Al Mustaqbal University College
Department of Pharmacy
4th stage
Toxicology

Lect. 6

TOXIC RESPONSE OF THE BLOOD (PART1)

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Hematotoxicology

- Hematotoxicology is the study of adverse effects of chemicals, including pharmaceutical drugs, on the blood and blood-forming tissues.
- The vital functions that blood cells perform, together with the susceptibility of this highly proliferative tissue to intoxication, make the hematopoietic system unique as a target organ.

Hematotoxicology

- The blood can be considered as a tissue in its own right, as it comprises around 7% of the body weight of a typical adult who has 4·7 to 5·5 L of blood·
- Some of the vital functions that the blood performs include the delivery of oxygen to tissues throughout the body, maintenance of vascular integrity, and provision of the many affector and effector immune functions necessary for host defense·
- All of these functions require a prodigious proliferative and regenerative capacity·

Hematotoxicology

- The consequences of direct or indirect damage to blood cells and their precursors are predictable and potentially life-threatening.
- They include hypoxia, hemorrhage, and infection.
- In cancer treatment and other clinical settings, hematotoxicity is usually assessed in the context of risk versus benefit.

Hematotoxicology

- **Hematotoxicity may be regarded as:**
- primary, where one or more blood components are directly affected,
- or secondary, where the toxic effect is a consequence of other tissue injury or systemic disturbances.

Hematotoxicology

- Primary toxicity is regarded as among the more common serious effects of xenobiotics, particularly drugs.
- Secondary toxicity is exceedingly common, due to the propensity of blood cells to reflect a wide range of local and systemic effects of toxicants on other tissues.

Hematopoiesis

- The production of blood cells, or hematopoiesis, is a highly regulated sequence of events by which blood cell precursors proliferate and differentiate to meet the vital functions of blood.
- The bone marrow is the principal site of hematopoiesis in humans.

Hematopoiesis

- However, the lung has also recently been shown to be a major site of hematopoiesis and harbors blood stem cells.
- The spleen has little function in blood cell production in the healthy human but plays a critical role in the clearance of defective or senescent cells, as well as in host defense.

Hematopoiesis

- In the human fetus, hematopoiesis can be found in the liver, spleen, bone marrow, thymus, and lymph nodes.
- The bone marrow is the dominant hematopoietic organ in the latter half of gestation and the major blood-cell-producing organ at birth.

Hematopoiesis

- All marrow is active, or "red marrow," at birth.
- During early childhood, hematopoiesis recedes in long bones and, in adults, is confined to the axial skeleton and proximal humerus and femur.

Hematopoiesis

- **While the central function of bone marrow is hematopoiesis and lymphopoiesis,** bone marrow is also one of the sites of the mononuclear phagocyte system (MPS), contributing monocytes that differentiate into a variety of MPS cells located in liver (Kupffer cells), spleen (littoral cells), lymph nodes, and other tissues.

Toxicology of erythron

The erythron consists of:

- The circulating red blood cells (erythrocytes; RBCs) in the blood.
- Their precursors.
- All the body elements concerned in their production.

The Erythrocyte

- Erythrocytes make up 40% to 45% of the circulating blood volume and serve as:

1. The principal vehicle of transportation of oxygen from the lungs to the peripheral tissues.
2. In addition, erythrocytes are involved in the transport of carbon dioxide from tissues to the lung, maintenance of a constant pH in blood, and regulation of blood flow to tissues.

The Erythrocyte

3. Erythrocytes also regulate vascular homeostasis through their ability to transport, produce, and secrete the vasoactive compounds nitric oxide.
4. Erythrocytes express high levels of complement receptor 1 (CR1), through which they regulate the complement pathway and clear C3-opsonized immune complexes.

The Erythrocyte

- Xenobiotics may affect the production, function, and/or survival of erythrocytes.
- These effects are most frequently manifest as a change in the circulating red cell mass, usually resulting in a decrease (anemia).

