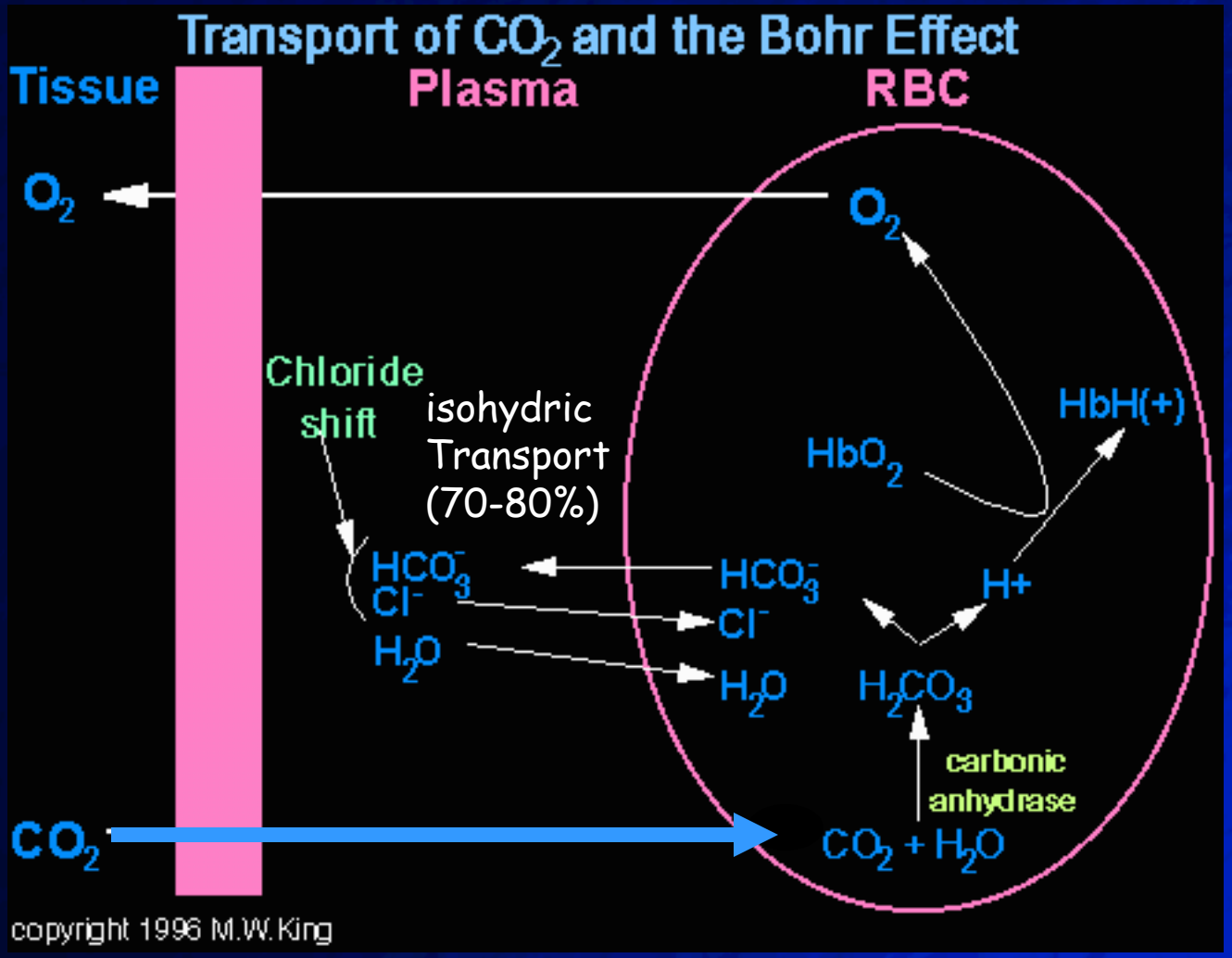
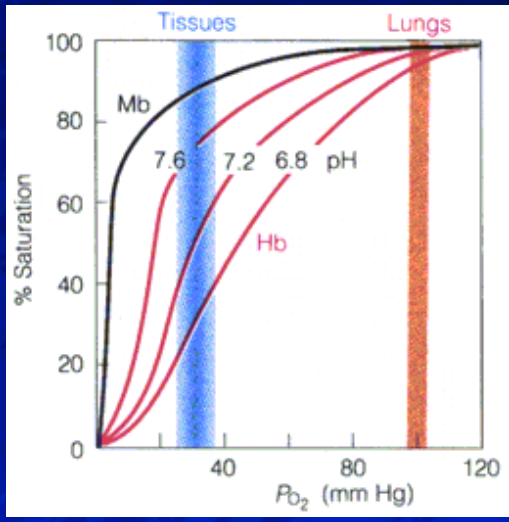
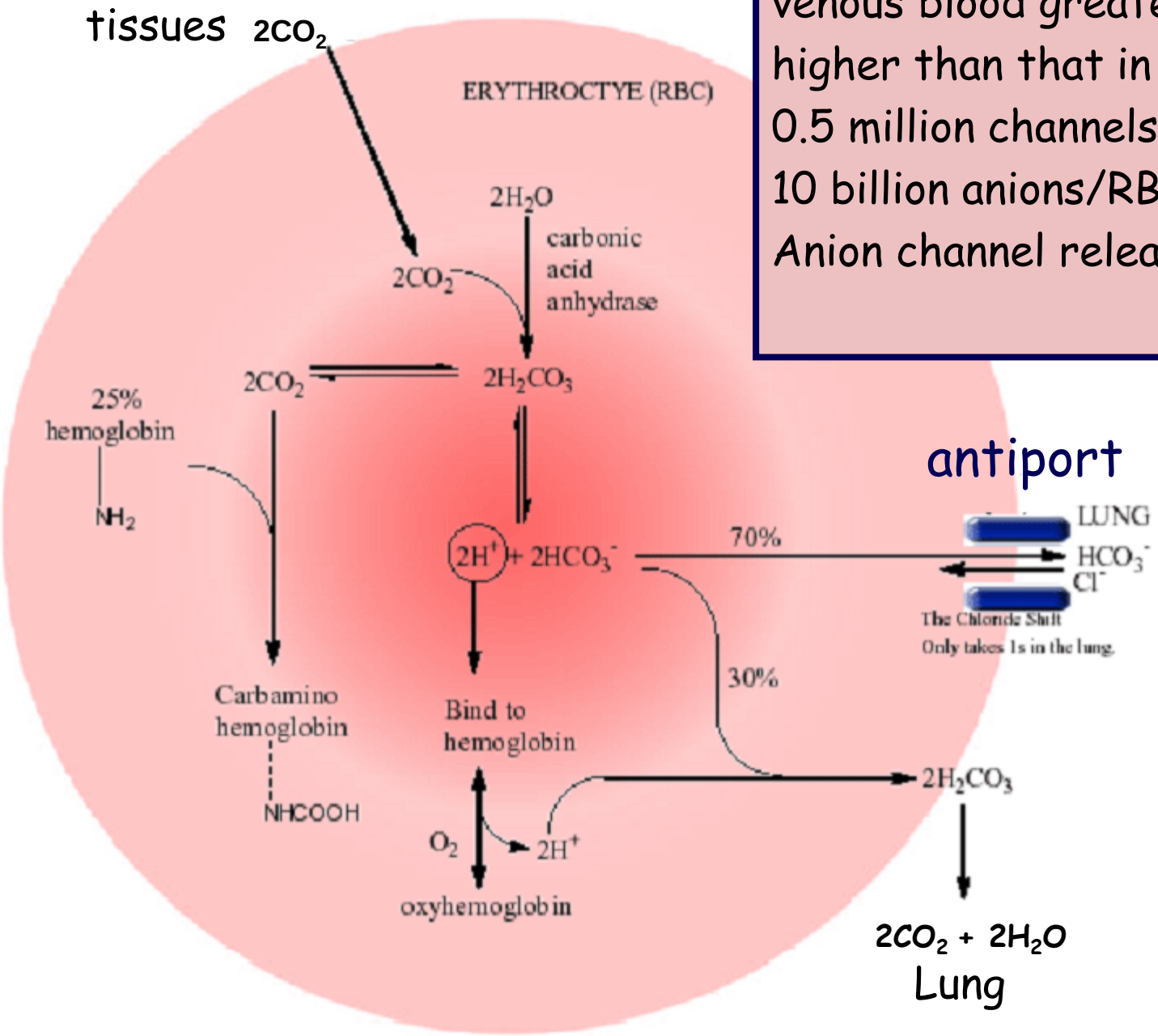
Isohydric transport:





