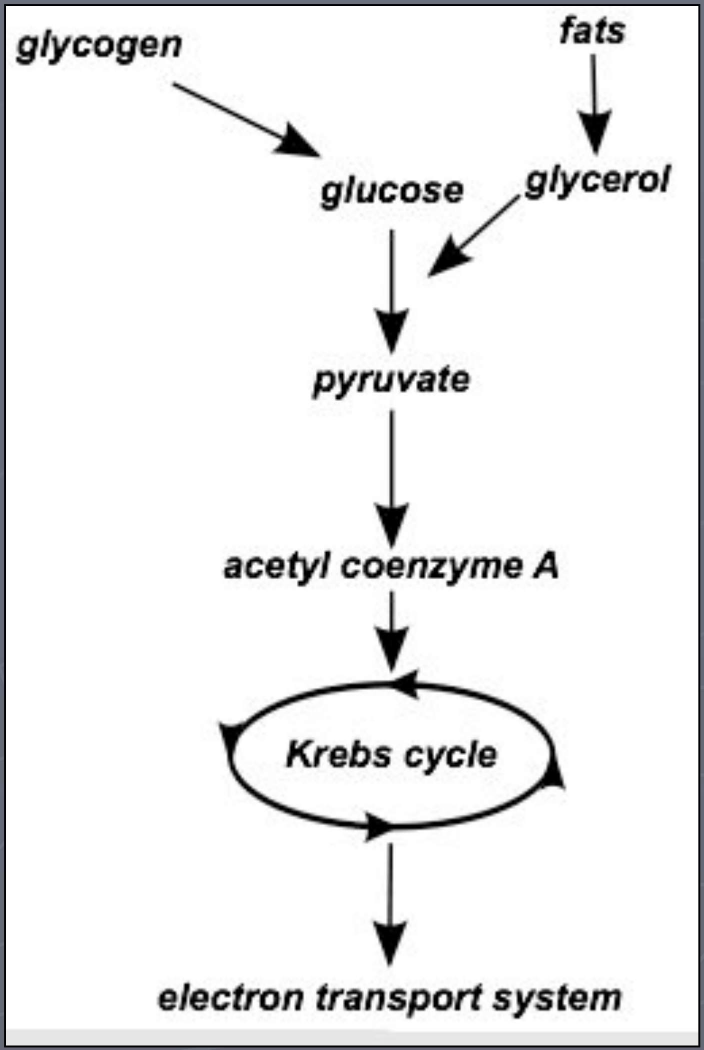
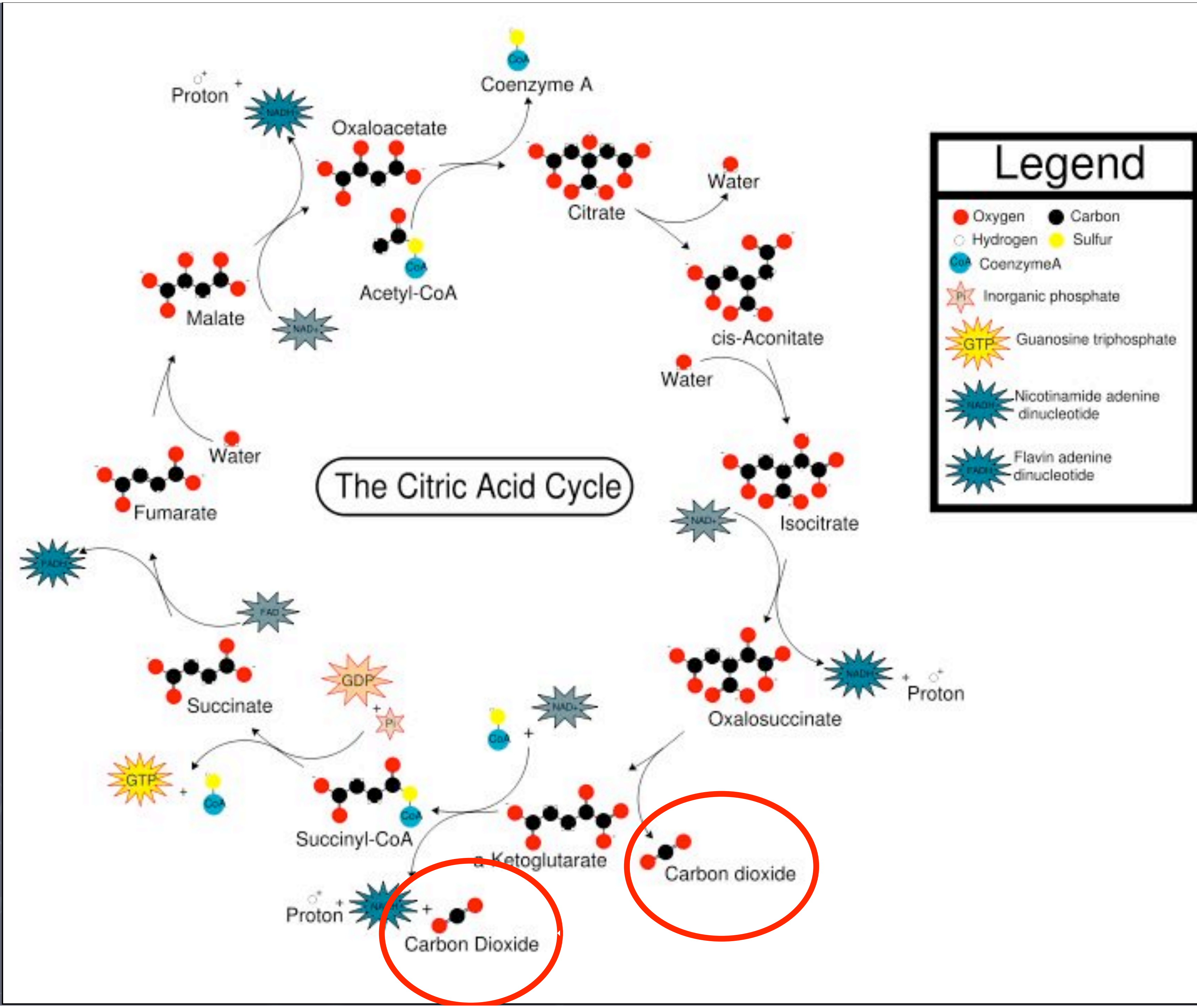
Blood and Gas Transfer

James Tucker
MD/PHD Program (Year 3)
University of Utah School of Medicine
University of Utah Neuroscience Program
james.tucker@hsc.utah.edu

Cellular Respiration

- Converts dietary nutrients into cellular fuel (primarily ATP)
- Consumes O_2
- Generates CO_2



