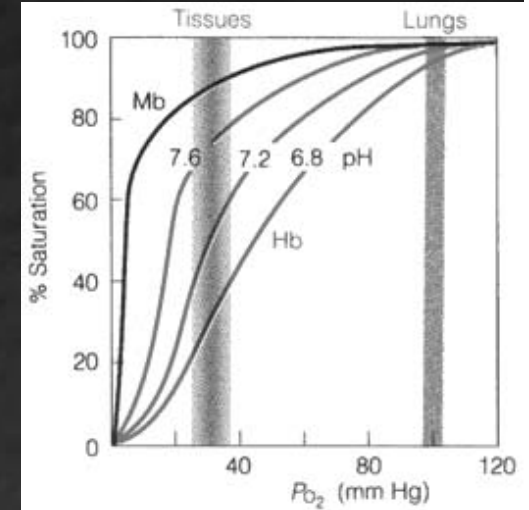
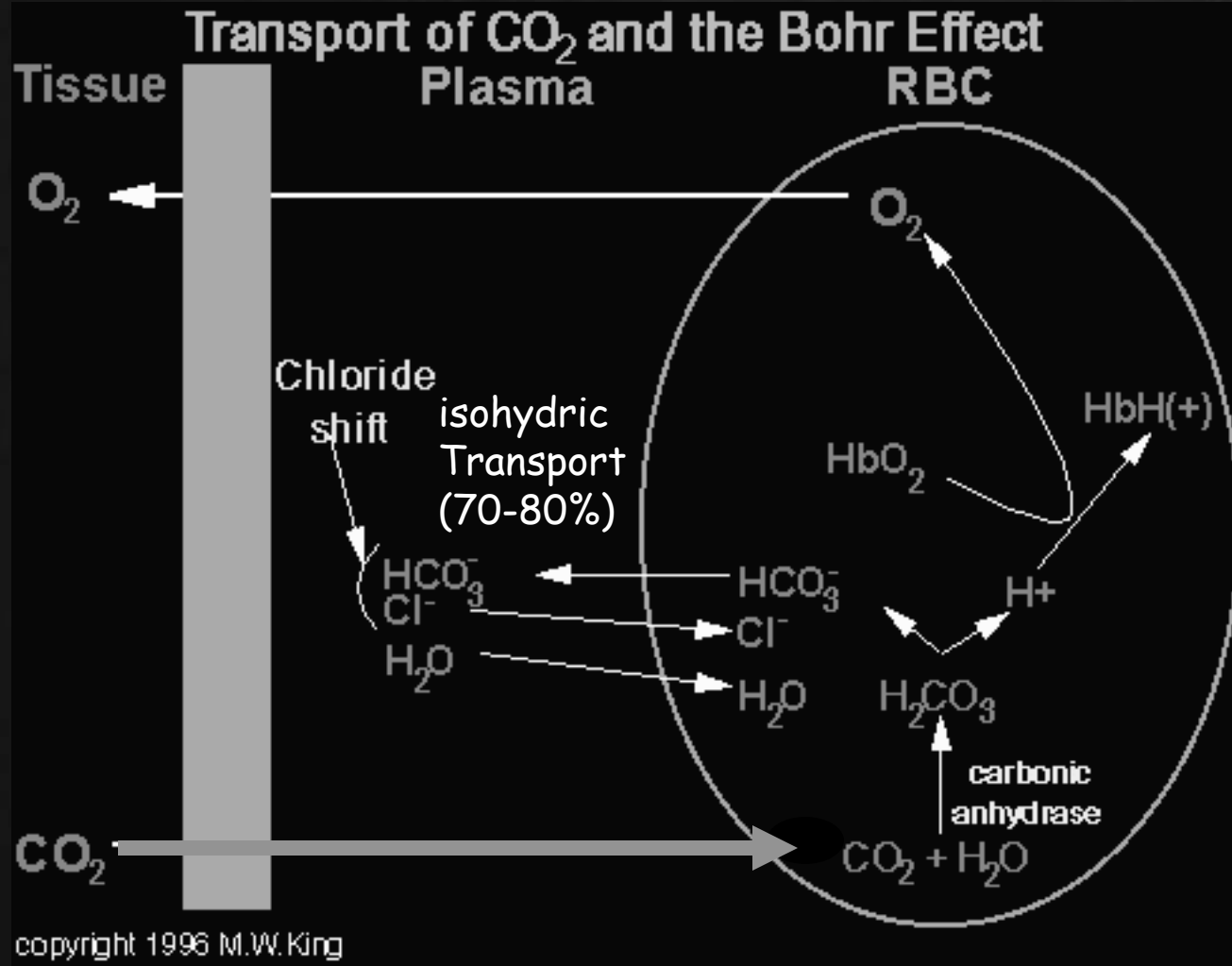
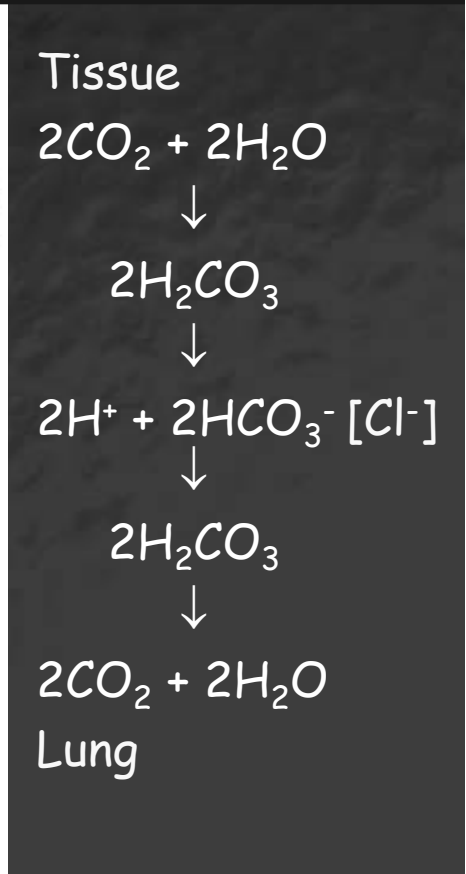
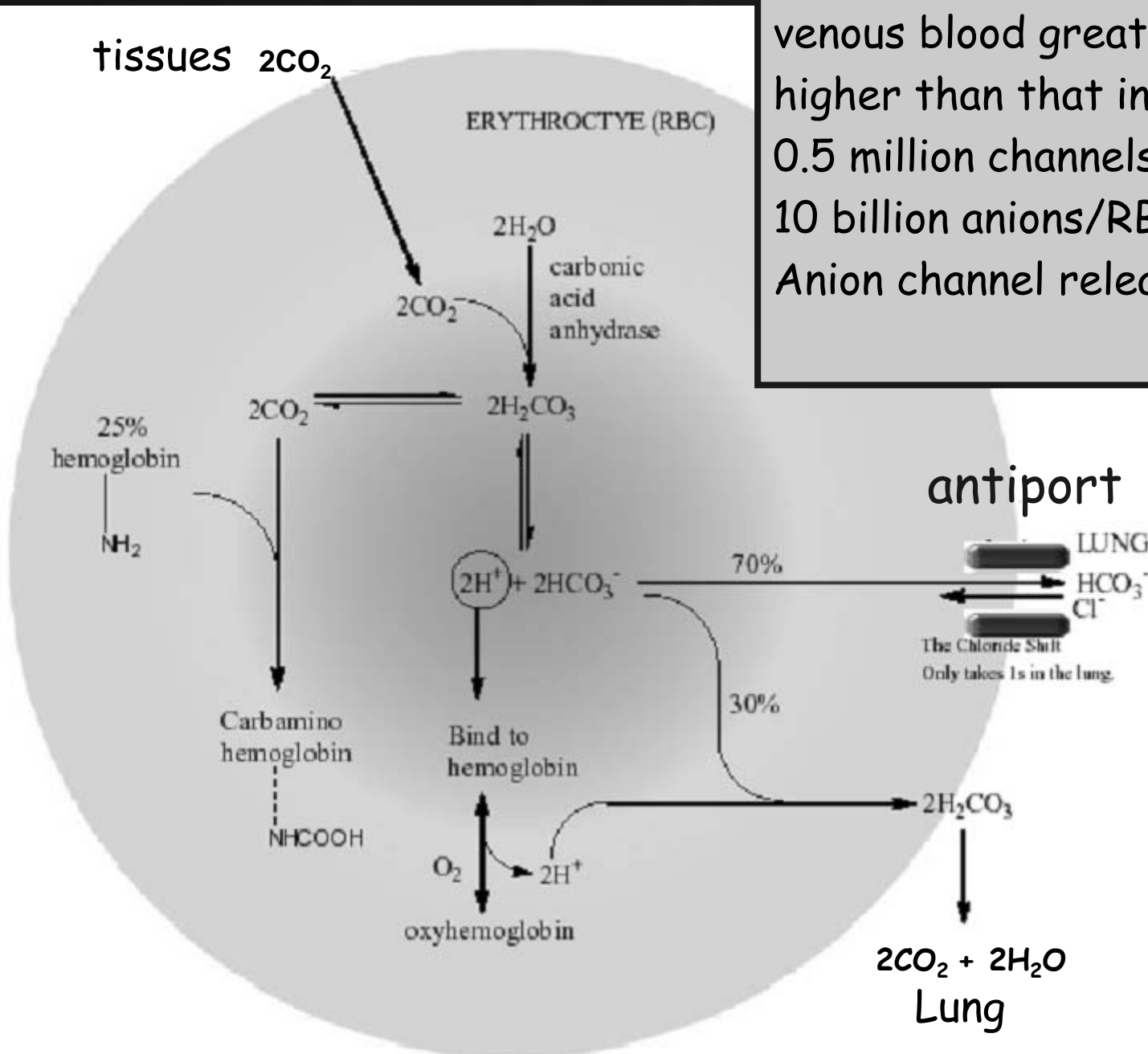