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 HCO_3^- in lung.



antiport

Tissue

$2CO_2 + 2H_2O$

↓

$2H_2CO_3$

↓

$2H^+ + 2HCO_3^- [Cl^-]$

↓

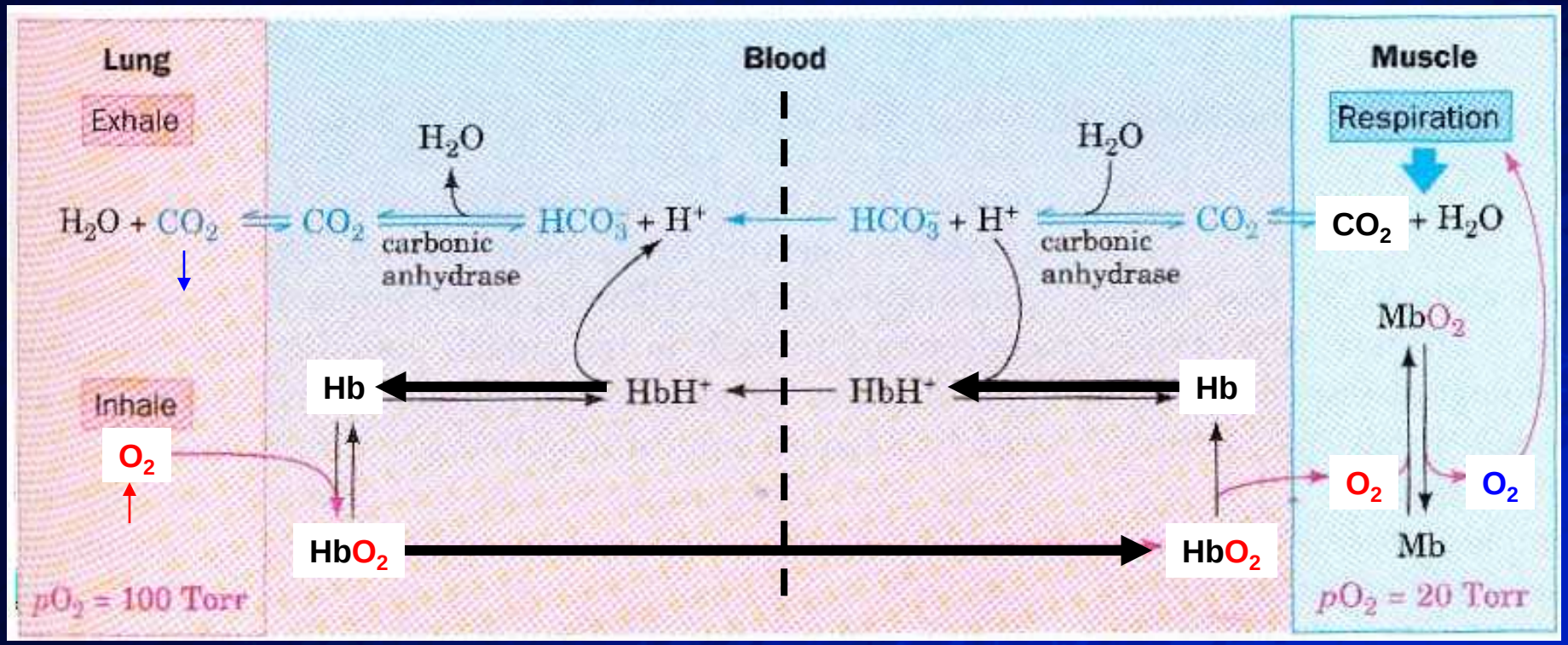
$2H_2CO_3$

↓

$2CO_2 + 2H_2O$

Lung

Systemic O_2 delivery:



Lungs: low CO_2 ∴ Hb picks up O_2

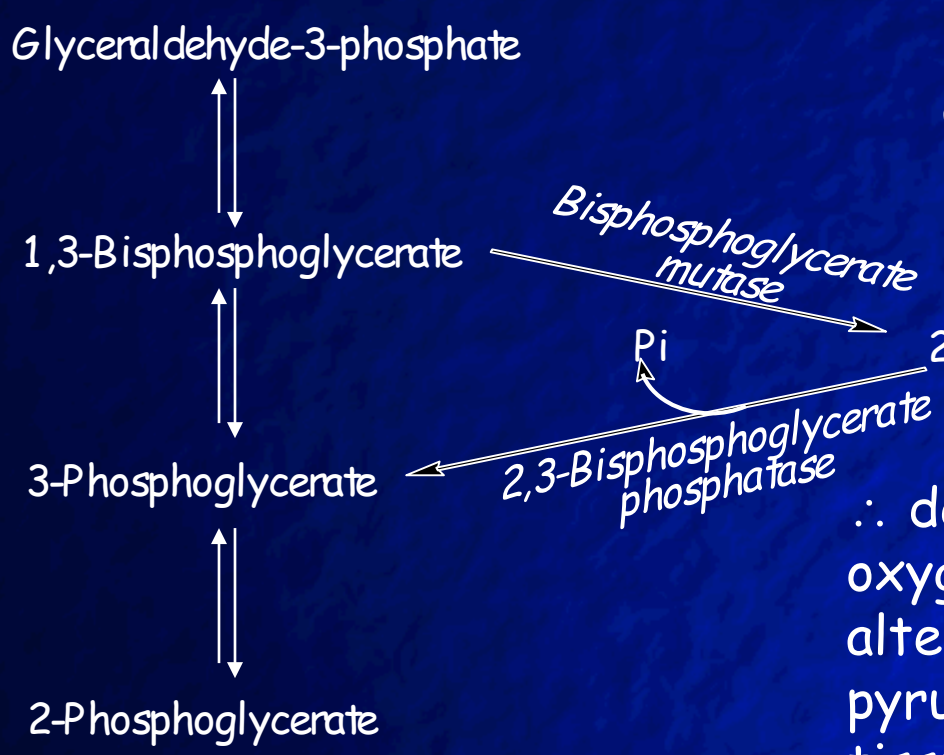
Tissues: high CO_2, low pH ∴ Hb releases O_2

See Devlin 9.43

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

-2,3 DPG is synthesized as a side reaction from glycolysis (Raport-Luenberg)

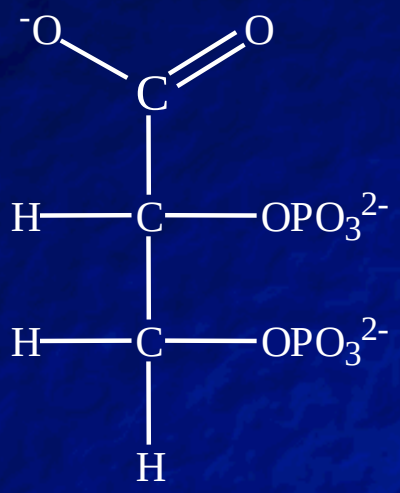
- 2,3 DPG decreases the O2 affinity of Hb by stabilizing the deoxygenated form of hemoglobin through ionic cross-linking of beta chains (salt bridges). It therefore acts to enhance O_2 release.



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:



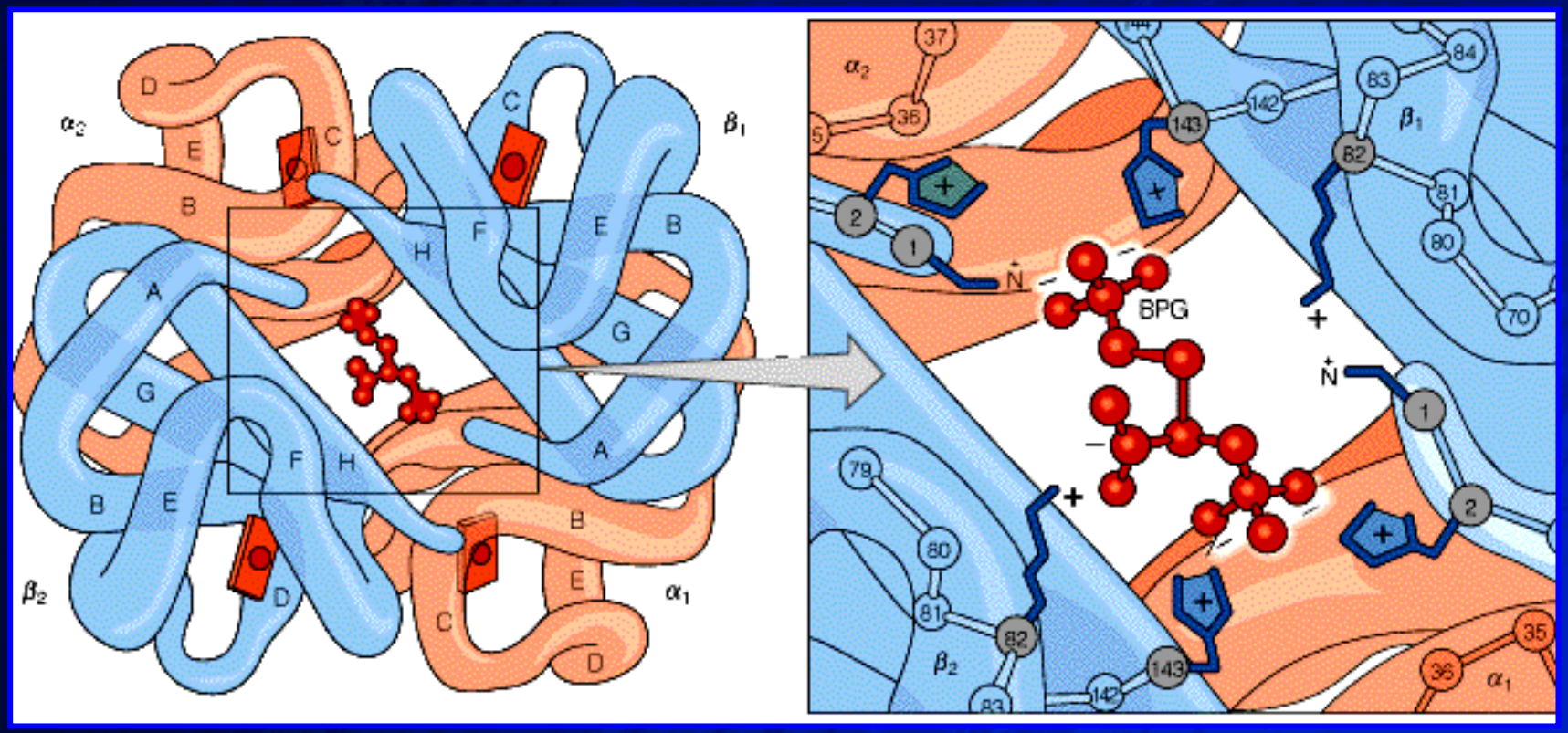
2,3-BPG

- 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 interations)