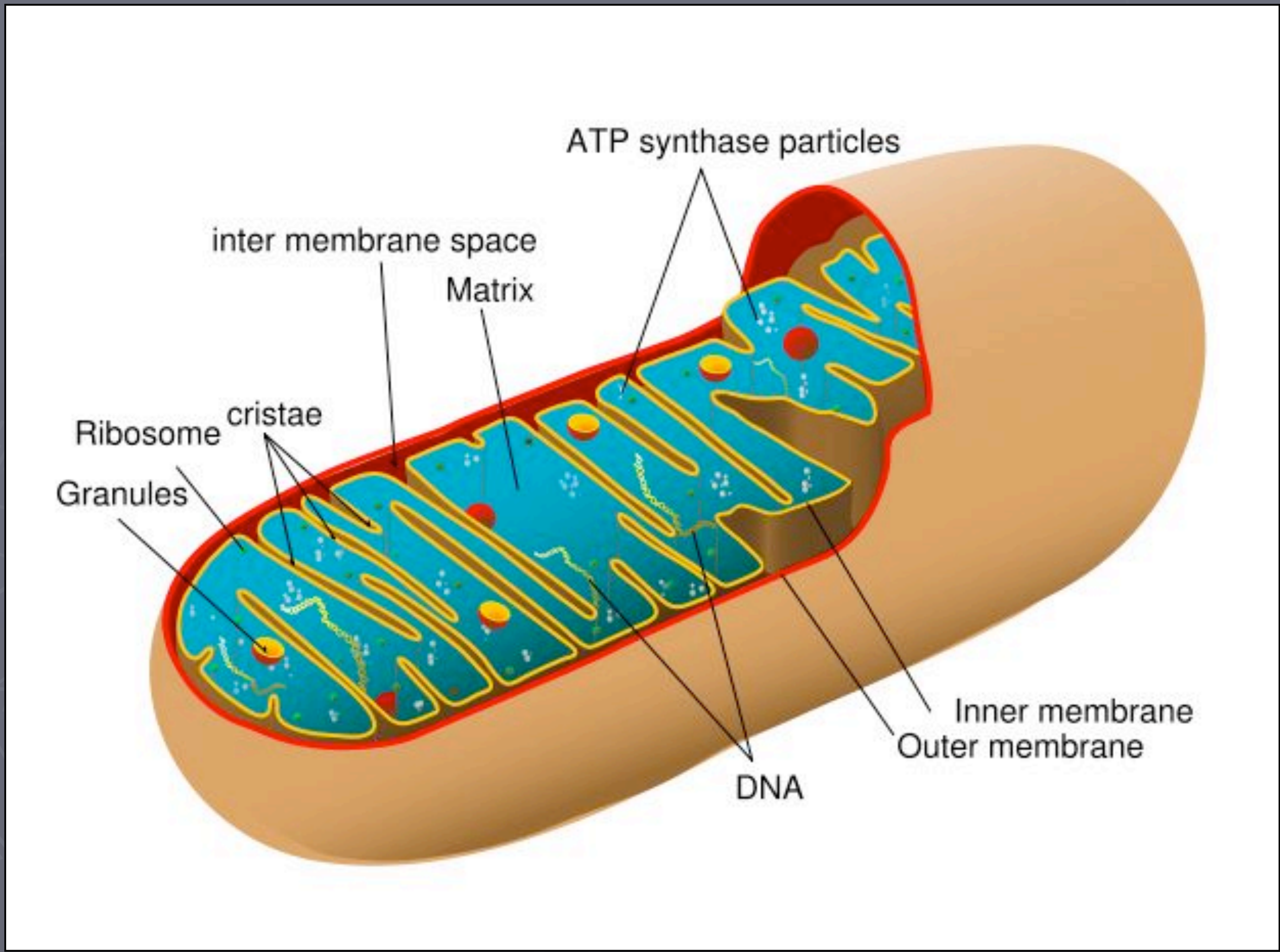


The Citric Acid Cycle
Legend
Oxygen
Carbon
Hydrogen
Sulfur
CoenzymeA
Inorganic phosphate
Guanosine triphosphate
Nicotinamide adenine dinucleotide
Flavin adenine dinucleotide
Coenzyme A
Oxaloacetate
Proton
Acetyl-CoA
Citrate
Water
cis-Aconitate
Water
Isocitrate
Proton
Oxalosuccinate
Carbon dioxide
α-Ketoglutarate
Carbon Dioxide
Proton
Succinyl-CoA
GDP
Pi
GTP
Succinate
FAD
FADH
Fumarate
Water
Malate
NAD+
NADH

The Citric Acid Cycle

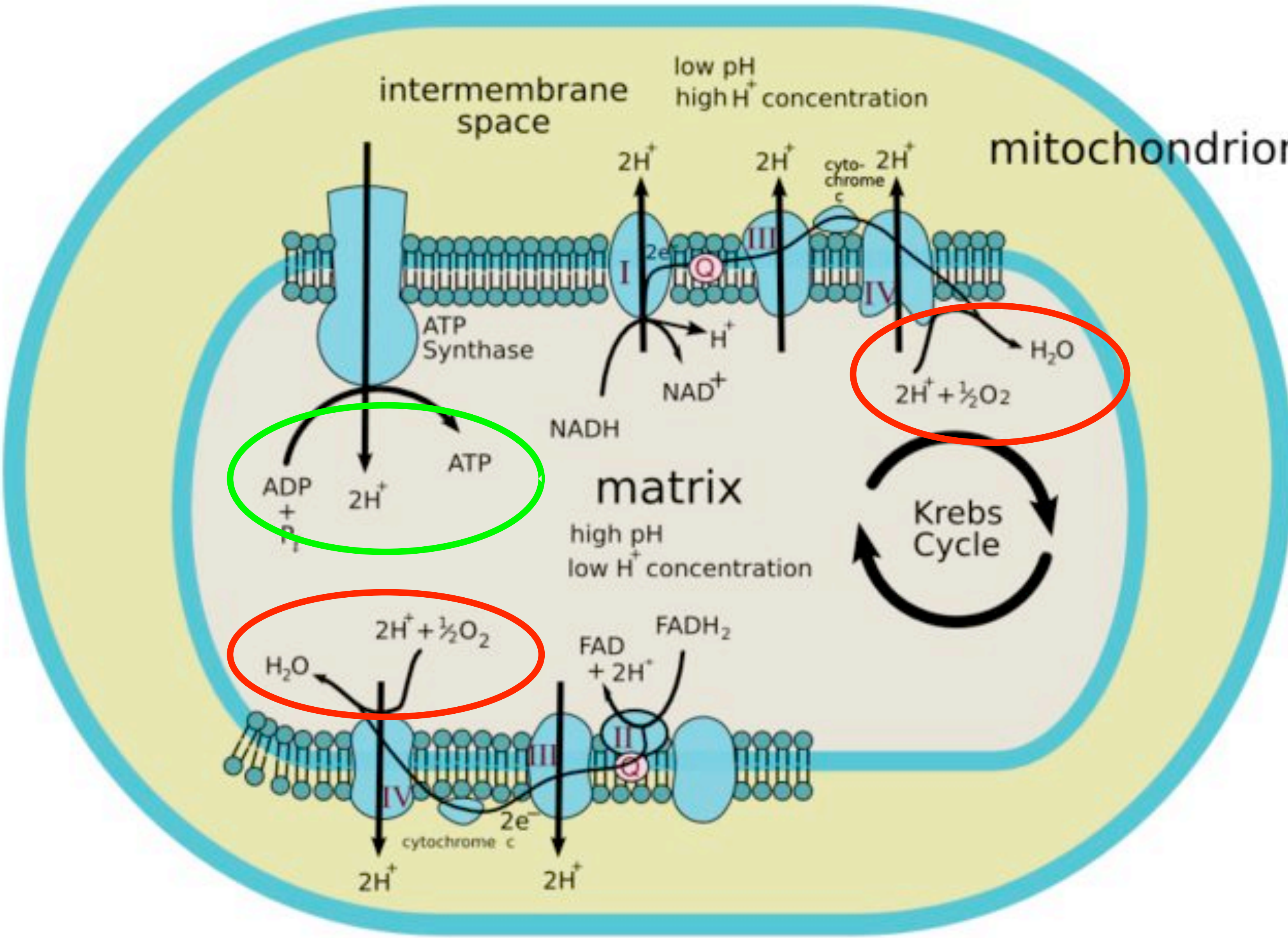
Acetyl-CoA		CoA-SH
3 NAD+		3 NADH
FAD	→	3 H+
GDP		$FADH_2$
Pi		GTP
2 H_2O		**+ 2 CO_2**

Mitochondria
The cellular powerhouse



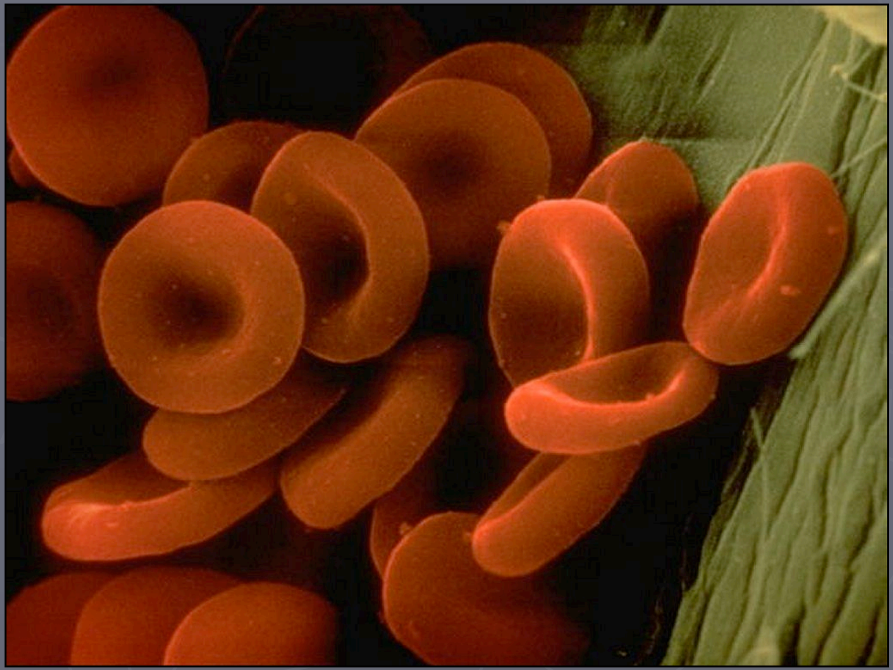
Mitochondria
The cellular powerhouse

Mitochondrial Electron Transport Chain



What role does blood play?

