Blood Toxicology

- Introduction
  - Hematopoiesis – Bone Marrow
    - Pluripotent Cell
    - Megakaryocytes, Erythrocytes, Leukocytes
  - Functions of Blood
    - Immunity & non specific defenses
    - CO₂ & O₂ transport
    - pH
    - Coagulation
    - Osmotic balance
    - Nutrient & Waste transport
    - Communications path

Toxic Effects & Pathology

- Erythropoiesis
  - Immature RBCs – reticulocytes & nucleated blast forms
  - Chronic hemolytic diseases
  - Megaloblastic macrocytic anemia
  - Microcytic hypochromic anemia
  - Pancytopenia
  - Aplastic Anemia
Toxic Effects & Pathology

• Platelets
  – Aggregation
    • Aspirin
    • NO
  – Thrombocytopenia <20,000/µL
    • Congenital hemorrhage disorders
    • Myelosuppressive drugs
    • Immune suppressors – Quinedine & Phenacetin

Toxic Effects & Pathology

• Leukocytes
  – Inhibition of diapedesis – glucocorticoids
  – Granulocytopenia <3,000/µL
    • Alkylating agents & antimetabolites
    • Anti-inflammatory drugs
    • Anticonvulsants
    • Toxic shock

Toxic Effects & Pathology

• Erythrocytes
  – Anemia
    • Hemolysis
    • Immunologic sensitization
  – Polycythemia
    • Altitude effect
    • Erythropoietin
    • Co ion
Chemically Induced Hypoxia

- Arterial hypoxia – lower than normal $P_{O_2}$ in arterial blood.
- Anemic hypoxia – lowered oxygen carrying capacity when arterial $P_{O_2}$ and rate of blood flow is normal or elevated.
- Stagnant (hypokinetic) hypoxia – decreased rate of blood flow, as in heart failure & uncorrected vasodilatation.
- Histotoxic hypoxia – under normal oxygenation or elevated $P_{O_2}$, tissue cells are unable to utilize $O_2$.

O$_2$ Binding to Hemoglobin

- Hemoglobin (Hb) – MW=67k; four globin chains, 2$\alpha$ and 2$\beta$, noncovalently bound to porphorynic heme groups.
- Reversible $O_2$ binding involving cooperativity between the chains:
  - $Hb(O_2)_4 \leftrightarrow Hb(O_2)_3 + O_2$ K$_1$
  - $Hb(O_2)_4 \leftrightarrow Hb(O_2)_2 + O_2$ K$_2$
  - $Hb(O_2)_4 \leftrightarrow Hb(O_2)_1 + O_2$ K$_3$
  - $Hb(O_2)_4 \leftrightarrow Hb + O_2$ K$_4$

O$_2$ Binding to Hemoglobin

- Physiological regulators
  - pH – Bohr effect
  - 2,3-diphosphoglycerate (2,3 – DPG)
- Toxin effects on dissociation curve
  - Left shift – increased affinity for $O_2$: aromatic Benzaldehydes
  - Right shift – decreased affinity for $O_2$: Clofibric acid, Benzaafibrate
Hemoglobin Dissociation

Methemoglobin

- Methemoglobin production
  \( \text{HbFe}^{2+} \rightarrow \text{HbFe}^{3+} \)
  - \( \text{NaNO}_2, \text{H}_2\text{NOH} \)
  - Aromatic amino and nitro compounds – aniline, nitrobenzene, p-Aminopropiophenone
- Methemoglobin reductase (cyt b₅)
  - NADH and NADH diaphorase
  - Alternative reduction pathway – NADPH diaphorase
Histotoxic Hypoxia

- Interference with utilization of O₂ as the final e⁻ acceptor.