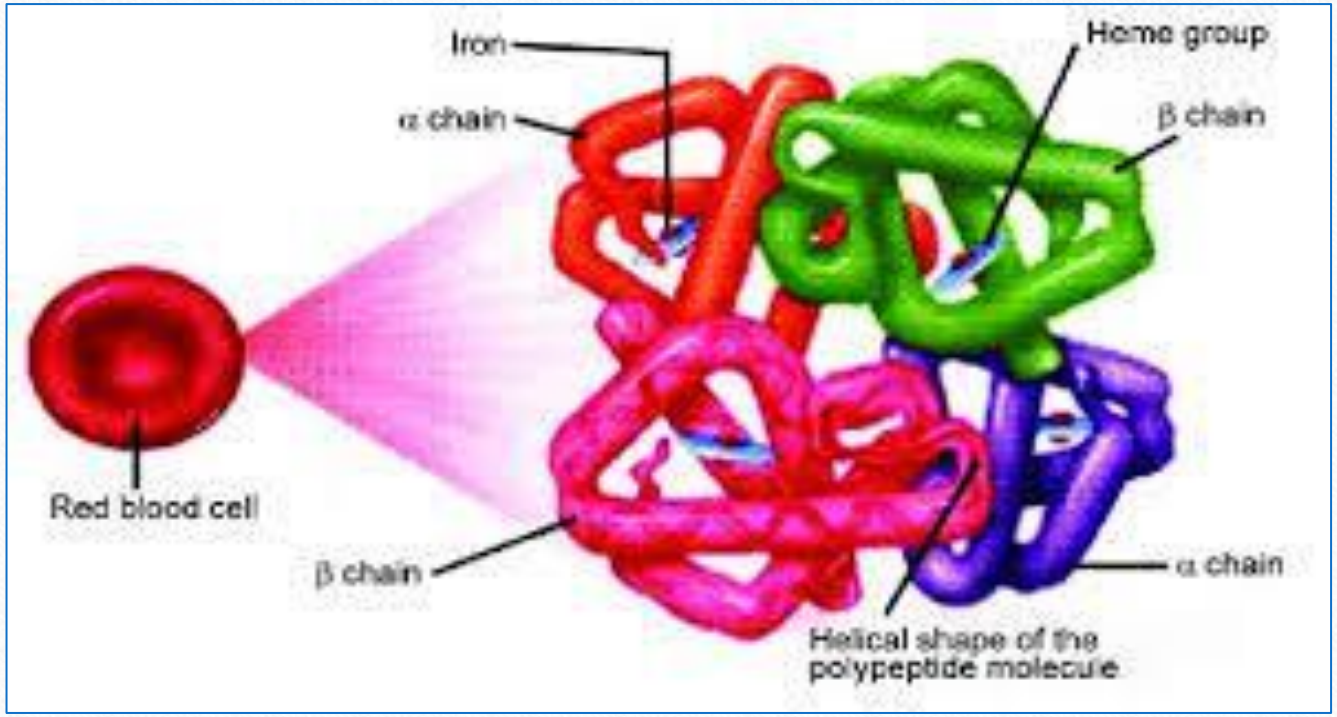
The Erythrocyte

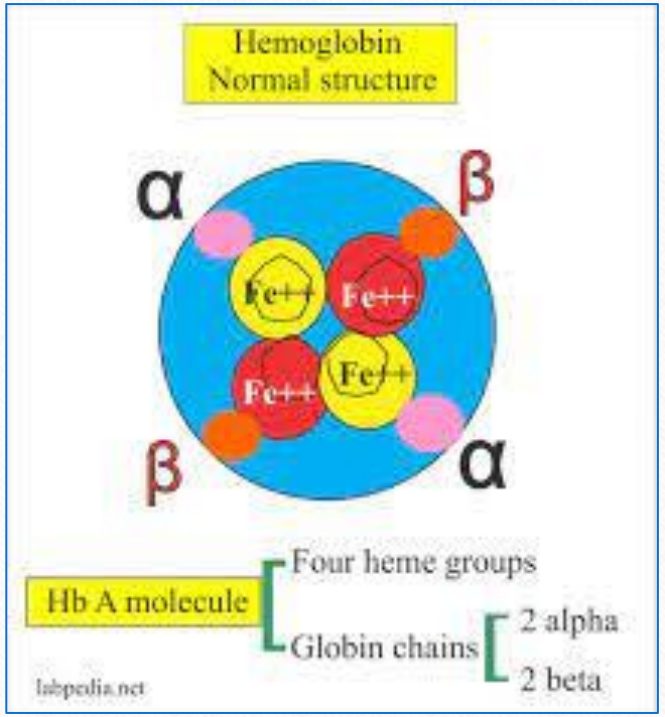
- Occasionally, chemicals that increase oxygen affinity lead to an increase in red cell mass (erythrocytosis), which can be caused by polycythemia, but this is distinctly less common.
- polycythemia (an overproduction of RBCs in absence of an appropriate stimulus, e.g., altitude).

Alterations in Red Cell Production

- Erythrocyte production is a continuous process that is dependent on frequent cell division and a high rate of hemoglobin synthesis.
- Human adult hemoglobin (hemoglobin A), the major constituent of the erythrocyte cytoplasm, is a tetramer composed of two α-globin and two β-globin chains, each with a heme residue located in a stereospecific pocket of the globin chain.
- Synthesis of hemoglobin is dependent on coordinated production of globin chains and heme moieties.