- Red Blood Cells:
  - Transport O_2 from the air to the tissues
  - Help transport CO_2 from the tissues to the air

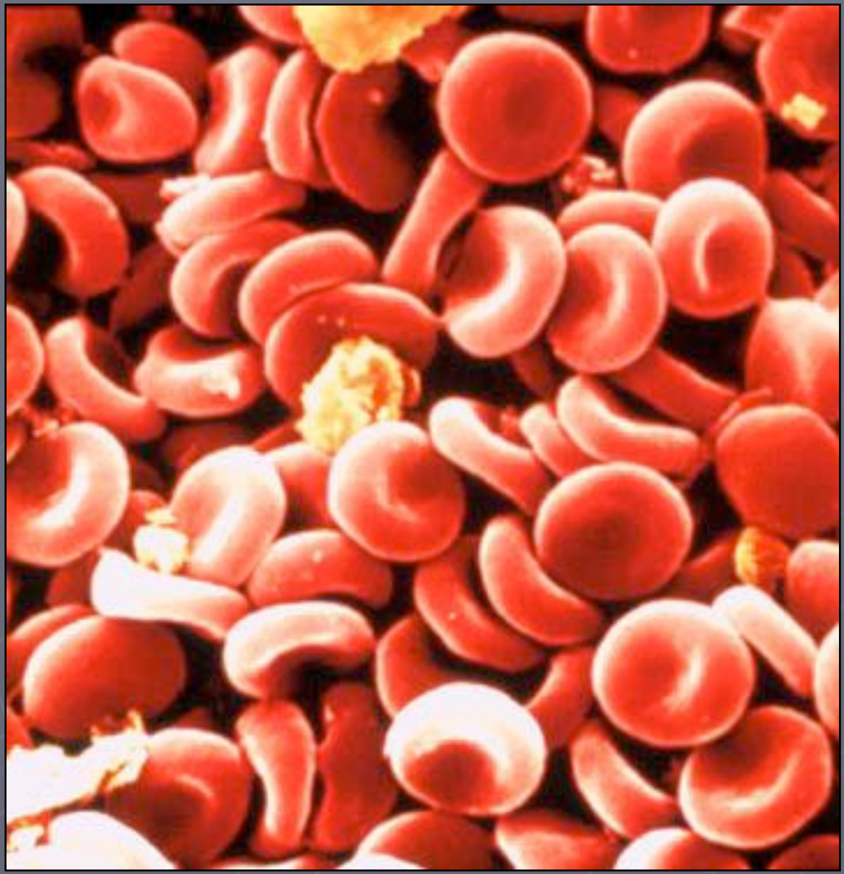


Red Blood Cells

- Made in Bone Marrow
  - Erythropoeitin (EPO)
- Expel organelles, including nucleus
  - Can't make protein
  - 120 day lifespan
  - Destroyed by spleen
- Mostly Hemoglobin (Hb)

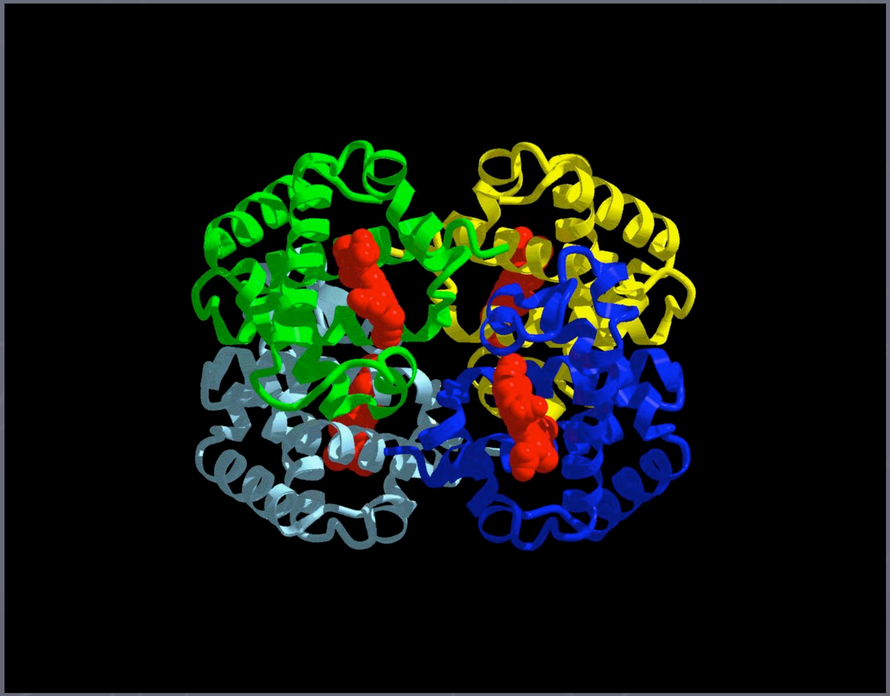
Red Blood Cells

- Gas transfer into and out of the cell is proportional to surface area/volume ratio
- Specialized "biconcave" membrane shape maximizes surface area/volume ratio
- Hb acts as O2/CO2 carrier



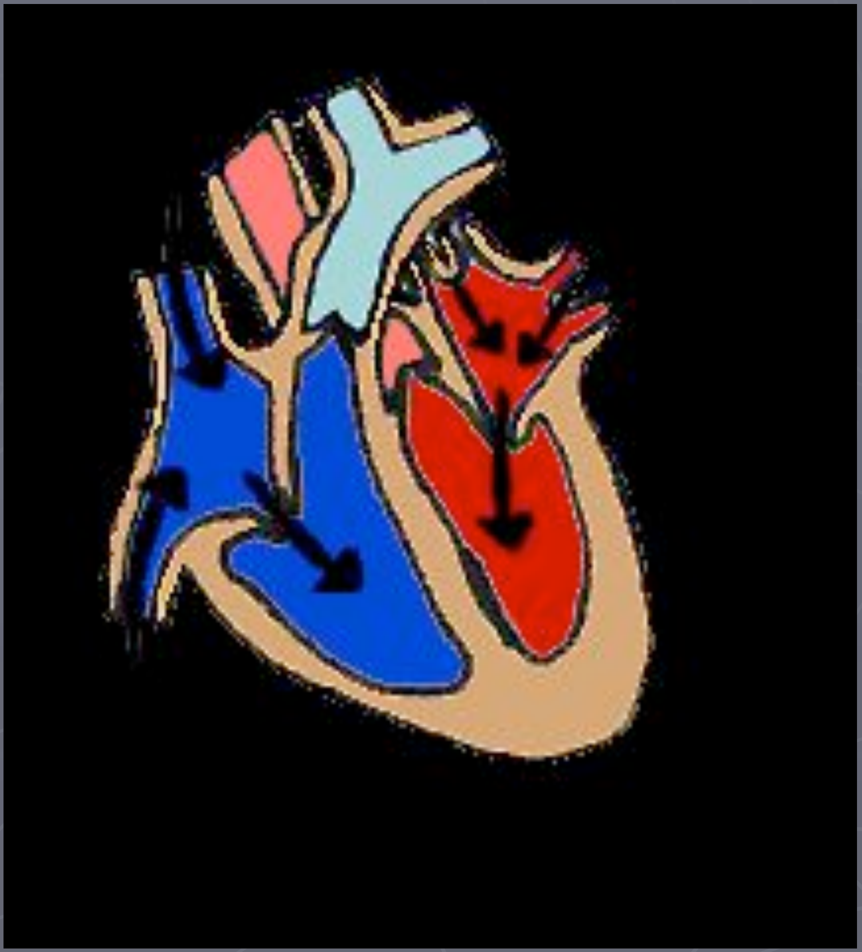
Hemoglobin

- Blood plasma can carry very little dissolved oxygen in solution (~2%)
- Hemoglobin is required to carry the vast majority of the oxygen (98%)



Hemoglobin

- If the body had to depend upon dissolved oxygen in the plasma to supply oxygen to the cells, the heart would have to pump 140 liters per minute (instead of 4 liters per minute).