Isohydric transport:

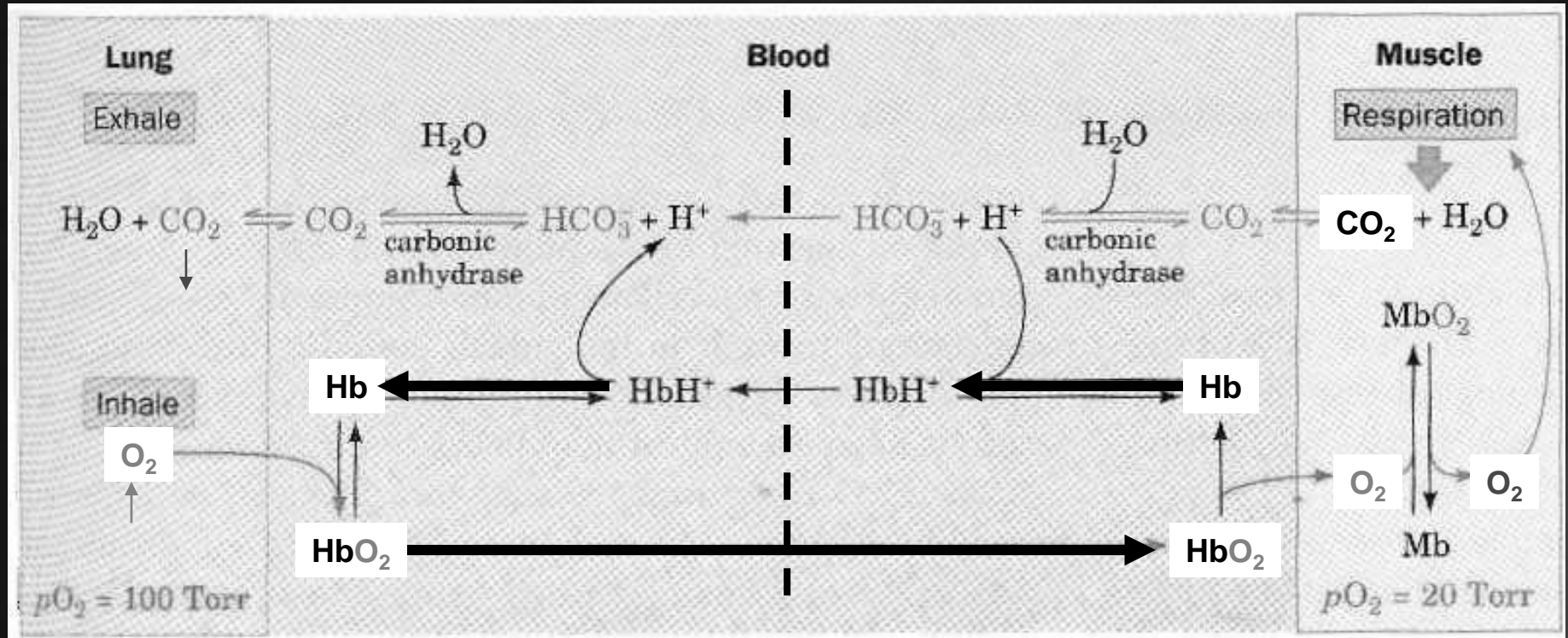


CO₂ induces chloride shift:

The chloride content of red cells in venous blood greater than 20 fold higher than that in arterial blood.
 0.5 million channels/RBC
 10 billion anions/RBC
 Anion channel releases HCO₃⁻ in lung.



Systemic O₂ delivery:

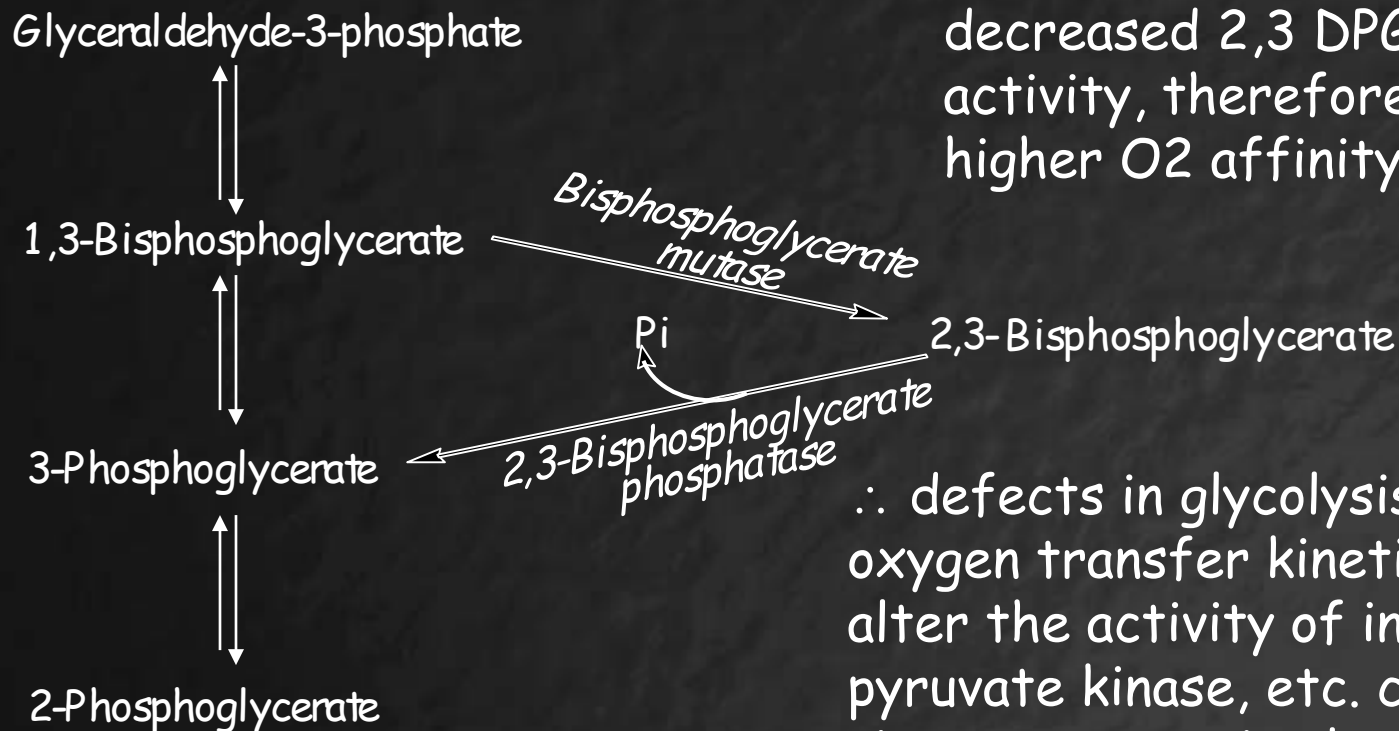


Lungs: low CO₂ ∴ Hb picks up O₂

Tissues: high CO₂, low pH ∴ Hb releases O₂

One more trick: 2,3 bisphosphoglycerate (BPG):