↓ O_2 affinity of Hb by keeping Hb in deoxy. conformation

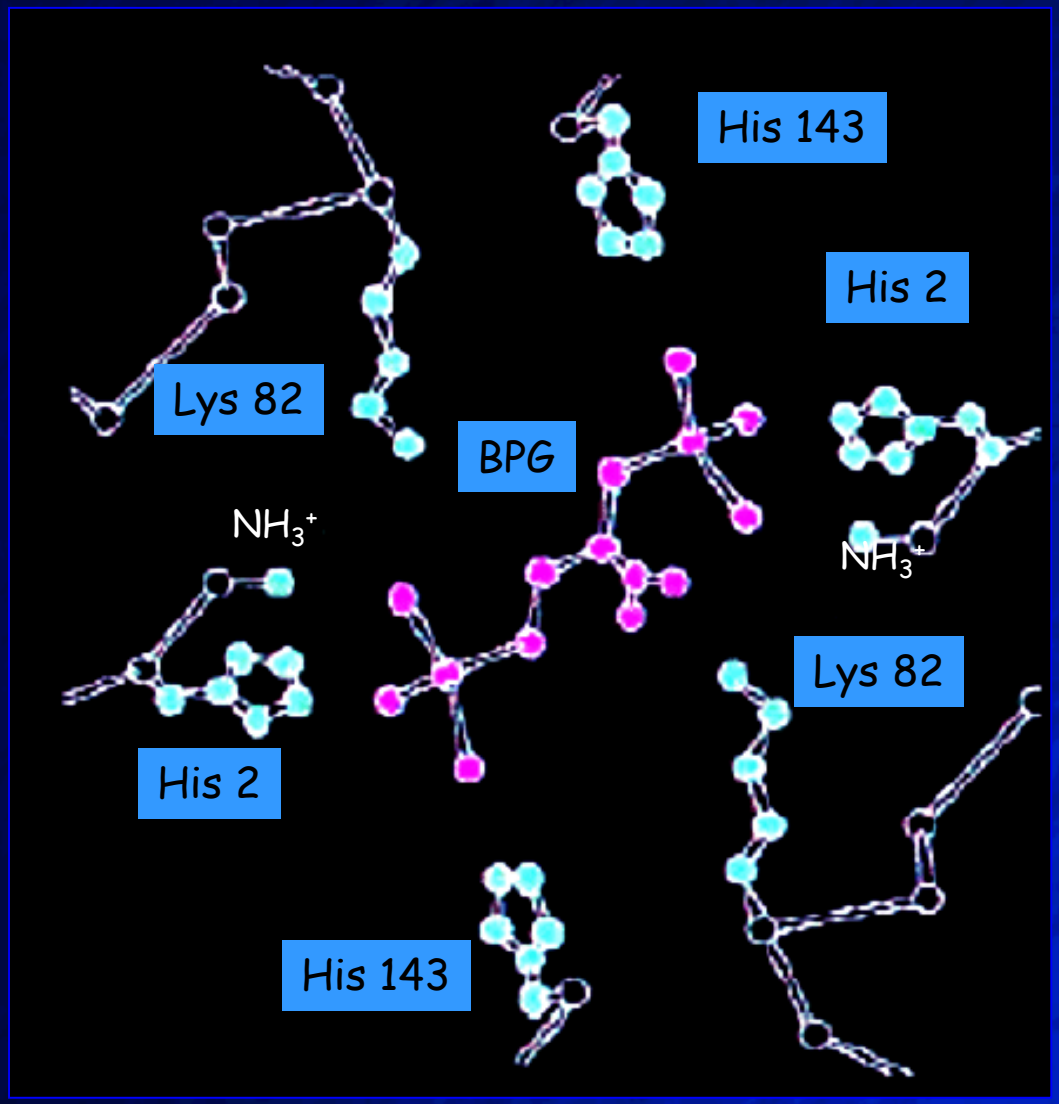
- allows unloading of O_2 in tissues (increases P_{50} of Hb)

Interaction of 2,3 BPG with Hemoglobin:



(from Devlin 9.47)

Interaction of 2,3 BPG with Hemoglobin:



Stryer Fig. 7-26

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

Regulatory features of 2,3 BPG:

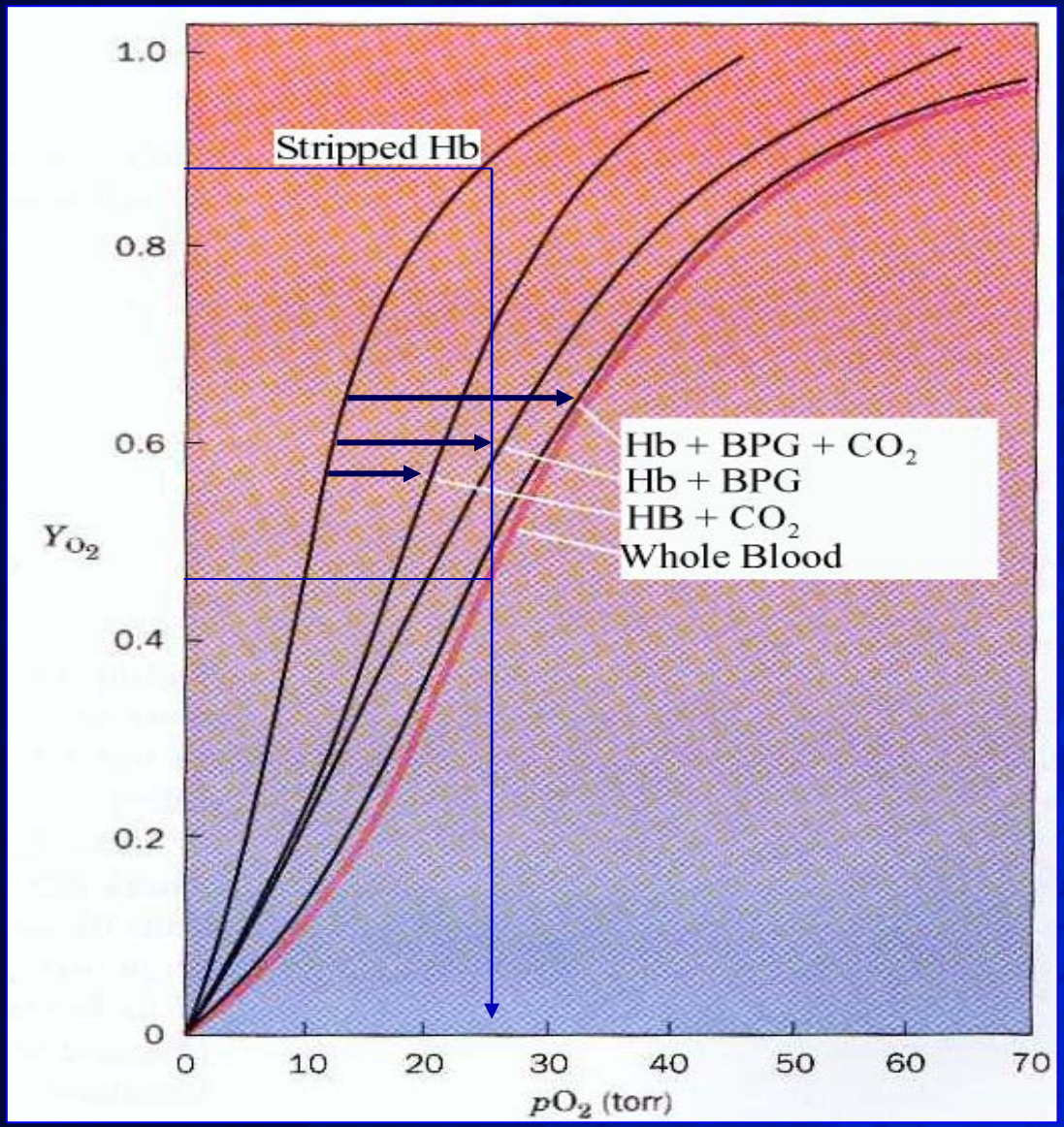
High altitudes adaptation:

2,3-BPG levels double after 2 days ∴↑ 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} ↓ so ↑ O_2 transfer to fetus from mothers Hb.

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



P_{50}Hb: 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 polysaccarides (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?).

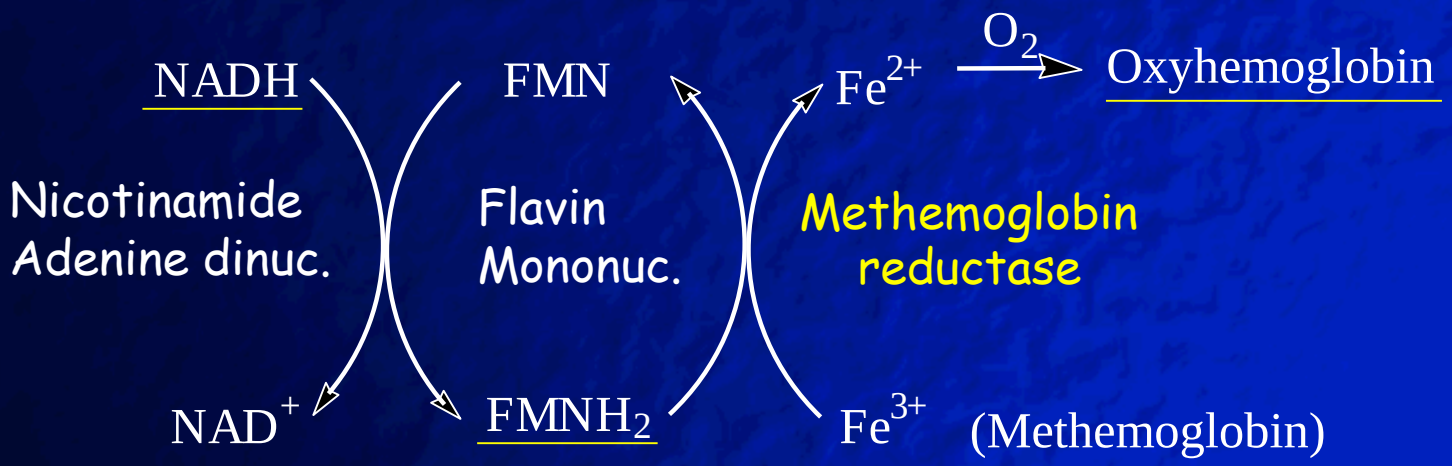
Unique role of glycolysis in erythrocytes:

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 → Details
   b) Ca^{2+} pump/ATPase → Details
   c) Sustain glycolysis

   Decreased ATP increases cell size

2. Supplies NADH for methemoglobin reductase:



Sodium/potassium pump (erythrocytes):

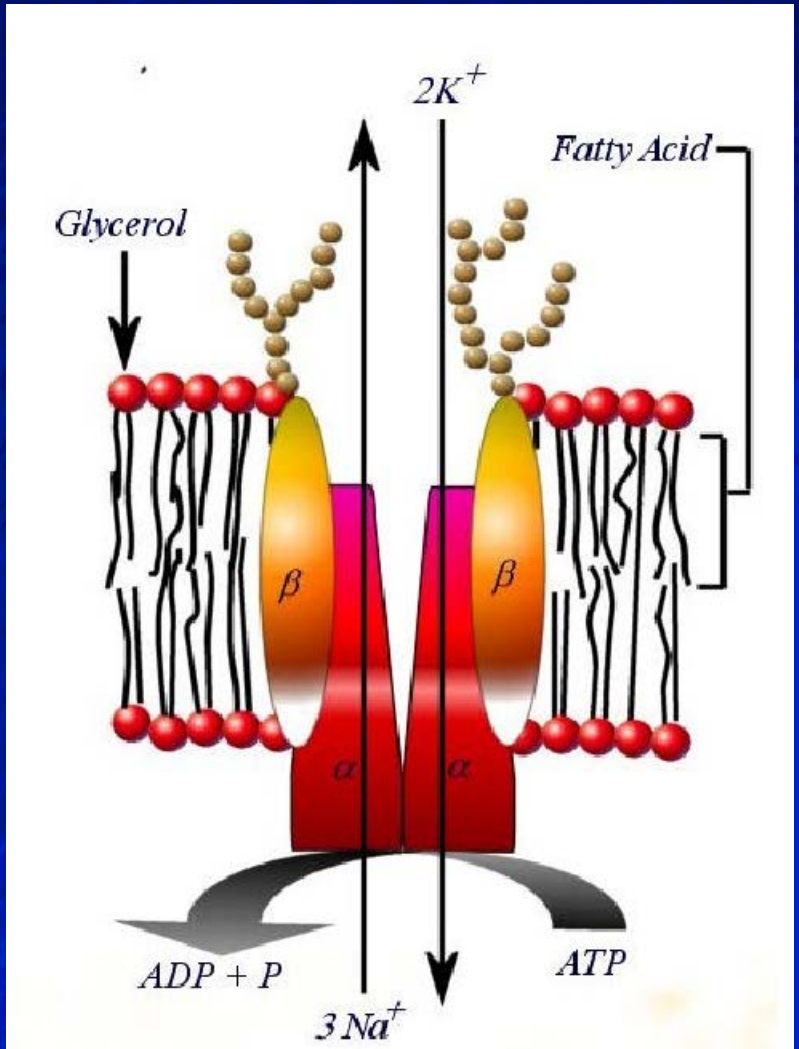
Na+/K+ pump: (300 per cell)