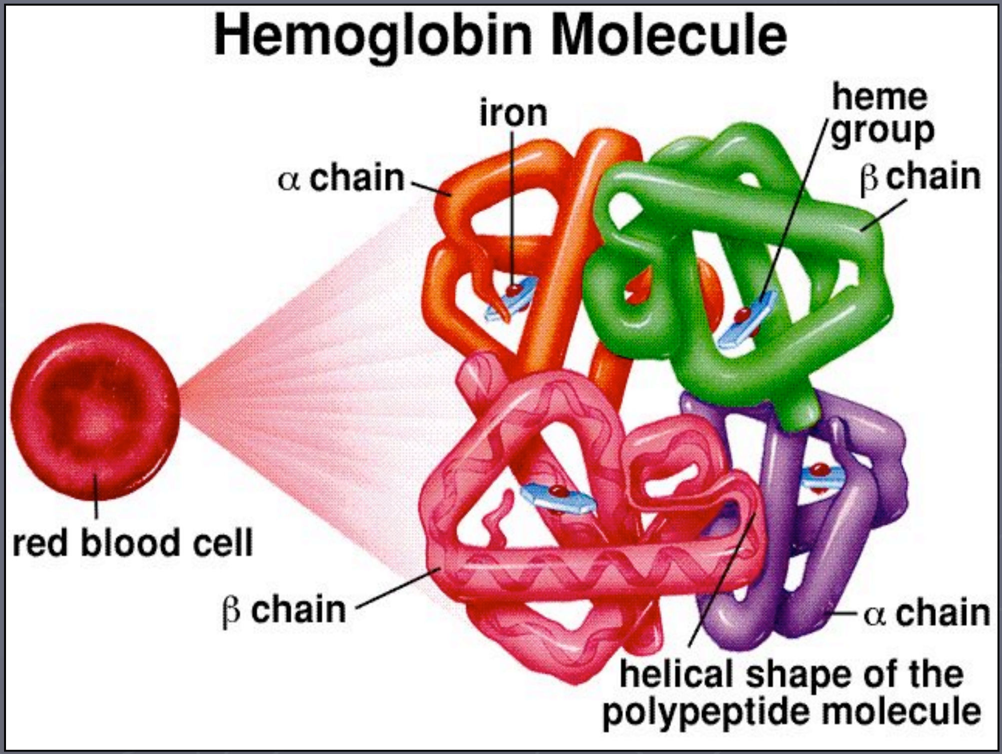


Hemoglobin

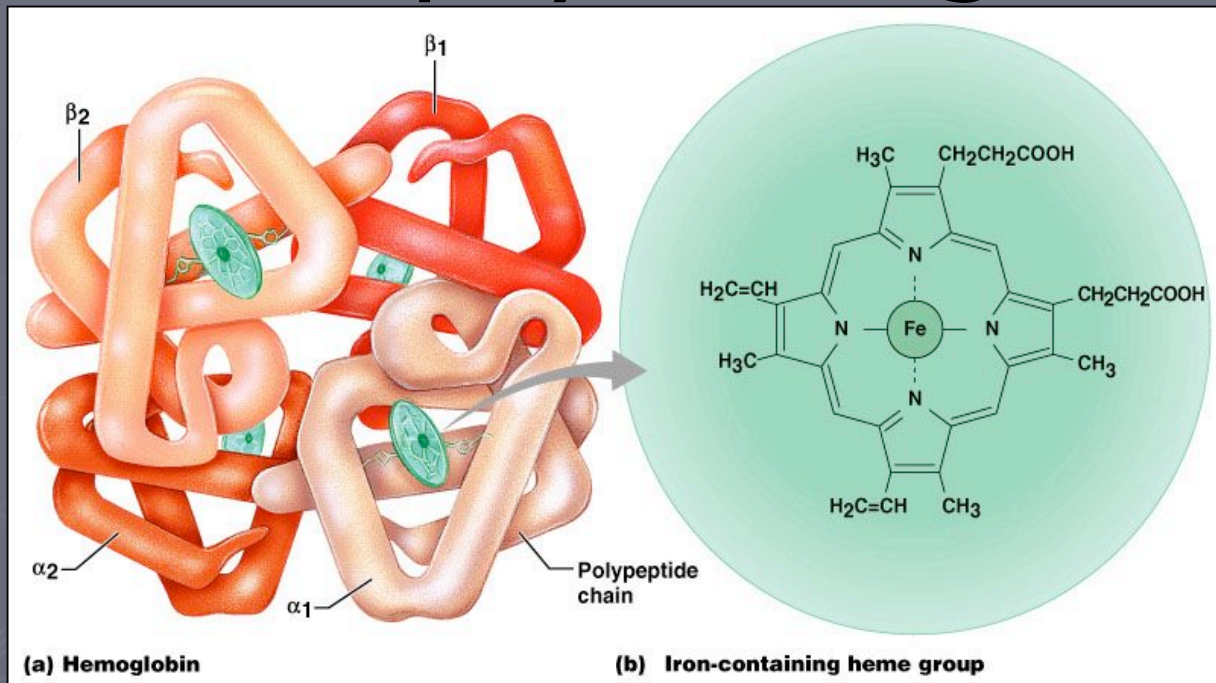
- Each red blood cell can carry about one million molecules of oxygen
- Hemoglobin is 97% saturated when it leaves the lungs
- Under resting conditions is it about 75% saturated when it returns.

Hemoglobin

- Hemoglobin has two protein components: alpha and beta
- 2 alpha + 2 beta
- Work together to bind and release oxygen



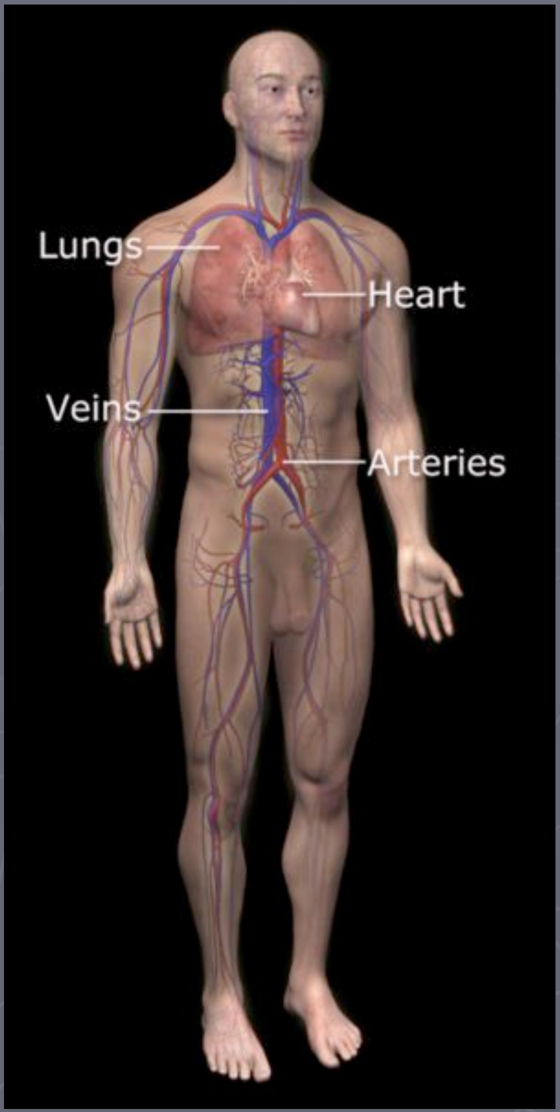
Porphyrin Ring



- At the core of the molecule is porphyrin ring which holds an iron atom.
- An iron containing porphyrin is termed a heme.
- This iron atom is the site of oxygen binding.