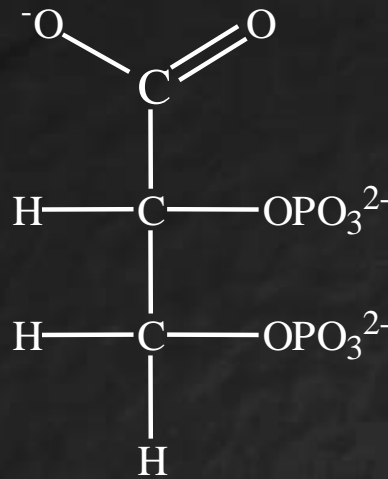
- 2,3 DPG is synthesized as a side reaction from glycolysis (Raport-Luenberg)
- 2,3 DPG decreases the O₂ affinity of Hb by stabilizing the deoxygenated form of hemoglobin through ionic cross-linking of beta chains (salt bridges). It therefore acts to enhance O₂ release.



Fetal hemoglobin shows decreased 2,3 DPG binding activity, therefore it exhibits higher O₂ affinity

∴ defects in glycolysis will alter oxygen transfer kinetics. Drugs which alter the activity of in hexokinase, pyruvate kinase, etc. can thus alter tissue oxygenation levels.

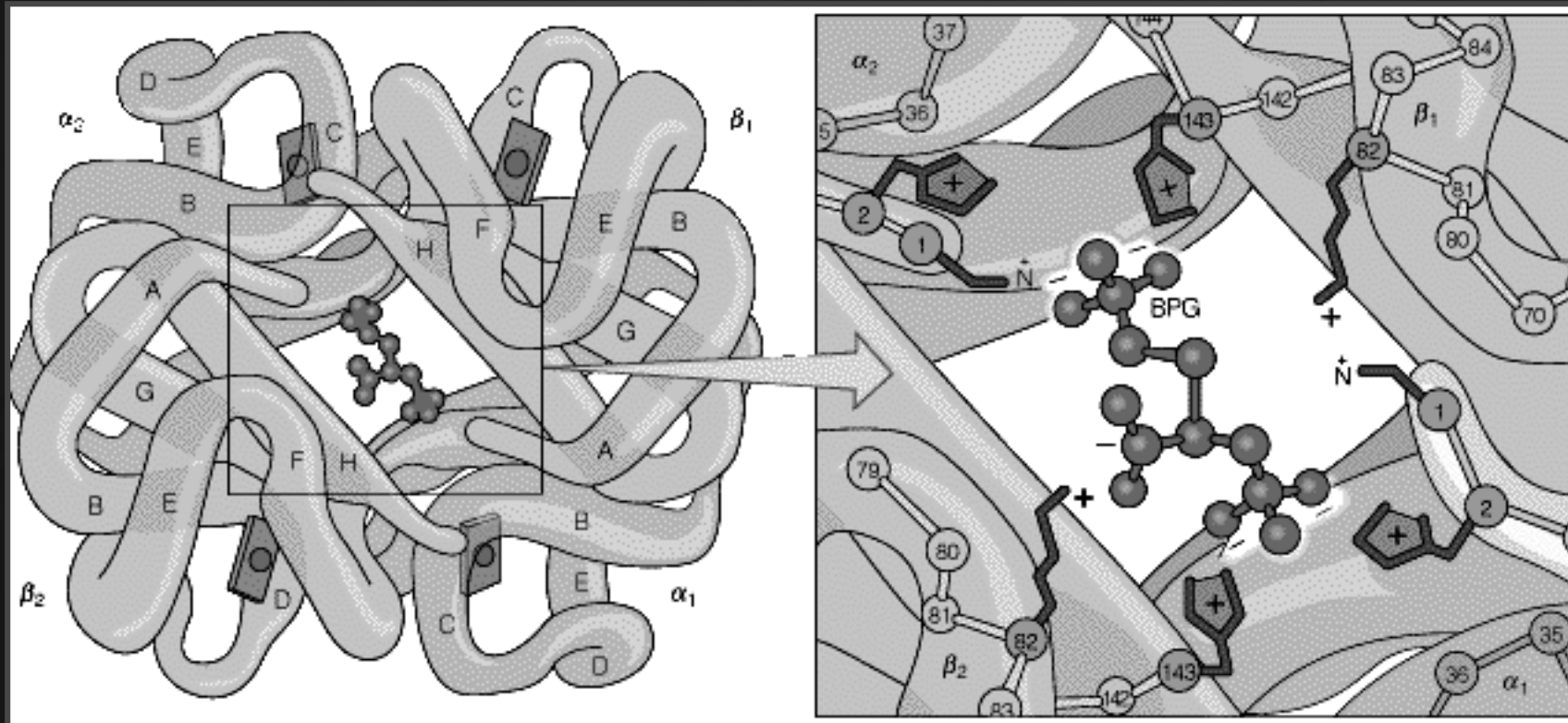
Role of 2,3 bisphosphoglycerate in O₂ transport:



2,3-BPG

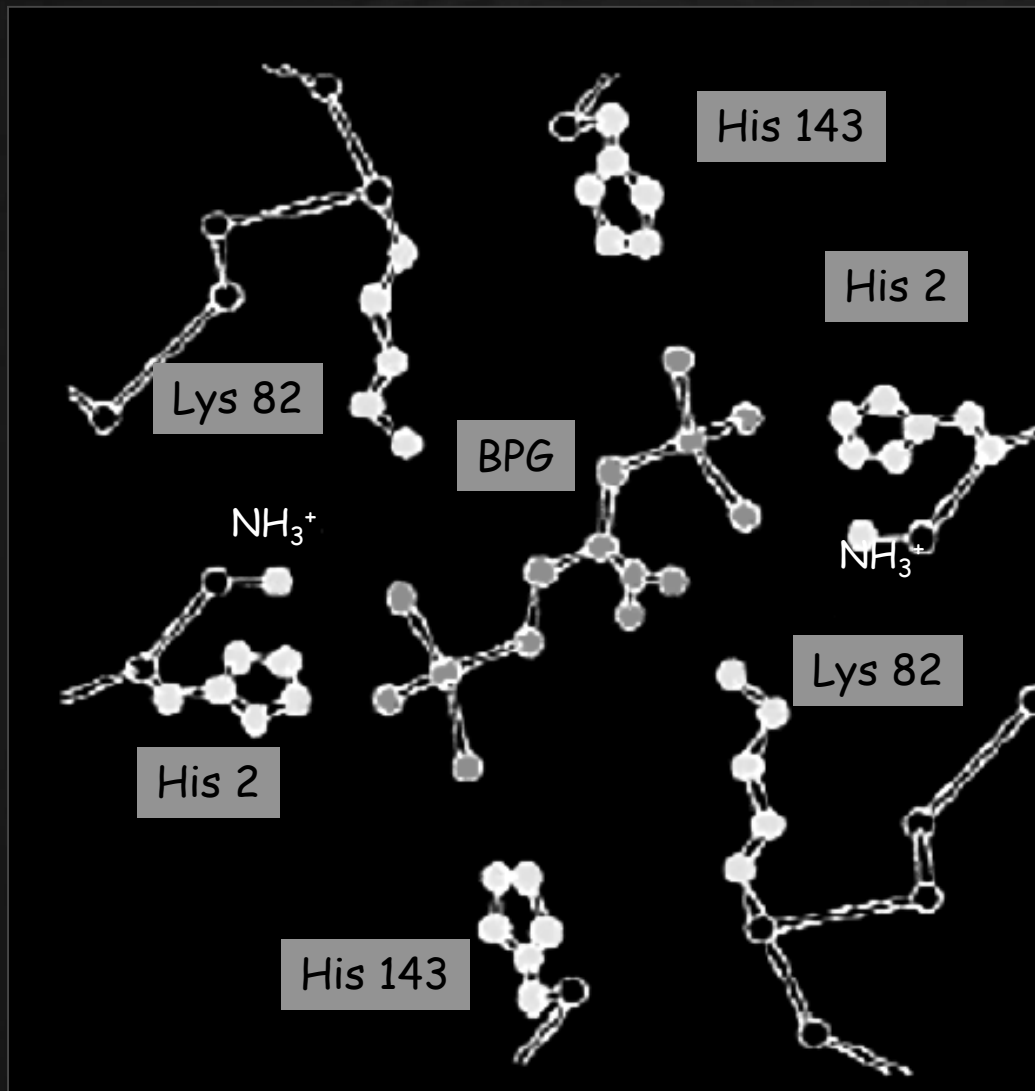
- 5 negative charges and binds electrostatically
- 2,3-BPG binds tightly to deoxyHb, weakly to oxyHb
(i.e. stabilizes the T form of Hb through B-B interactions)
- ↓ O₂ affinity of Hb by keeping Hb in deoxy. conformation
- allows unloading of O₂ in tissues (increases P₅₀ of Hb)