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)

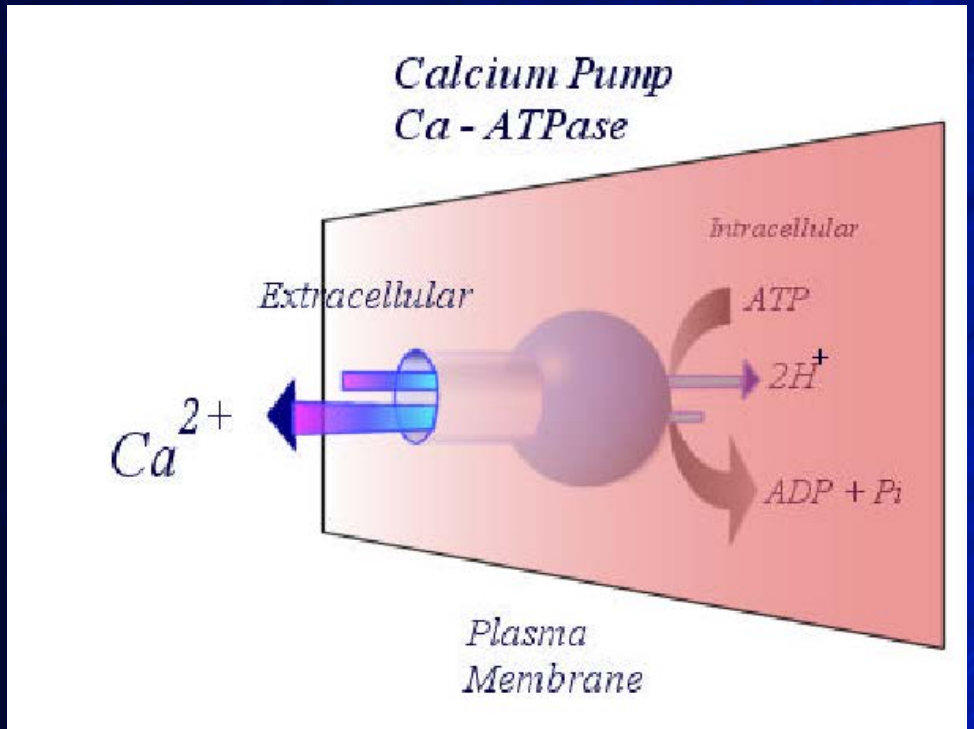


Energy needs of erythrocytes:

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 *



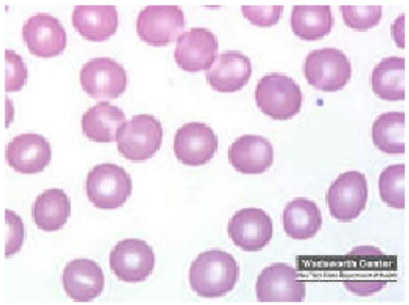
If Ca^{2+} leaks into the cell, changes in cell shape and rigidity occur - the cell becomes an echinocyte.

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.

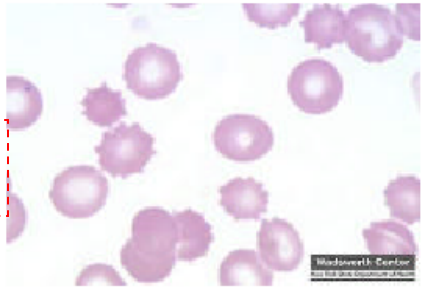
Biconcave Disk



Pictures from Wadsworth Centre of Health.

Membrane Damage

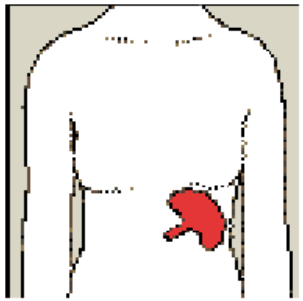
Echinocyte (Spiculated Sphere)



Dehydrated Crenated Cell

Ca^{2+}/ATPase → Ca^{2+} → CALMODULIN protects by binding Ca^{2+} and activating Ca^{2+} pump