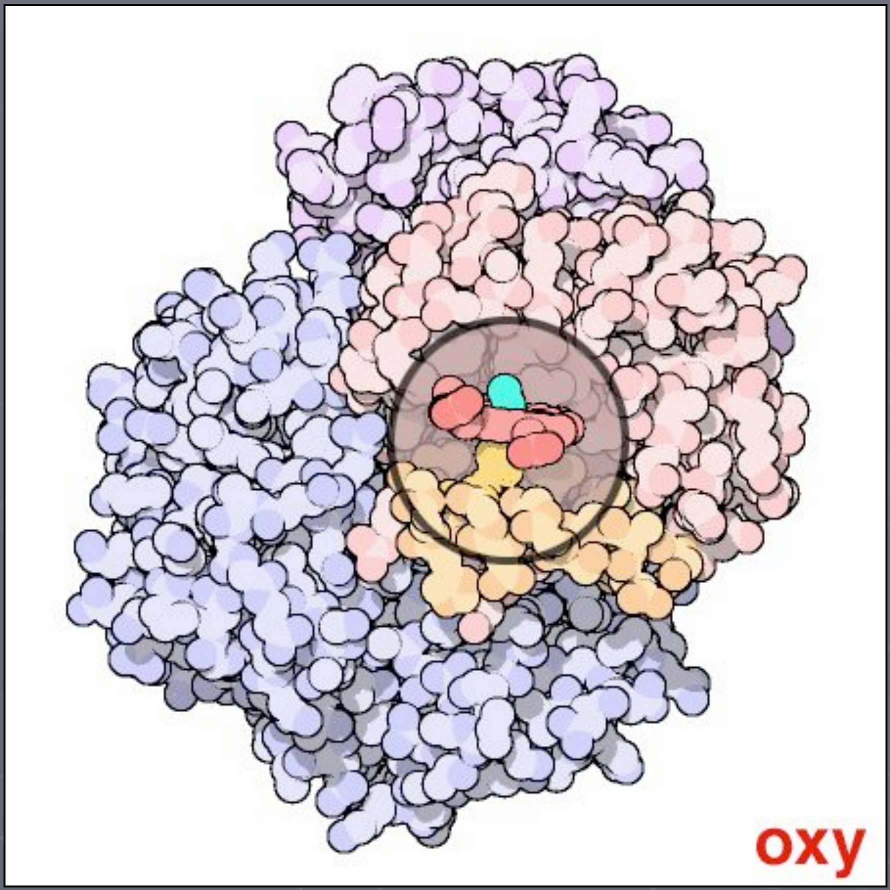
The Delivery Problem

- Do we want Hb to have a high or low affinity for oxygen?
- BOTH!
- Lungs: high affinity
  - Hb steals O2 from air
- Tissue: low affinity
  - Hb gives up O2 to cells
- Can we have our cake and eat it too?



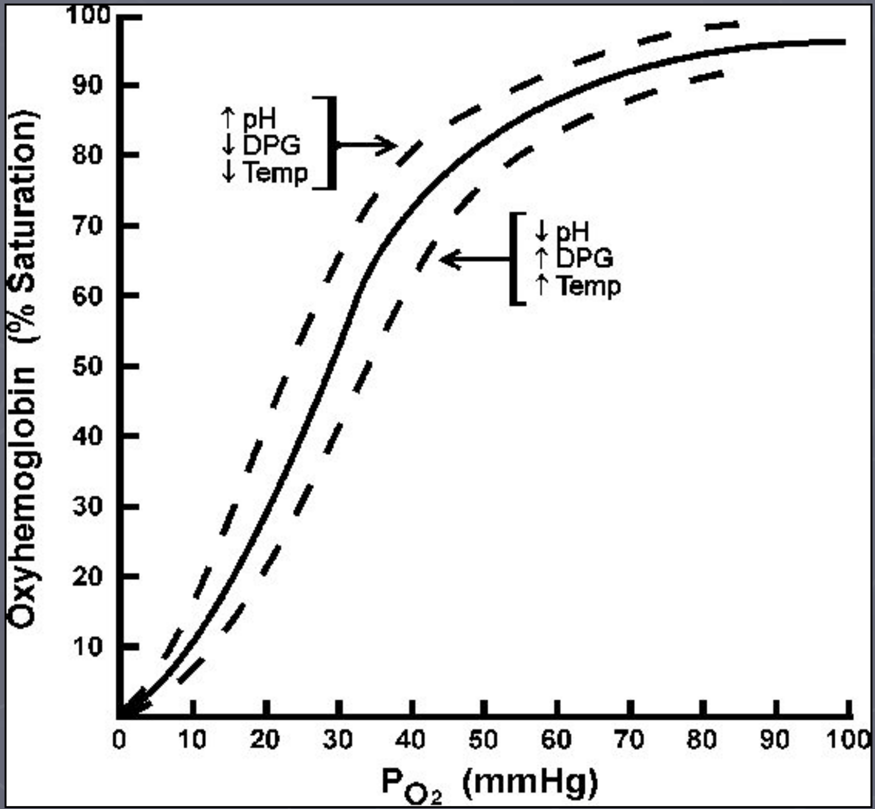
T and R states

- **Lungs**: oxy-Hb in the **R-state**
  - Hb "relaxed", exposing O_2 binding sites
  - **High affinity for O_2**
- **Tissues**: deoxy-Hb in the **T-state**
  - O_2 binding sites "tightly" guarded
  - **Low affinity for O_2**



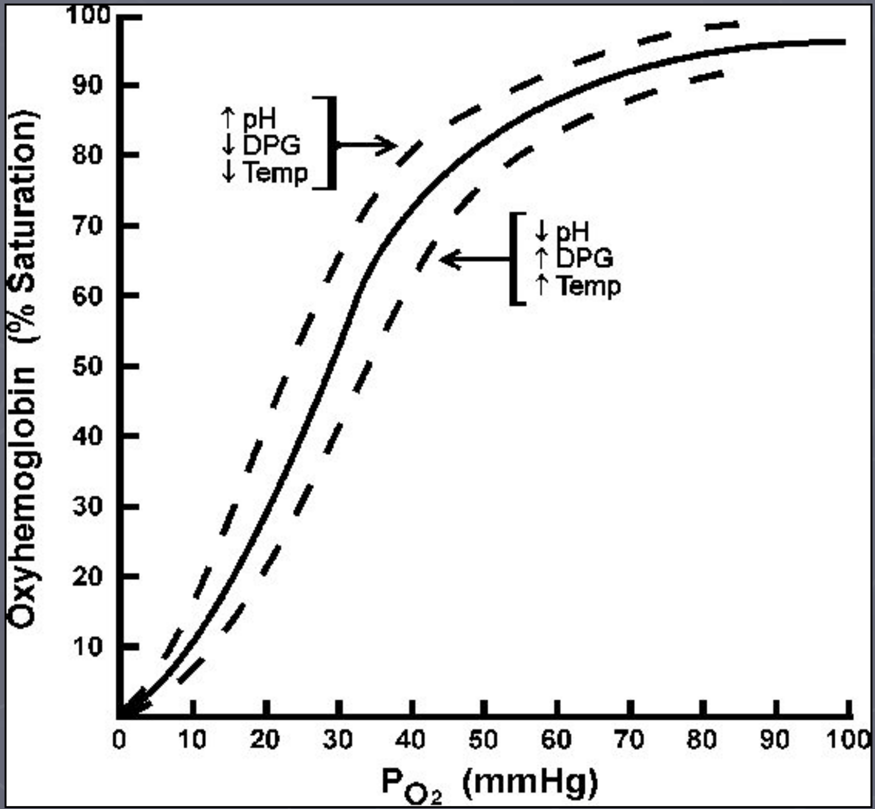
Cooperativity - Lungs

- All four O_2 binding sites don't **bind O_2** all at once
- Once the first heme binds oxygen, it introduces small changes in the structure of that alpha or beta chain, starting the **T** → **R** transition
- Each successive O_2 binds more easily
- **O_2 loads quickly**



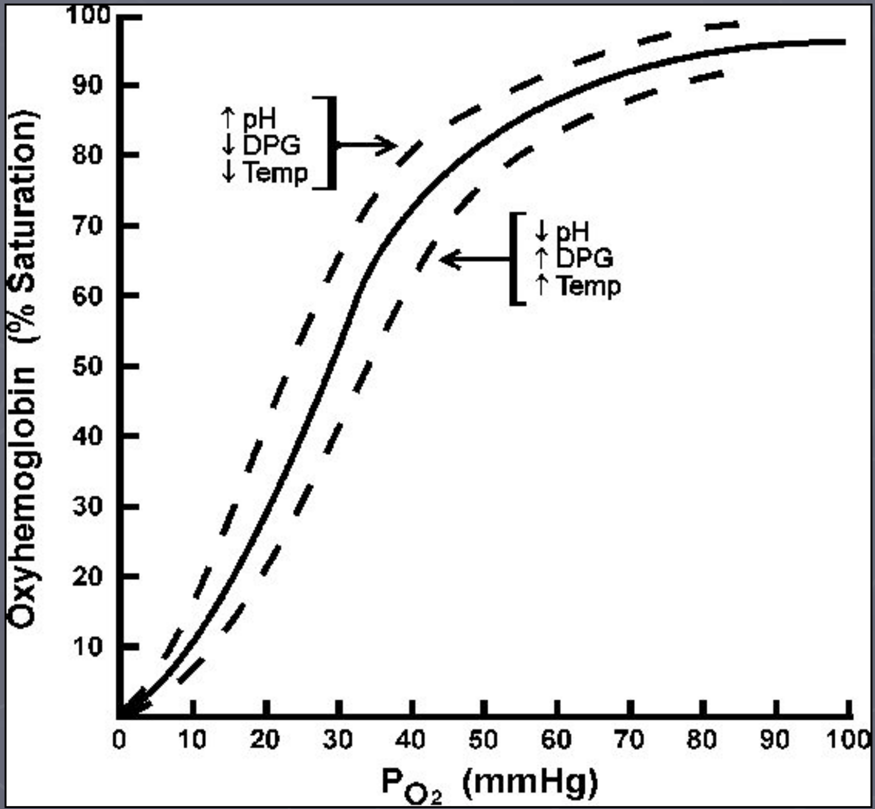
Cooperativity - Tissues

- All four O_2 binding sites don't **release O_2** all at once either
- Once the first heme releases oxygen, it introduces small changes in the structure of that alpha or beta chain, starting the **R** → **T** transition
- Each successive O_2 releases more easily
- **O_2 unloads quickly**