Interaction of 2,3 BPG with Hemoglobin:



(from Devlin 9.47)

Interaction of 2,3 BPG with Hemoglobin:



The five negative charges on DPG coordinate with positive charge on the globin chain. Coordination stoichiometry is 1:1.

Stryer Fig. 7-26

Regulatory features of 2,3 BPG:

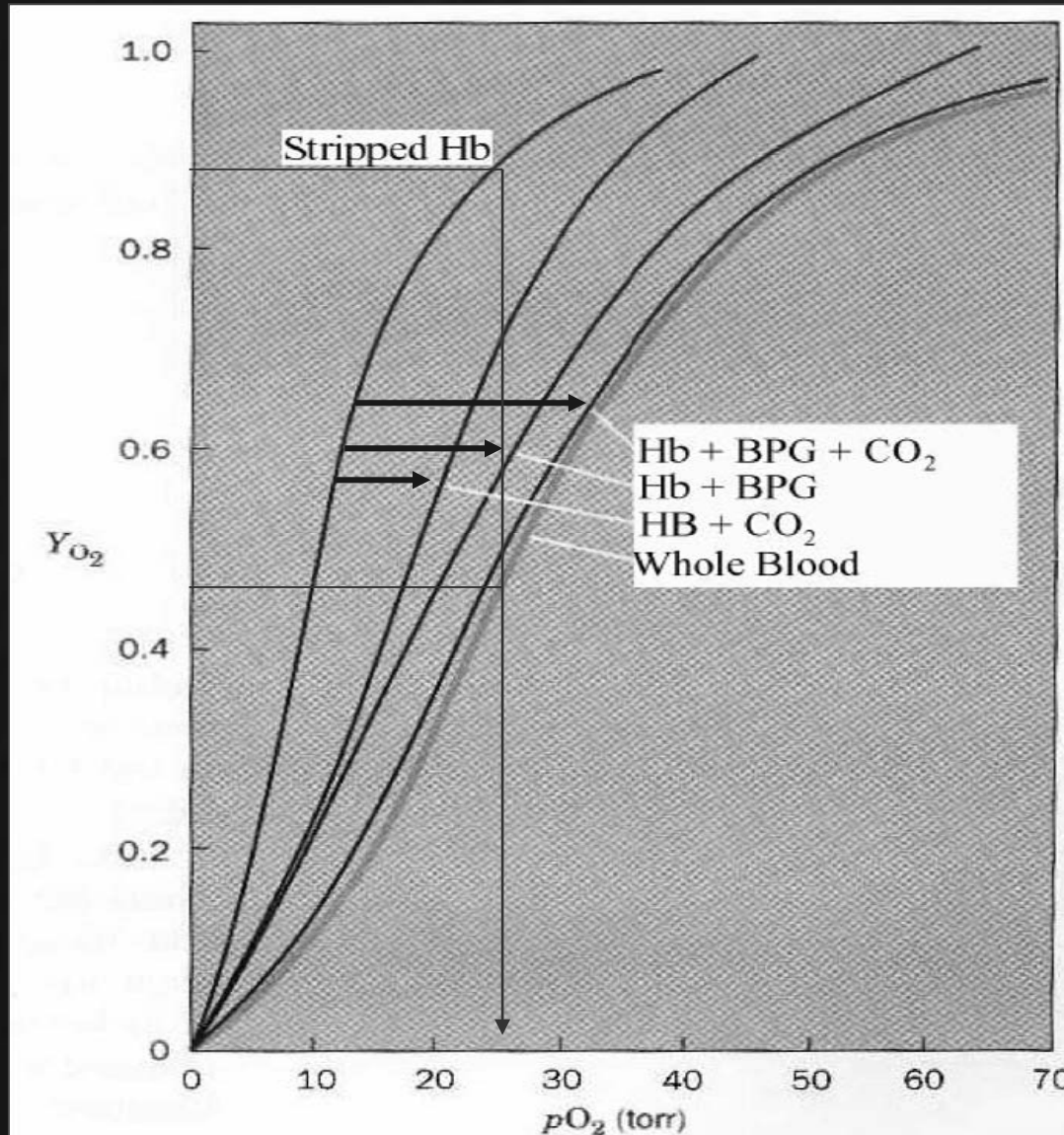
High altitudes adaptation:

2,3-BPG levels double after 2 days $\therefore \uparrow P_{50}$ so more O_2 unloaded in tissues

Fetal RBCs:

In the fetus, BPG binding to Hb is weaker than mother's Hb,
Therefore: $P_{50} \downarrow$ so $\uparrow O_2$ transfer to fetus from mother's Hb.

Effect of CO₂, 2,3 BPG on Hemoglobin O₂ dissociation curve:



P_{50Hb} : 26 torr (blood)

Voet fig 7-14

ENERGY METABOLISM (ERYTHROCYTES)

Adequate dietary intake (North America):

Carbohydrates and Fats used as primary fuel, or stored (as glycogen or in adipose tissue). Common monosaccharides: glucose(6), galactose(6), fructose(6); Disaccharides: sucrose (g+f), lactose (g+ga) and maltose (g+g) Starch, glycogen and cellulose are all polysaccharides (carbohydrates).

Proteins - (amino acids) used for cellular protein and nucleotide metabolism.

Starvation conditions (24 hours):

Blood glucose and glycogen used as primary fuel

Glycerol from fat, amino acid from protein begin to be converted to glucose through gluconeogenesis (liver).

Glucose remains dominant fuel supply for brain, erythrocytes, bone marrow, WBC's and renal medulla.

Prolonged starvation (weeks):

Fat and protein degradation can no longer maintain bodily needs, ketone body formation begins. Brain begins to utilize ketone bodies (max. starv. 100 days).

Glycolysis :

1. First metabolic pathway completely described. Glycolysis is also termed the Embden-Meyerhof (Parnas) pathway in honour of its discoverers.
2. The most universal metabolic pathway in living organisms (bacteria, plants, yeast, man).
3. Name derived from the Latin *glycos* (sweet) and *lysis* (break, loosen).
4. Primary form of anerobic ATP production in higher organisms (per mole glucose: 2 ATP, 2 NADH, 2 pyruvate). It is the DOMINANT form of energy production in RBC's (consequences?).
5. Glycolysis not used as the primary source of ATP production in the majority of mammalian cells due to its relative efficiency (7% of aerobic respiration - so why use it at all?).