Hemoglobulin A structure

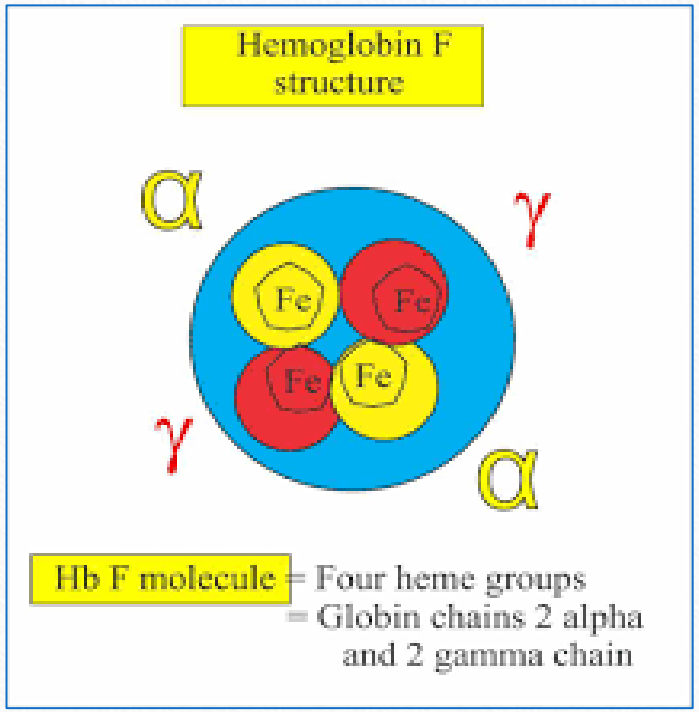




Alterations in Red Cell Production

- The γ -globin chains are a normal constituent of hemoglobin during fetal development, replacing the β chains in the hemoglobin tetramer (hemoglobin F, α2 γ2).
- Hemoglobin F has a higher affinity for oxygen than hemoglobin A and can protect against crystallization (sickling) of deoxyhemoglobin S in sickle cell disease.

Hemoglobulin F structure



Alterations in Red Cell Production

- An imbalance between α- and β-chain production is the basis of congenital thalassemia syndromes and results in decreased hemoglobin production and microcytosis.
- Xenobiotics can affect globin chain synthesis and alter the composition of hemoglobin within erythrocytes.
- The most well-known example is hydroxyurea, which increases the synthesis of γ-globin chains.

Anemia

- There are two general mechanisms that lead to true anemia either decreased production or increased erythrocyte destruction.
- Both mechanisms may be operative in some disorders, or a combination may arise due to the imposition of a second disorder on a compensated underlying problem.
- For example, patients with compensated congenital hemolytic anemias are very susceptible to additional insults that may precipitate an acute drop in a previously stable red cell mass, such as parvovirus infection-associated suppression of erythropoiesis.

Iron deficiency anemia

- Synthesis of heme requires incorporation of iron into a porphyrin ring.
- Iron deficiency is usually the result of dietary deficiency or increased blood loss.
- Drugs that contribute to blood loss, such as nonsteroidal anti-inflammatory drugs, with their increased risk of gastrointestinal ulceration and bleeding, may potentiate the risk of developing iron deficiency anemia.

Sideroblastic anemia

- Defects in the synthesis of porphyrin ring of heme can lead to sideroblastic anemia, with its characteristic accumulation of iron in bone marrow erythroblasts.
- A number of xenobiotics can interfere with one or more of the steps in erythroblast heme synthesis and result in sideroblastic anemia.

Sideroblastic anemia

- The most well-known of these is lead, which inhibits two enzymes in the heme synthesis pathway, aminolevulinic acid dehydratase (ALAD) and ferrochelatase.
- Others are include Ethanol, Chloramphenicol, Isoniazid, Copper chelation/deficiency, Pyrazinamide, and Zinc intoxication.

Megaloblastic anemia

- Hematopoiesis requires active DNA synthesis and frequent mitoses.
- Folate and vitamin B12 are necessary to maintain synthesis of thymidine for incorporation into DNA.
- Deficiency of folate and/or vitamin B12 results in megaloblastic anemia, with its characteristic morphologic and biochemical changes.

Megaloblastic anemia

- A number of xenobiotics may contribute to a deficiency of vitamin B12 and/or folate, leading to megaloblastic anemia.
- B12 DEFICIENCY is caused by Colchicine, Cycloserine, Ethanol, and Isoniazid. While FOLATE DEFICIENCY is caused by Ampicillin, Antimetabolites, Chloramphenicol, Cholestyramine ...etc

Megaloblastic anemia

Drugs that cause megaloblastic anemia have a number of different mechanisms of action including:

1·Modulation of purine metabolism,
2·Interference with pyrimidine synthesis,
3·Decreased absorption of folic acid,
4·Folate analogue activity,
5·Decreased absorption of vitamin B12,
6·Increased excretion of vitamin B12

Aplastic anemia

- Drug-induced aplastic anemia may represent either a predictable or idiosyncratic reaction to a xenobiotic.
- This life-threatening disorder is characterized by peripheral blood pancytopenia, reticulocytopenia, and bone marrow hypoplasia.

Aplastic anemia

- Agents such as benzene and radiation have a predictable effect on hematopoietic progenitors, and the resulting aplastic anemia corresponds to the magnitude of the exposure to these agents.
- In contrast, idiosyncratic aplastic anemia does not appear to be related to the dose of the agent initiating the process.

Aplastic anemia

- A long list of chemicals has been associated with the development of aplastic anemia among them:
- Penicillin, Allopurinol, Tetracycline, Methicillin, Sulfonamides, Chlortetracycline, ... etc

THANK YOU FOR YOUR ATTENTION