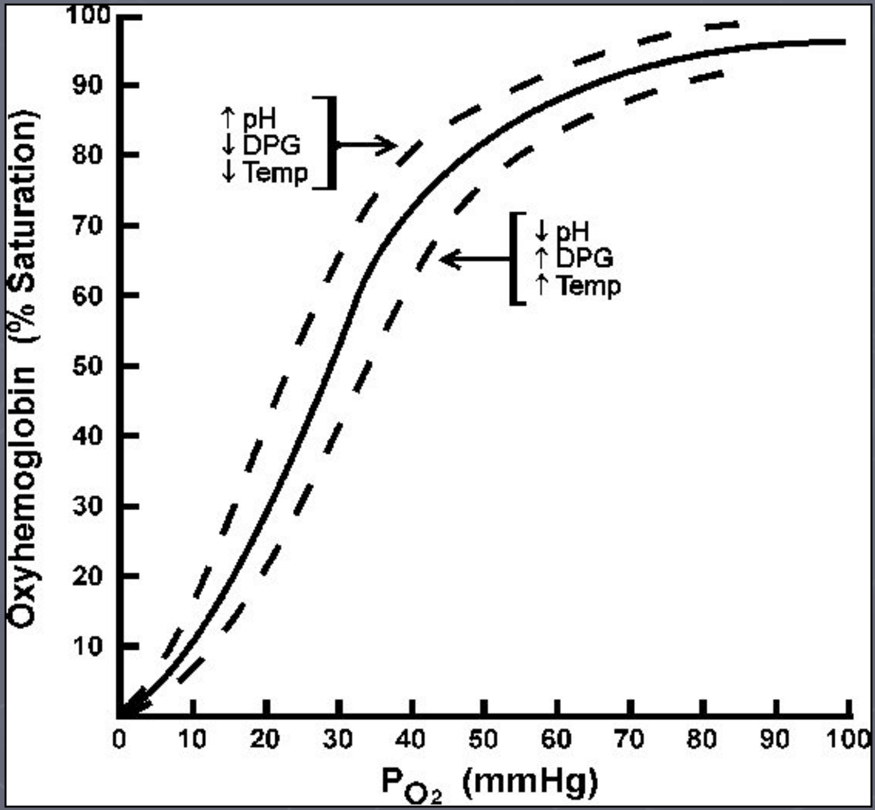
Bohr Effect

- Hemoglobin is also pH sensitive
- CO_2 is an acid in water (blood)
- Lungs → low CO_2 → "base" environment encourages oxygen binding R-state
- Tissues → high CO_2 → "acid" environment encourages oxygen releasing T-state



2,3-Bisphosphoglycerate (DPG)

- Production induced by hypoxia (altitude, exercise, etc.)
- Binds to Hb to stabilize the T state (low affinity for O2)
- Causes Hb to give up O2 to the tissues more easily



What role does blood play?

- Red Blood Cells:
  - Transport O_2 from the air to the tissues
  - Help transport CO_2 from the tissues to the air

Removal of CO_2 by RBCs

- Like O_2, very little CO_2 dissolves directly in the blood
- Carbonic anhydrase (in RBCs) catalyzes conversion to bicarbonate and acid (water soluble)
- Increases the CO_2 carrying capacity of the blood
- Deoxy-Hb can also bind a small amount of CO_2

<u>carbonic anhydrase</u>

$$CO_2 + H_20$$

$$\downarrow\uparrow$$

$$H_2CO_3$$

$$\downarrow\uparrow$$

$$HCO_3^- + H^+$$

Removal of CO_2 by RBCs

- CO_2 is an acid in water (blood)
- Bohr Effect:
  - Tissues → high CO_2 → "acid" environment encourages oxygen releasing T-state Hb
  - Lungs → low CO_2 → "base" environment encourages oxygen binding R-state Hb

carbonic anhydrase

$$CO_2 + H_20$$

$$\downarrow\uparrow$$

$$H_2CO_3$$

$$\downarrow\uparrow$$

$$HCO_3^- + H^+$$

Blood Gas Measurements

- Arterial Blood Gases
- pH / pO_2 / pCO_2 / HCO_3^-
  - pH: 7.36-7.44
  - pO_2: 75-100 mmHg
  - pCO_2: 35-45 mmHg
  - HCO_3^-: 22-30 mmol/L

- Venous Blood Gases
- pH / pO_2 / pCO_2 / HCO_3^-
  - pH: 7.32-7.42 (-0.04)*
  - pO_2: 25-40 mmHg (-60)
  - pCO_2: 40-50 mmHg (+5)
  - HCO_3^-: 22-30 mmol/L (~) (more on this in renal lectures)

* Note: pH values don't change much. Deoxy-Hb in venous blood acts as a buffer to counteract the acidity of the CO_2. This is an example of a "homeostatic" mechanism.

* This difference in pH, while small, is the key to the respiratory drive

Hyperventilation

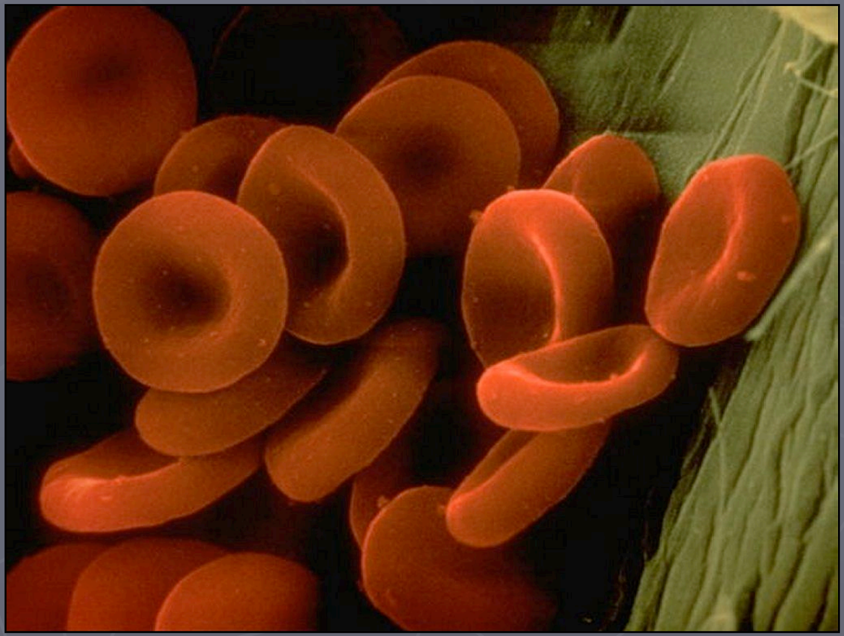
- ↓CO_2 → ↑pH (more basic)
  - "respiratory alkalosis"
  - Occurs normally during exercise (↑O_2)
  - Can also be a compensation for acidic blood
    - Methanol / ethylene glycol ingestion
    - Kidney failure
    - Diabetic ketoacidosis
    - All very dangerous!