Unique role of glycolysis in erythrocytes:

1. Supplies ATP for ion pumps. Erythrocytes have only an estimated 30-40 minute reserve of ATP. A majority of ATP in erythrocytes goes to perform:

a) Na^+/K^+ transport

b) Ca^{2+} pump/ATPase

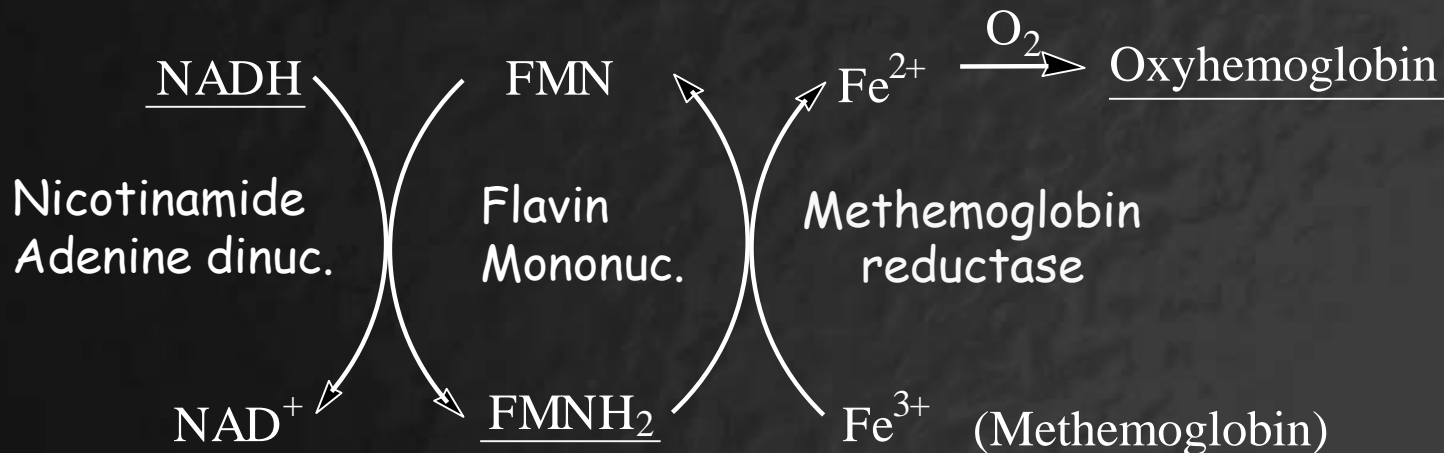
c) Sustain glycolysis

Details

Details

Decreased ATP increases cell size

2. Supplies NADH for methemoglobin reductase:



Sodium/potassium pump (erythrocytes):

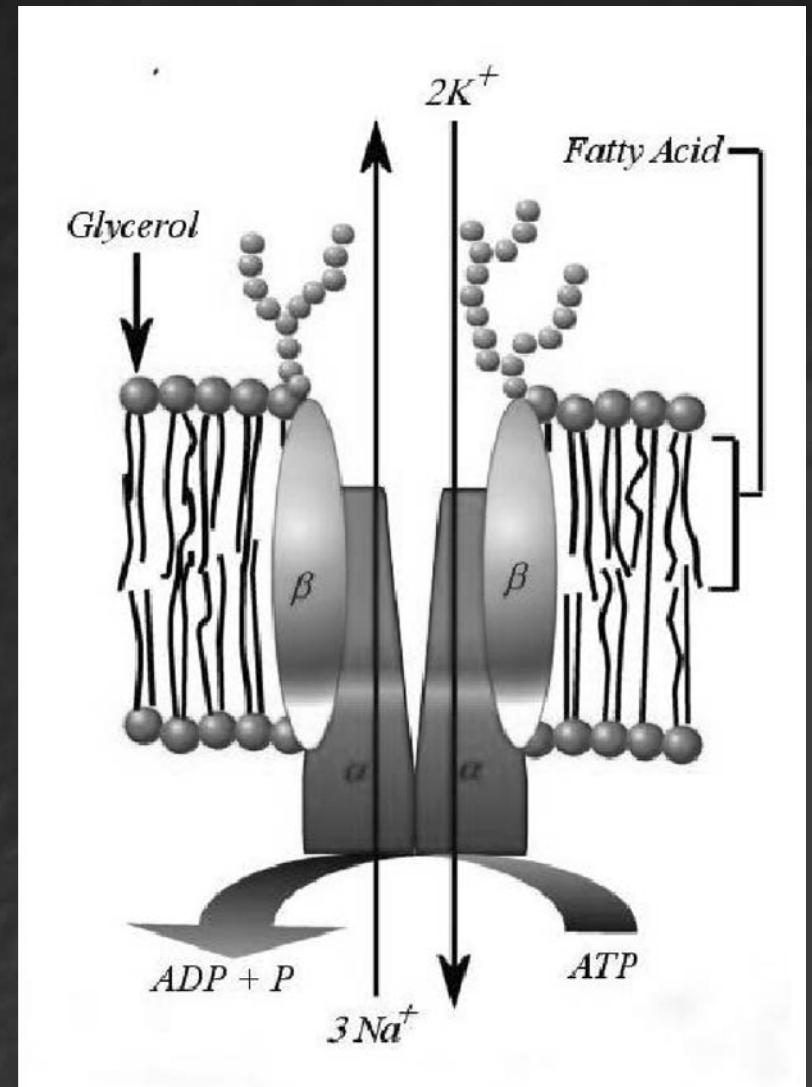
Na⁺/K⁺ pump: (300 per cell)

Red cells shrink when Na⁺ leaking in < K⁺ leaks out

Red cells swell when Na⁺ leaking in > K⁺ leaks out

Inhibitor: digitalis, ouabain

Used to enhance muscle contractility (angina)



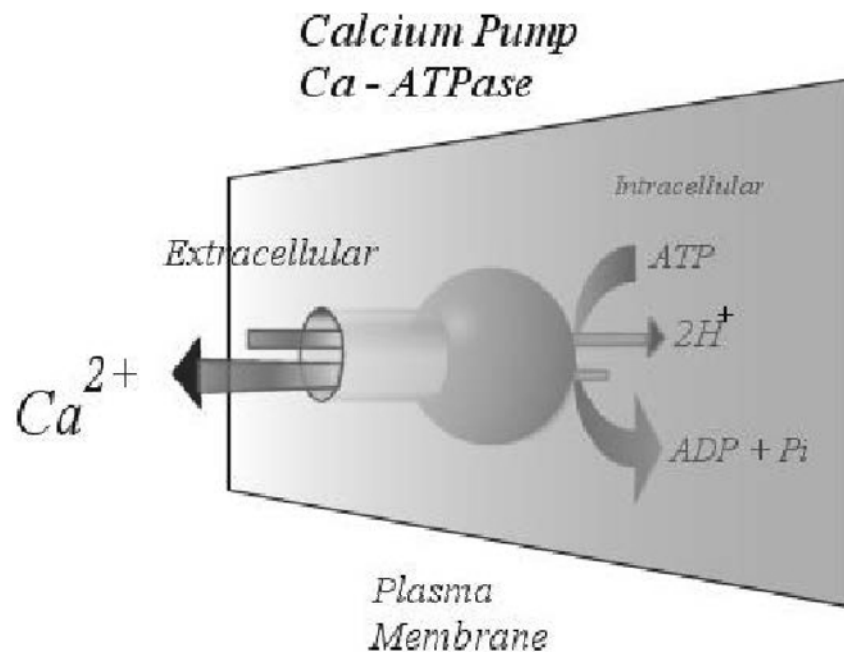
Energy needs of erythrocytes:

Ca²⁺-ATPase:

Cellular / Plasma conc.