Some Drugs → if ATP ↓ >80% or membrane damage



Picture in Microsoft Encarta
www.encarta.msn.com

Not Deformable Trapped By the Spleen, engulfed by macrophages

HEMOLYTIC ANEMIA

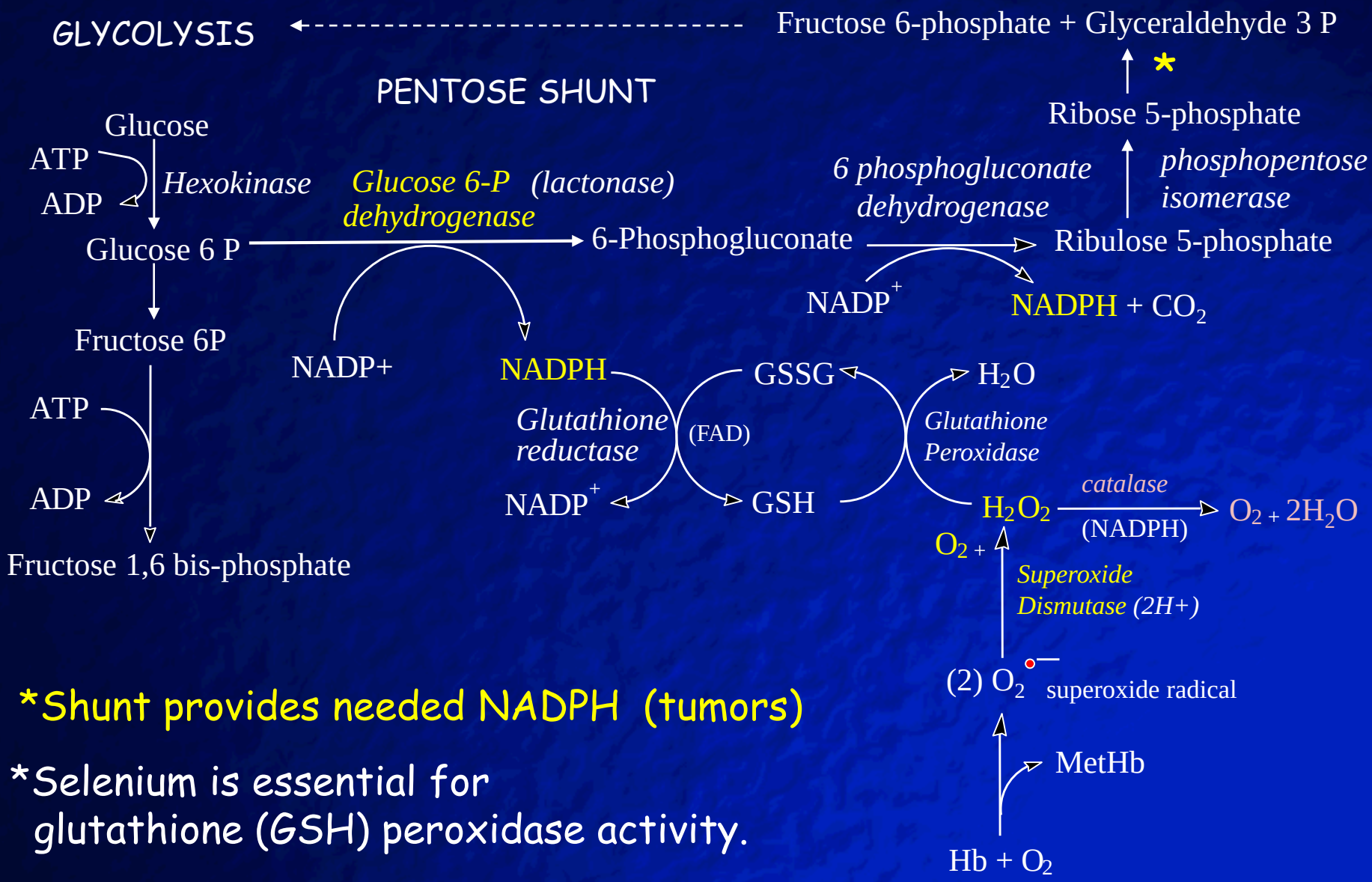
Glycolytic detours:

A side reaction of glycolysis known as the pentose mono-phosphate 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:

Xylulose (5C) + Ribose (5C)

Transketolase

Glyceraldehyde (3C) + Sedoheptulose (7C)

Transaldolase

Fructose (6C) + Erythrose (4C)

Ribose 5-phos. ⟷ Ribulose 5-phosphate (5C)

(ribulose 5 phospate epimerase)

Xylulose 5-phosphate (5C)

Stoichiometry
3 R5P's form:
2 F6P + 1 G3P

Xylulose (5C) + Erythrose (4C)

Transketolase

Glyceraldehyde 3 P (3C) + Fructose 6-phosphate (6C)

(Glycolysis)

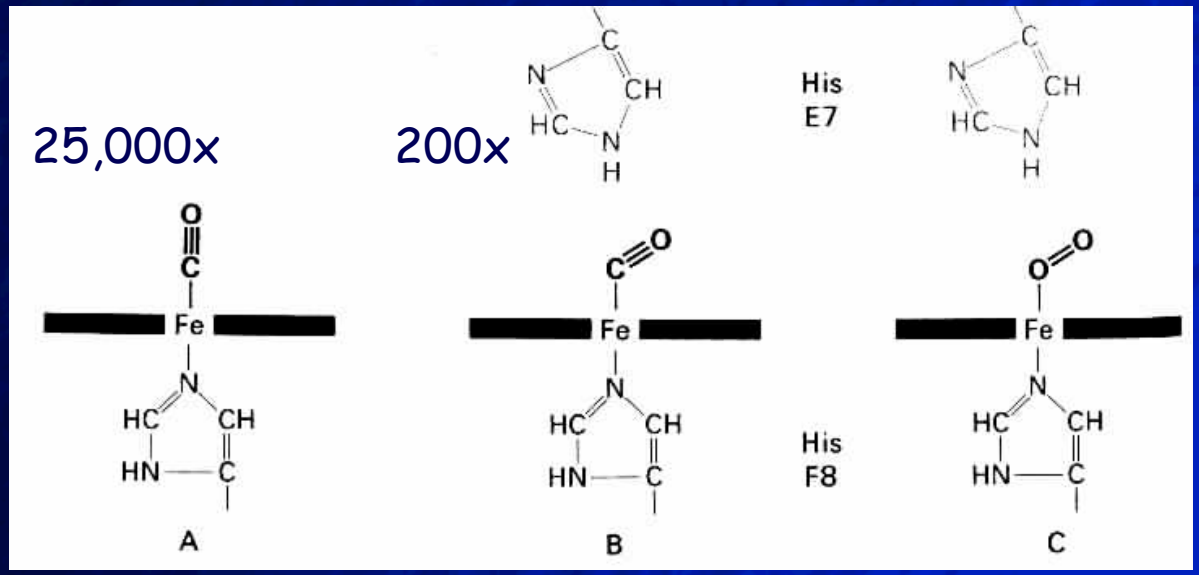
DRUGS AND TOXINS WHICH AFFECT ERYTHROCYTE FUNCTION

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 O2 due to distal histidine.
- CO can thus be life threatening at relatively low conc.