Hypoventilation

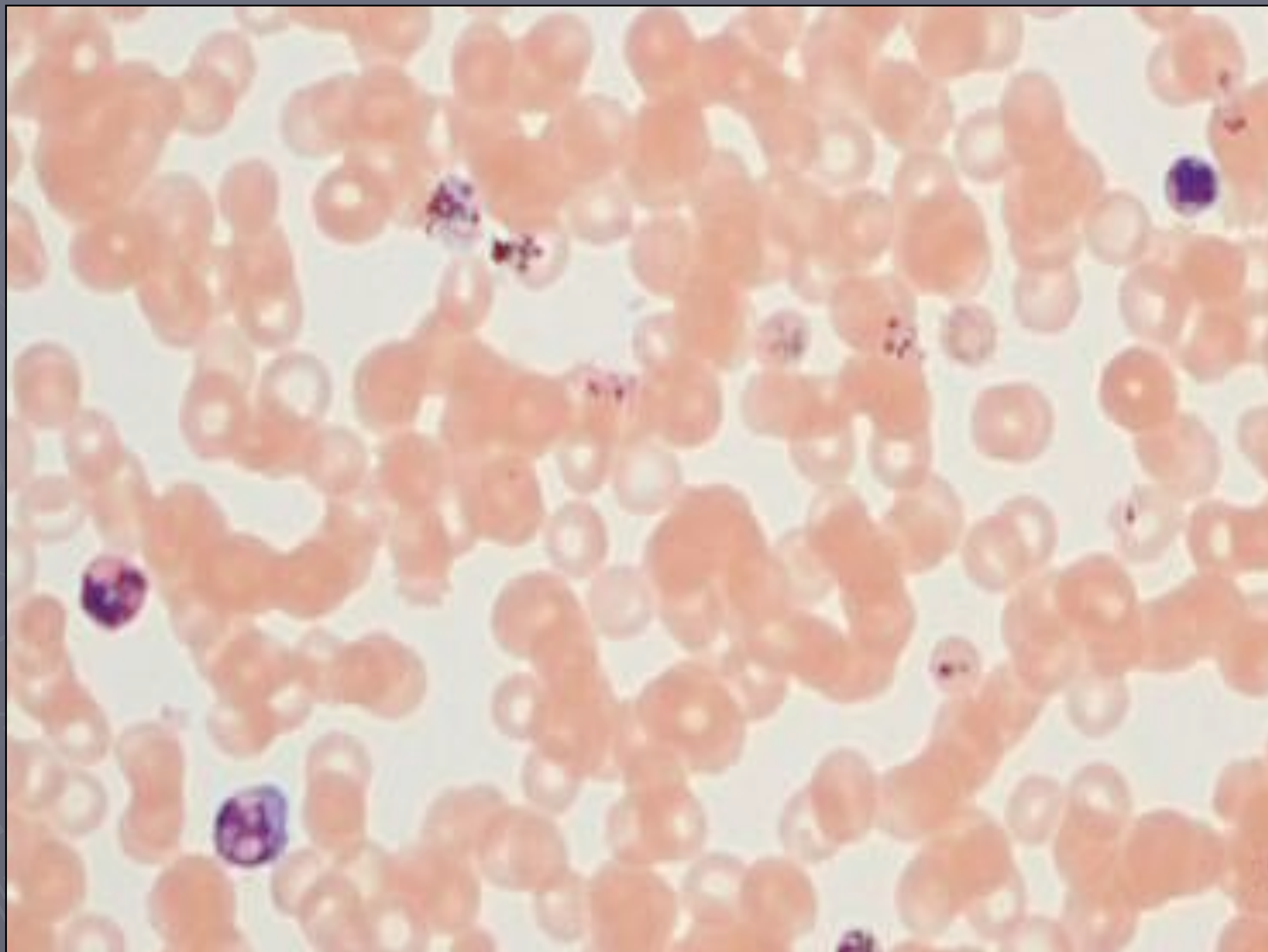
- ↑CO_2 → ↓pH (more acidic)
  - "respiratory acidosis"
  - Never normal! Very dangerous! (↓O_2)
  - Usually indicates failure of the respiratory drive
    - Drug overdose (Opiates, Benzos, Barbies, GHB, etc.)
    - Brain damage / spinal cord damage
    - MS, Polio, etc.

Diseases of Red Blood Cells

- Iron Deficiency
- Sickle Cell Anemia
- Thalassemia
- Porphyria
- Malaria

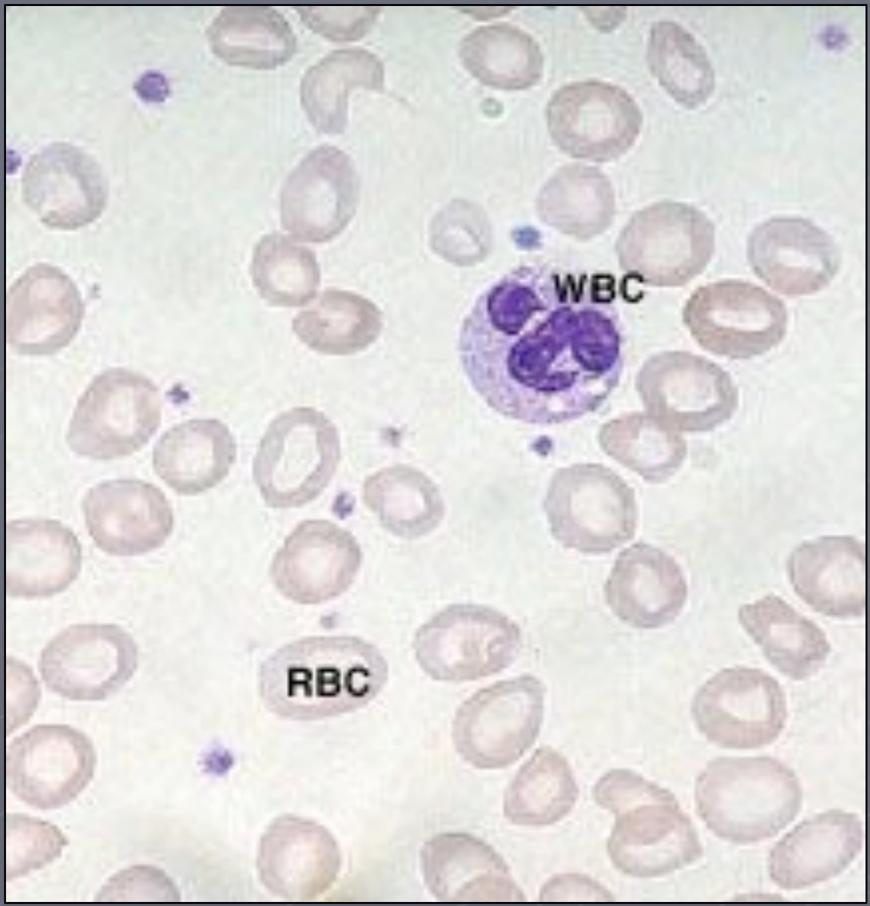


Normal Peripheral Blood Smear



Iron Deficiency

- Iron deficient red blood cells
- Low number of cells
- Note the hollow and blanched appearance of the red blood cells

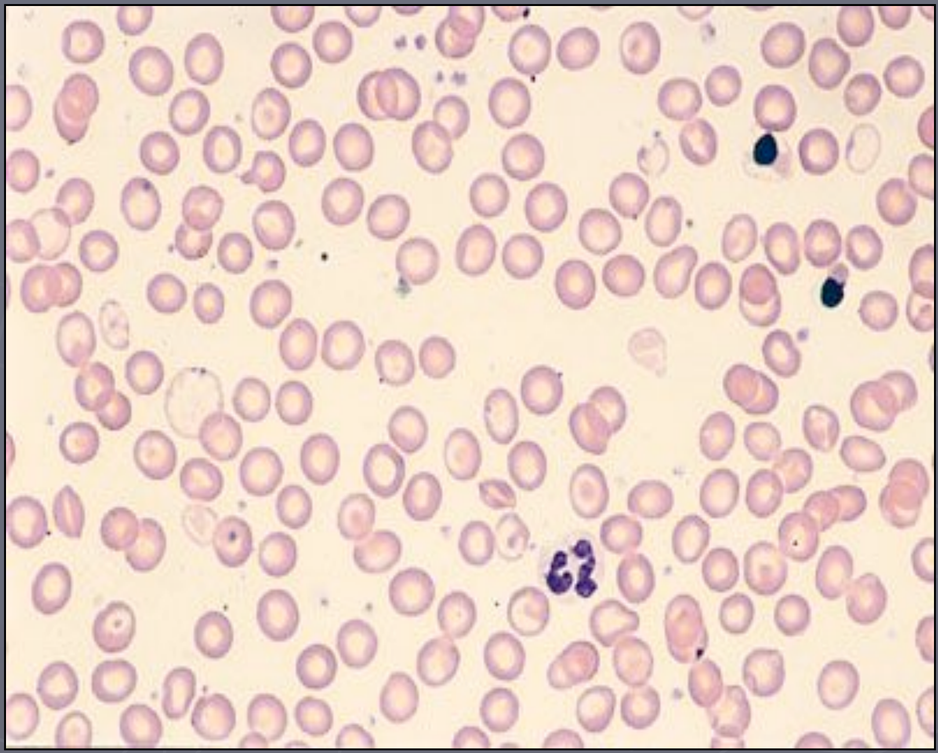


Sickle Cell anemia

- Genetic disorder characterized by hard, sticky, sickle-shaped red blood cells
- This disease is caused by a mutation in hemoglobin
- Causes RBCs to get stuck in tissues
- Painful, even fatal