	U mol / mL RBC	Plasma (mM)
Ca ²⁺	0.009	1 *
Na ⁺	6.2	140 *
K ⁺	102.4 *	4
Cl ⁻	4 or 80	100 *

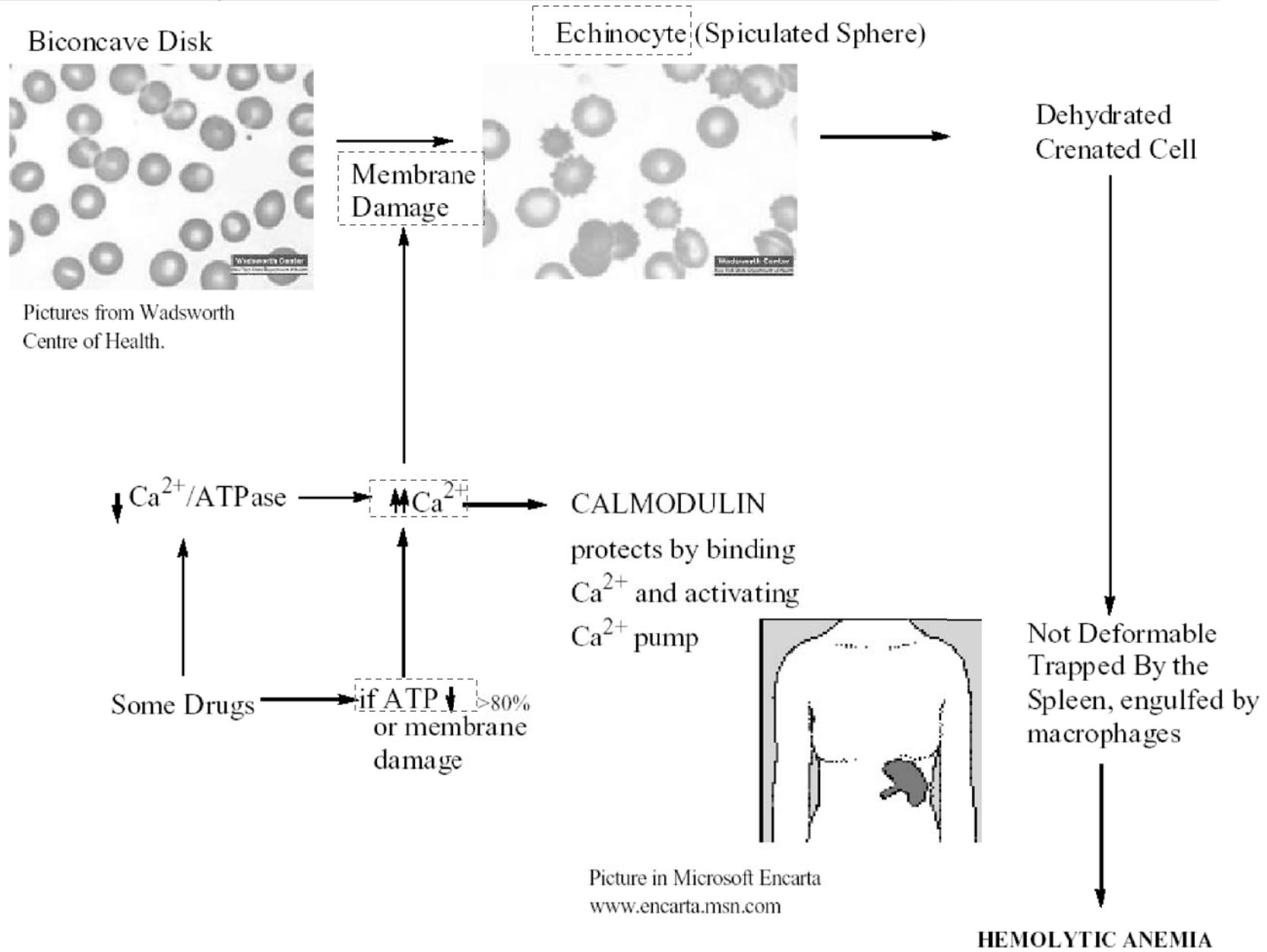
If Ca²⁺ leaks into the cell, changes in cell shape and rigidity occur - the cell becomes an echinocyte.



Progressive rise in intracellular calcium is closely tied to RBC aging.

Aged RBC's removed by reticulo-endothelial system in spleen (macrophages).

TOXIC CONSEQUENCES OF ATP DEPLETION = DISRUPTION of Ca^{2+} HOMEOSTASIS.



Glycolytic detours:

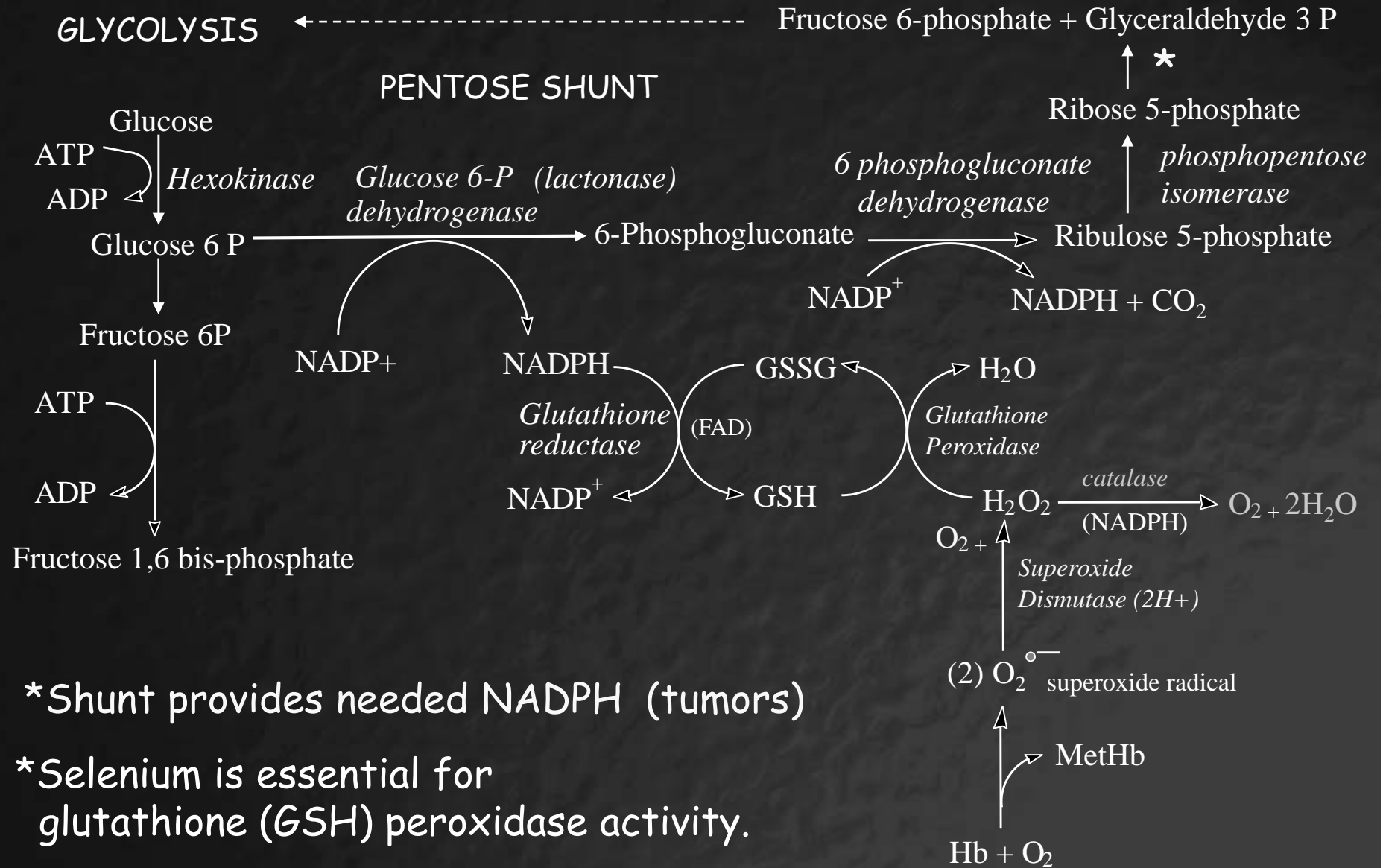
A side reaction of glycolysis known as the pentose monophosphate shunt is key to supplying the NADPH. Required to remove cellular reactants such as H_2O_2 . NADPH is utilized by glutathione (GSH), GSH reductase and GSH peroxidase. NADPH also utilized by catalase (active catalase contains 4 tightly bound NADPH molecules).

* Because of its dependence on the pentose monophosphate shunt, NADPH production is significantly impaired in individuals with deficiencies in G6PD.

Inhibitors of glycolysis include fluoride, and arsenate.

