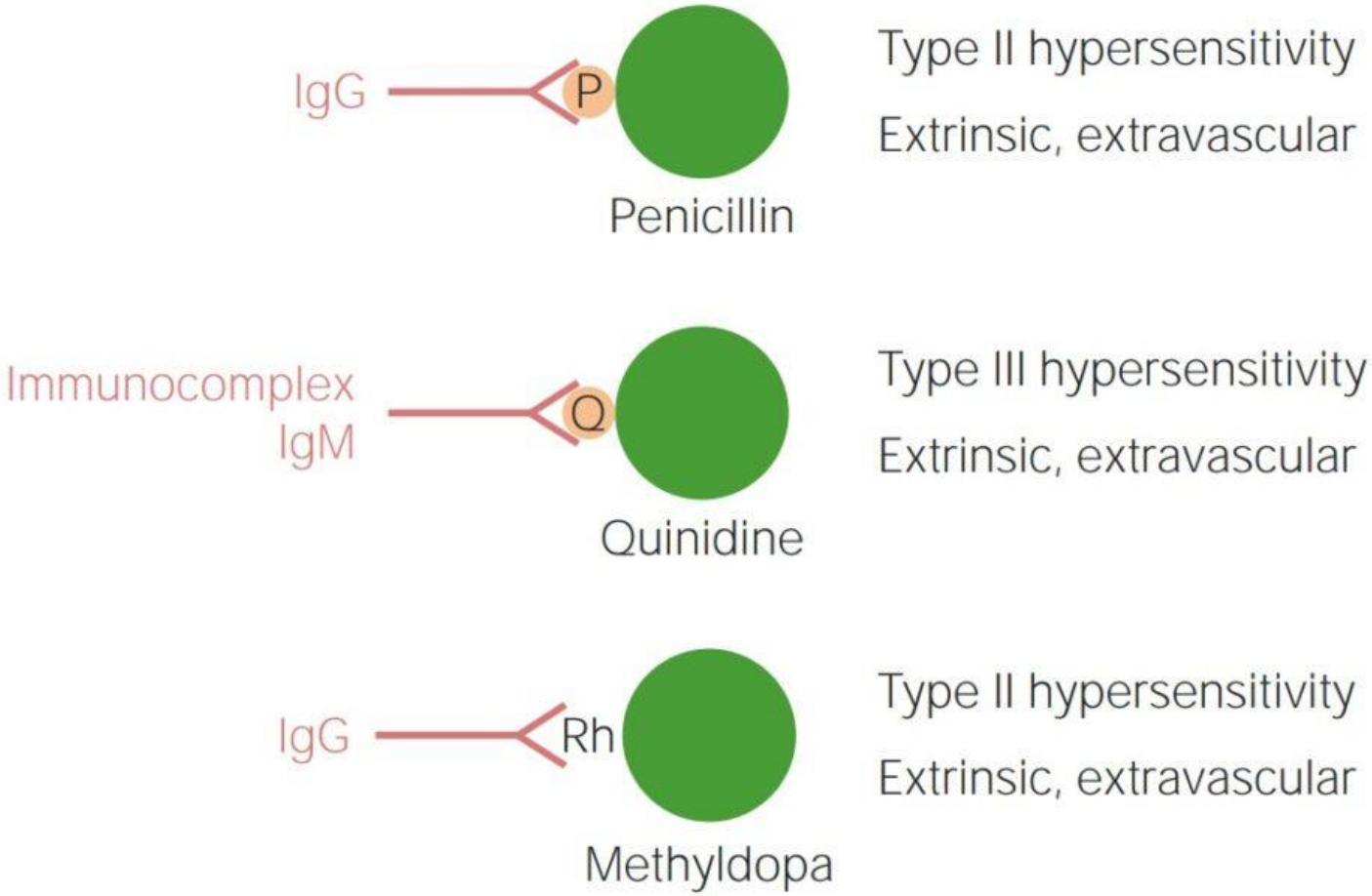
- ✓A number of mechanisms have been implicated in xenobiotic mediated antibody binding to erythrocytes.
- ✓Some drugs, of which **penicillin** is a prototype, appear to bind to the surface of the cell, with the “foreign” drug acting as a **hapten** and eliciting an immune response.
- ✓The **antibodies** that arise in this type of response only bind to **drug-coated erythrocytes.**



2. Immune mediated hemolytic anemia

- ✓Other drugs, of which quinidine is a prototype, bind to components of the erythrocyte surface and induce a conformational change in one or more components of the membrane.
- ✓A third mechanism, for which α-methyldopa is a prototype, results in the production of a drug-induced autoantibody that cannot be distinguished from the antibodies arising in idiopathic autoimmune hemolytic anaemia.

2. Immune mediated hemolytic anemia



THANK YOU
FOR YOUR ATTENTION