Voet Fig 7-13

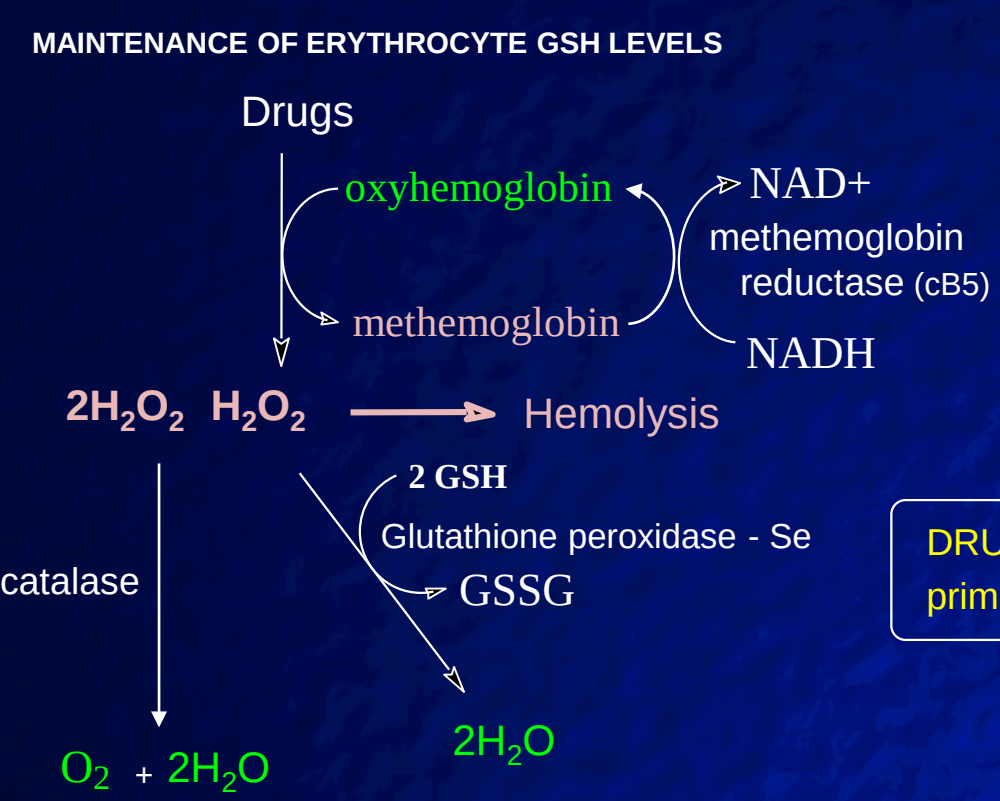
Oxidation of Fe^{2+}. Excessive oxidation of Fe^{2+} to Fe^{3+} (oxyhemoglobin to methemoglobin) can induce hypoxia.

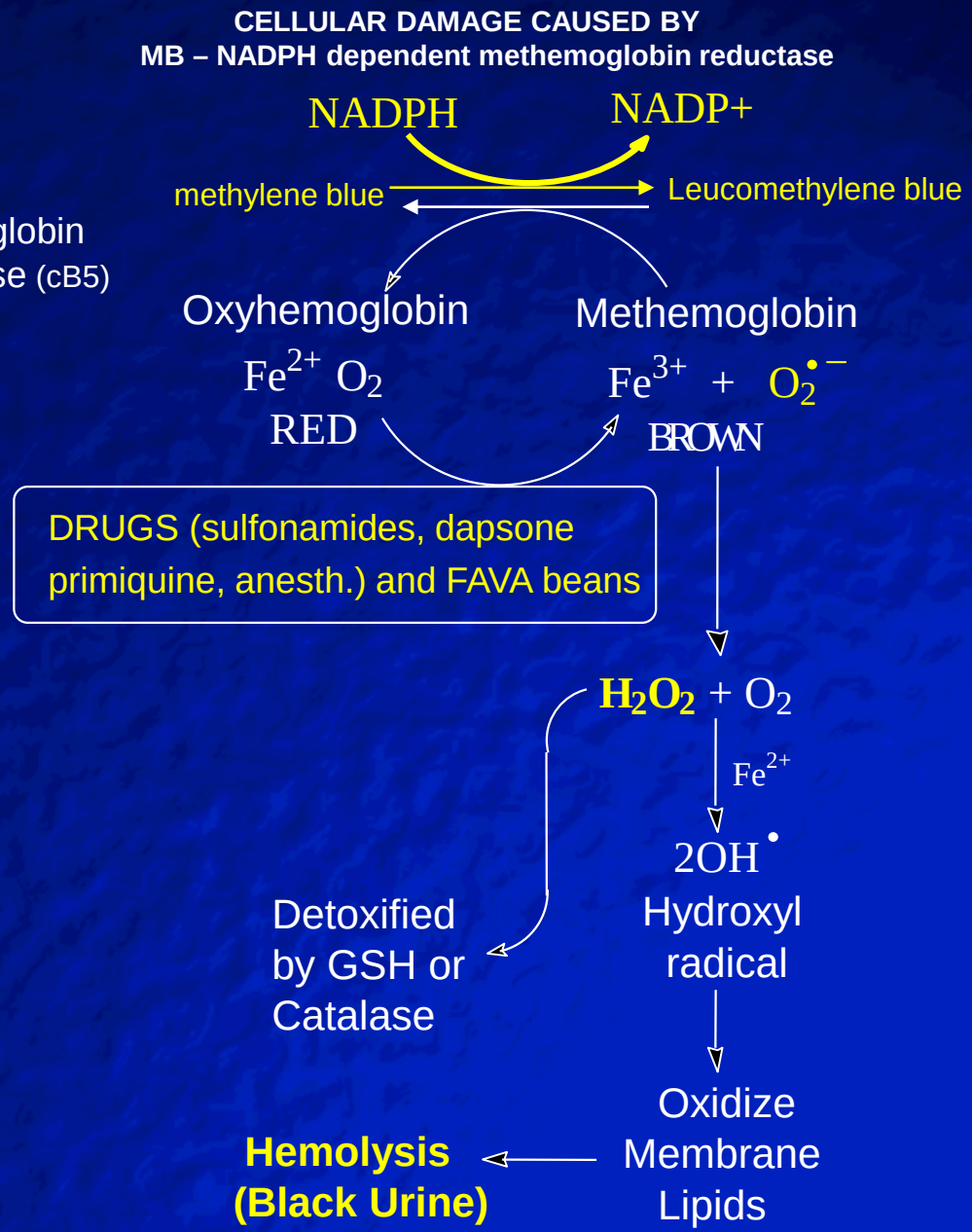
deoxyHb: Fe^{2+} (purple)
oxyHb: $Fe^{2+}O_2$ (bright red)
metHb: Fe^{3+} (brown) - *O_2 cannot bind to Fe(III)*
CyanHb: antidote for cyanide poisoning (amyl + Na nitrite)
Why? Nitrite converts Fe^{2+} to Fe^{3+}, creating binding sites for CN (better than Fe^{3+} center on cytochrome oxidase).

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:





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.