In the presence of arsenate, ATP normally formed in the conversion of 1,3-bisPG into 3-PG is lost (no net ATP prod.).

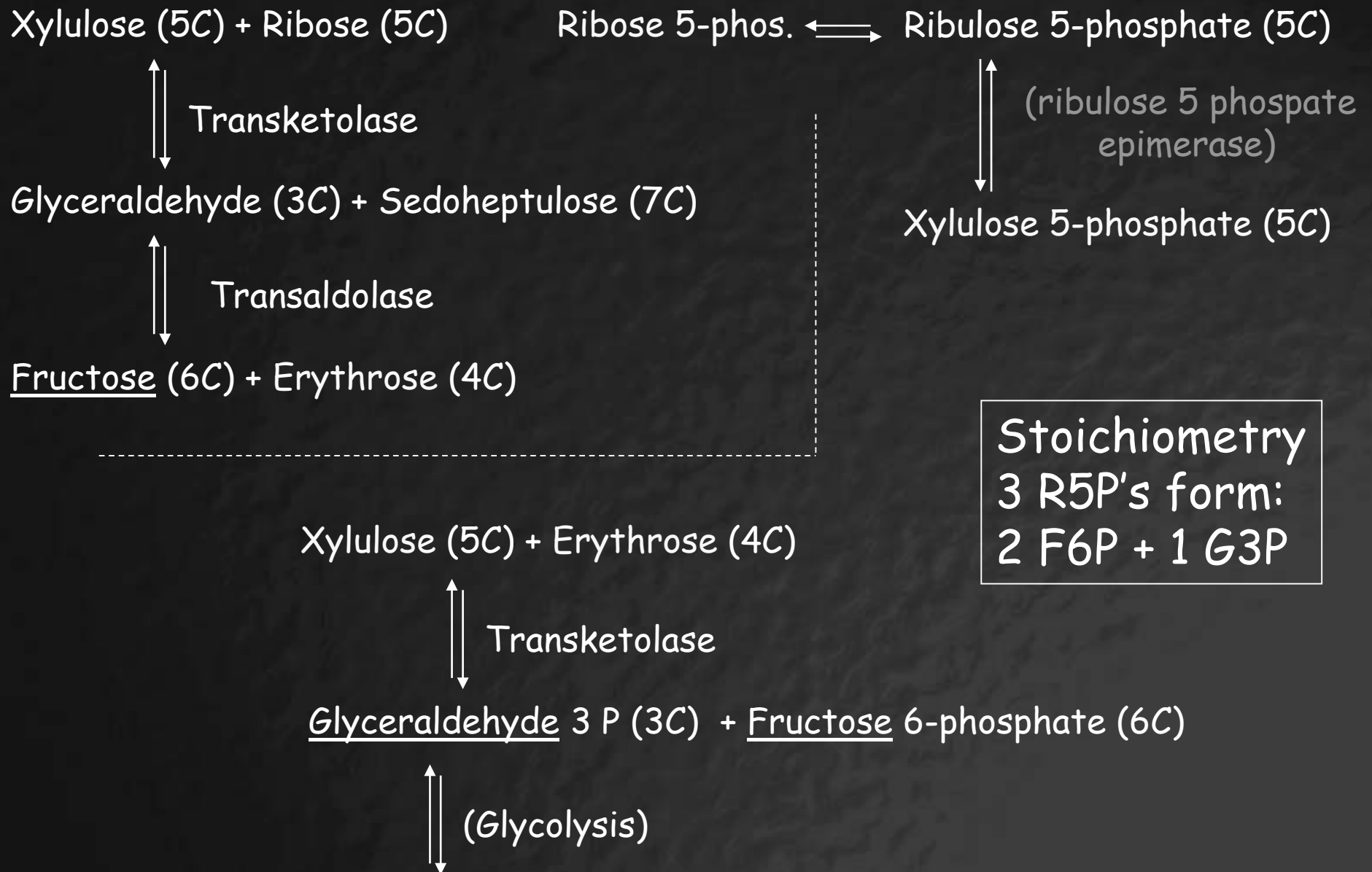
Pentose monophosphate shunt:



*Shunt provides needed NADPH (tumors)

*Selenium is essential for glutathione (GSH) peroxidase activity.

Pentose monophosphate shunt:



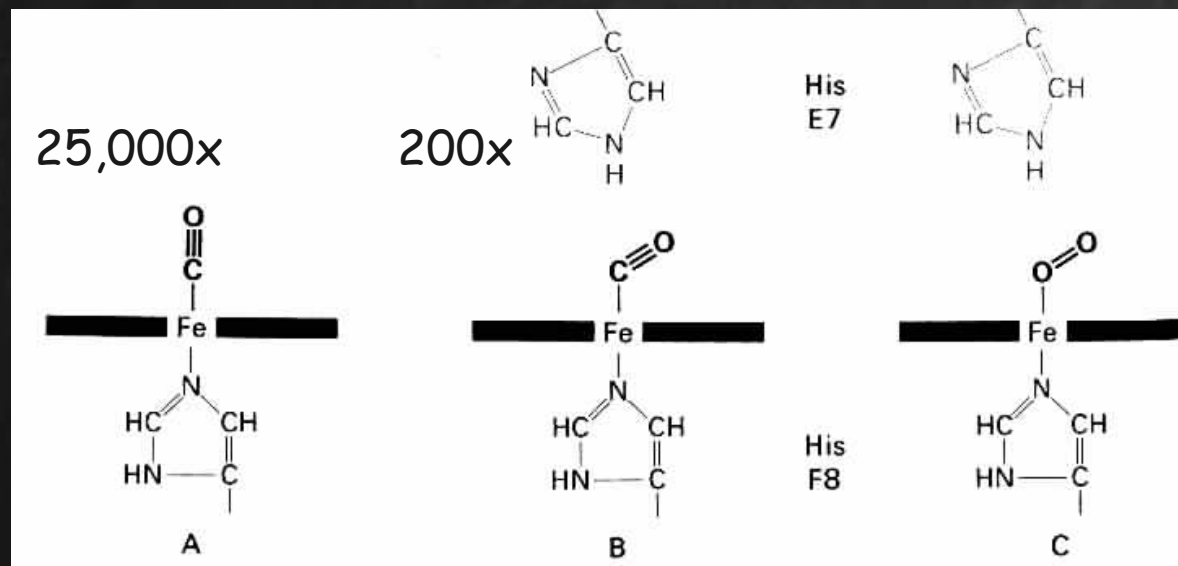
DRUGS AND TOXINS WHICH AFFECT ERYTHROCYTE FUNCTION

- a) Complex hemoglobin Fe^{2+}
- b) Oxidize hemoglobin Fe^{2+}
- c) Hemolysis (Hb, RBC destruction)
- d) Genetic diseases (G6PD, HbS, Thal.)

Toxins which affect erythrocyte function:

Carbon monoxide induces hypoxia by complexing Fe^{2+} Hb (victims - bright red).

- the avidity of heme group for CO is 25,000 times greater than for oxygen.
- the avidity of Mb / Hb for CO is only 200x greater than O_2 due to distal histidine.
- CO can thus be life threatening at relatively low conc.



Voet Fig 7-13

Oxidation of Fe^{2+} . Excessive oxidation of Fe^{2+} to Fe^{3+} (oxyhemoglobin to methemoglobin) can induce hypoxia.

deoxyHb: Fe^{2+} (purple)

oxyHb: $Fe^{2+}O_2$ (bright red)

metHb: Fe^{3+} (brown) - O_2 cannot bind to $Fe(III)$

CyanHb: antidote for cyanide poisoning (amyl + Na nitrite)

Why? Nitrite converts Fe^{2+} to Fe^{3+} , creating binding sites for CN (better than Fe^{3+} center on cytochrome oxidase).

METHEMOGLOBINEMIA can be induced by a variety of drugs. These include:

"aniline" drugs (dapsone, etc.)

nitro aromatic drugs

hydrazine drugs

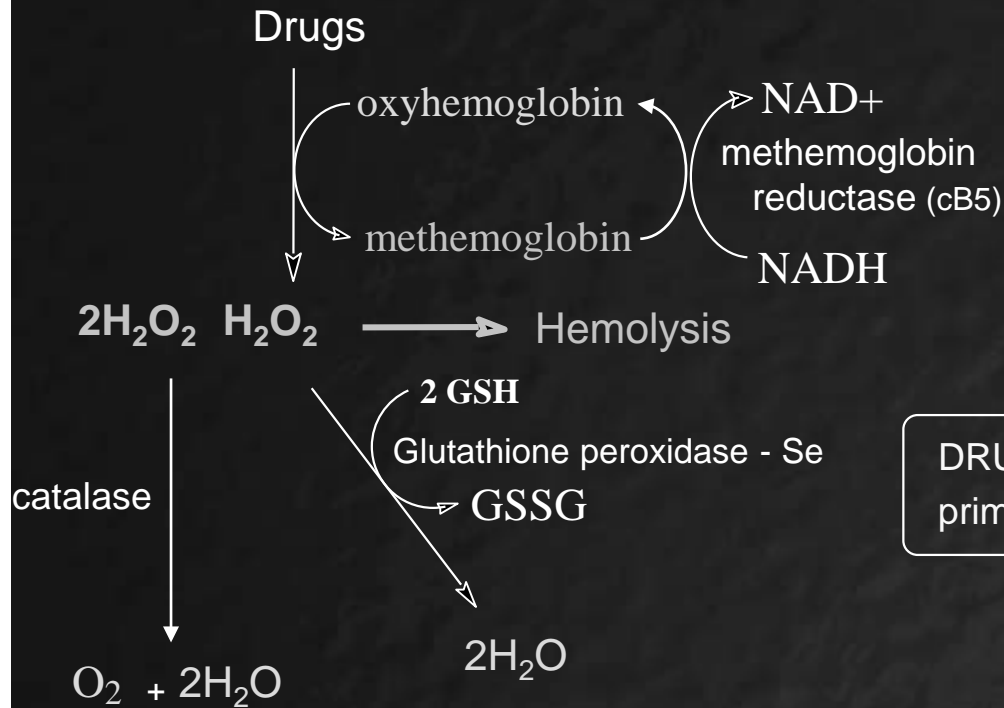
oxidants, chlorates, nitrites (cyanide antidote)

quinones, naphthalene, benzene

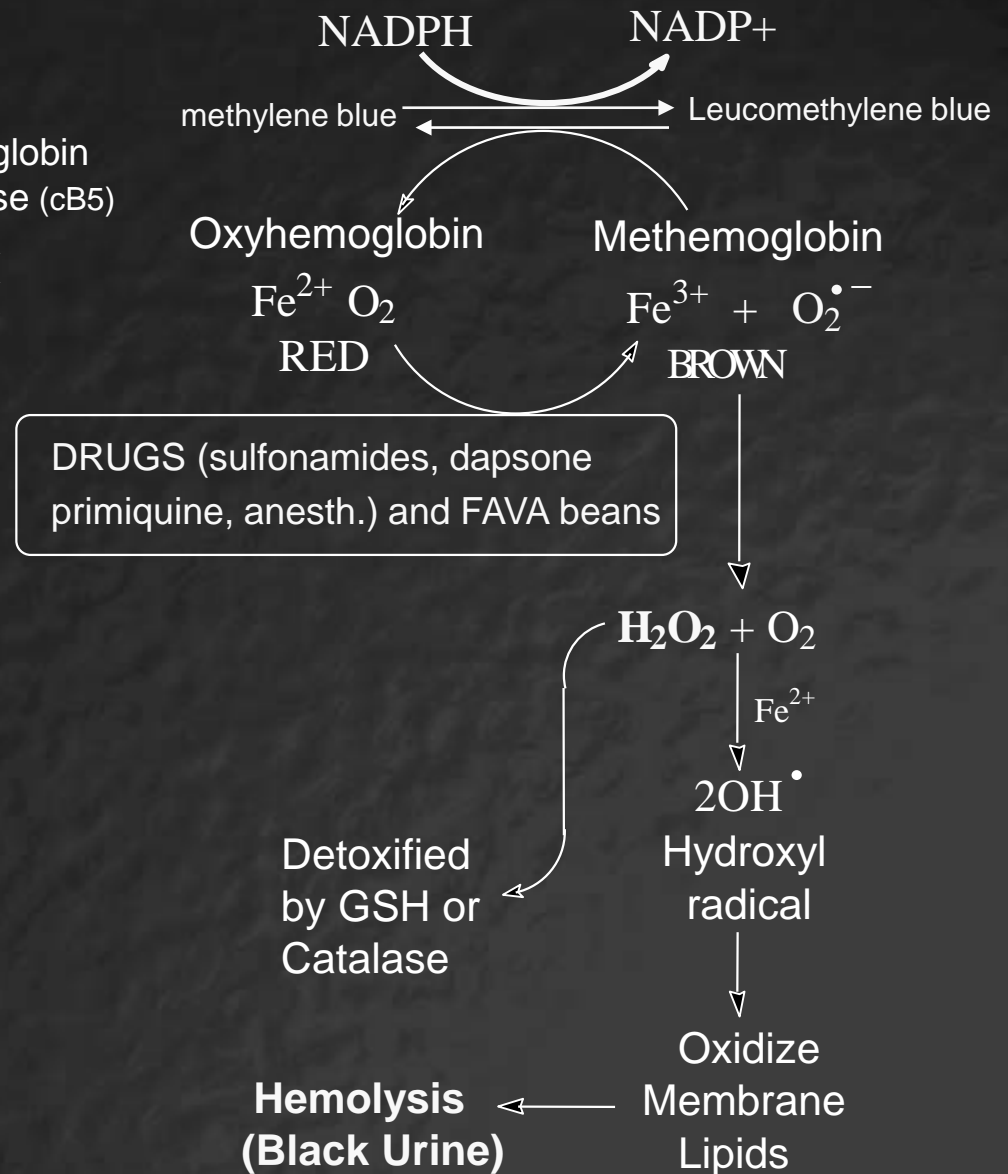
arsine

Role of GSH and catalase in detoxifying reactive oxygen species generated by genetic deficiency or xenobiotics:

MAINTENANCE OF ERYTHROCYTE GSH LEVELS



CELLULAR DAMAGE CAUSED BY MB – NADPH dependent methemoglobin reductase



Hemolysis. Hypoxia can also be induced by premature destruction of erythrocytes or their progenitors (Anemia).

Activated oxygen (oxygen free radicals) are released when oxyhemoglobin oxidized. These short-lived species can subsequently attack sites such as the erythrocyte membrane. This is frequently seen in cases of glucose 6-phosphate dehydrogenase deficiency (details later).

HEMOLYTIC ANEMIA

(due to excessive free radical generation) can be induced by a variety of different drugs. These include:

- aromatic amines
- nitro compounds
- hydrazines
- antimalarial drugs
- Fava beans

Muscle fibers and oxidative metabolism:

Fast twitch:

- Used for rapid contractions of brief duration.
- Energy primarily from anaerobic glycolysis, thus they can contract more rapidly than oxygen can be delivered to them.
- They fatigue quickly and go into oxygen debt until the lactic acid produced via glycolysis can be re-oxidized after activity.
- Glycogen content higher than slow fibers, mitochondrial content lower
- Fast fibers contain little myoglobin and appear white (white meat).

Slow twitch:

- Used for sustained activity, do not fatigue easily (oxygen debt).
- Derive energy from oxidative metabolism.
- Richly supplied with blood vessels (oxygen delivery)
- High mitochondrial content (oxidative metabolism)
- Large amount of myoglobin - reddish color (dark meat)

Anesthetics and calcium:

Malignant hyperthermia:

Susceptible individuals: 1:12,000 in children to 1:40,000 – 1:70,00 in adults.

Locus: chromosome 19 - Ryanodine receptor. Anesthetic produces excessive Ca^{2+} release in skeletal muscle, resulting in the following:

Excessive production of heat and lactic acid, ultimately resulting in acidosis and death.

Condition is reversible if caught in the first several MINUTES (cooling, dantrolene)

Other anesthetic risks:

20% of metabolism "toxic", can cause hepatic damage with repeated exposure.

Risk of spontaneous abortion in pregnant OR staff.