Thalassemia

- Each hemoglobin needs 2 alphas and 2 betas
- Need the SAME NUMBER of alphas and betas
- Deficiency of either causes deficiency of hemoglobin
- Leftovers are bad too - can aggregate and form "inclusion bodies" that harm the cell
- The result is anemia - not enough red blood cells

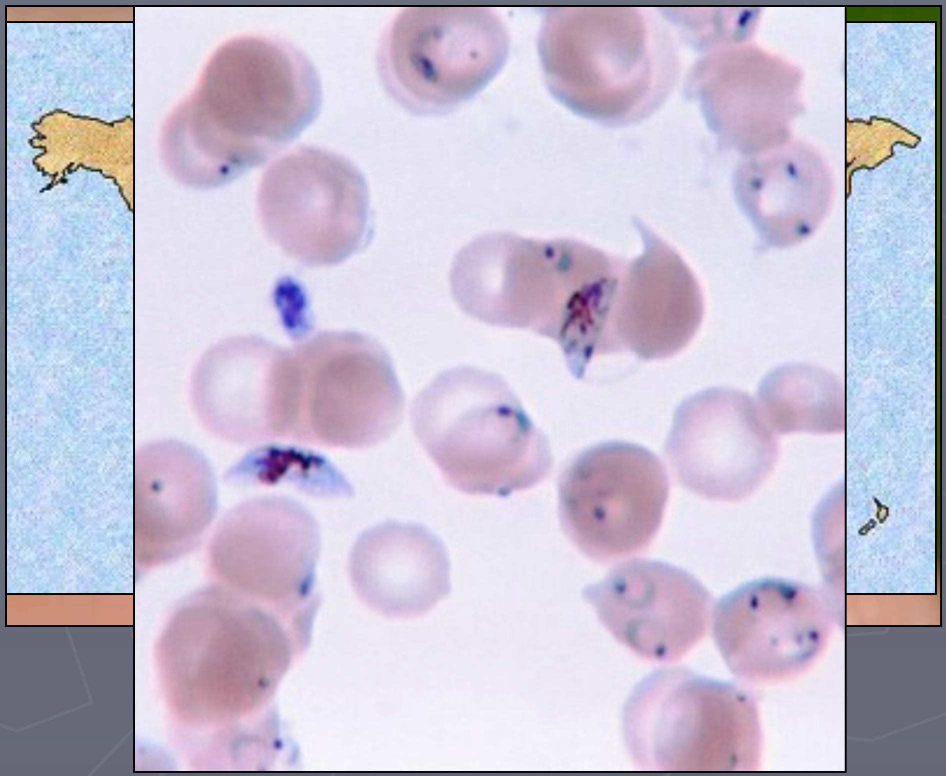


Porphyria

- Porphyria is a group of different disorders caused by abnormalities in the chemical steps leading to the production of heme
- It is characterized by extreme sensitivity to light (exposure to sunlight causes vesicular erythema), reddish-brown urine, reddish-brown teeth, and ulcers which destroy cartilage and bone, causing the deformation of the nose, ears, and fingers. Mental aberrations, such as hysteria, manic-depressive psychosis, and delirium, characterize this condition as well.

Malaria

- Anopheles mosquito
- Equatorial distribution
- Parasite infects RBCs
- Conditions that decrease RBC lifespan infer resistance (SCA, thalasemia, etc.)
- Race-specific disease incidence



Question 1

- Which of the following is true of the process of cellular respiration:
  - A) Generates O2, Consumes CO2
  - B) Consumes O2, Generates CO2
  - C) Causes overall increase in ATP
  - D) Causes overall decrease in ATP
  - E) A + C
  - F) A + D
  - G) B + C
  - H) B + D

Question 2

- Erythropoeitin (EPO) has which of the following effects:
  - A) Shifts Hb oxygenation curve to the right
  - B) Shifts Hb oxygenation curve to the left
  - C) Increase in hematocrit (↑ # of RBCs)
  - D) Decrease in hematocrit (↓ # of RBCs)
  - E) A + C
  - F) A + D
  - G) B + C
  - H) B + D

Question 3

- Which of the following is true of red blood cells:
  - A) They have a biconvex cellular membrane
  - B) They consume less O_2 than the average cell
  - C) They are normally very rigid and inflexible
  - D) They are increased in number in anemia
  - E) All of the above

Question 4

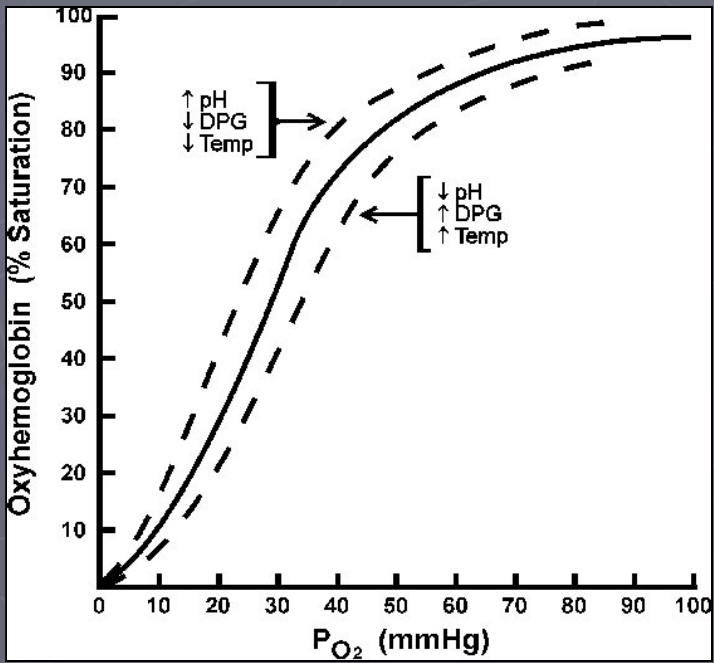
- Which combination makes a normal Hb molecule:
  - A) 2 α , 2 β, 2 porphyrin rings, 2 Fe atoms
  - B) 4 α , 4 β, 4 porphyrin rings, 4 Fe atoms
  - C) 4 α , 4 β, 4 porphyrin rings, 4 Fe atoms
  - D) 2 α , 2 β, 4 porphyrin rings, 4 Fe atoms

Question 5

- Which is true for a normal Hb molecule:
  - A) T state in Tissues, low affinity for O_2
  - B) T state in Lungs, low affinity for O_2
  - C) R state in Tissues, high affinity for O_2
  - D) R state in Lungs, high affinity for O_2
  - E) A + C
  - F) A + D
  - G) B + C
  - H) B + D

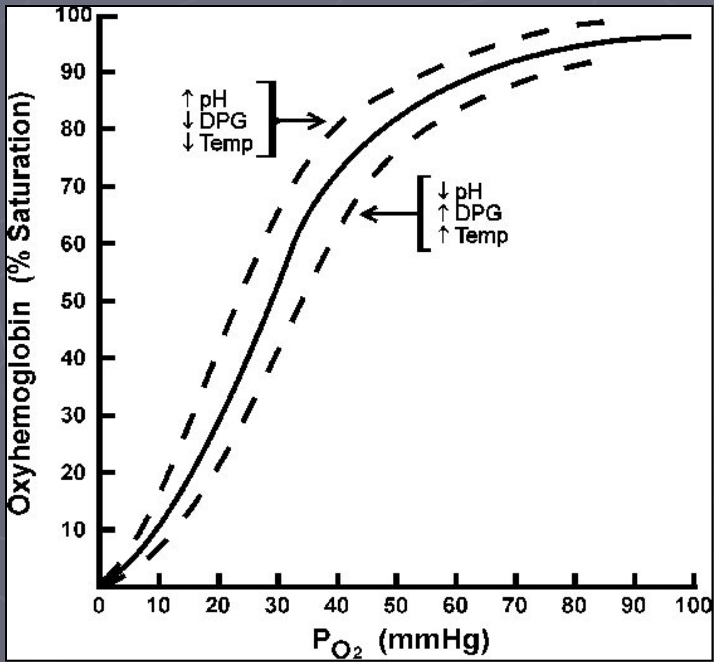
Question 6

- Cooperativity has what effect on the Hb-O_2 dissociation curve:
  - A) Gives the curve a sigmoid shape
  - B) Shifts the curve up
  - C) Shifts the curve down
  - D) Shifts the curve left
  - E) Shifts the curve right



Question 7

- By the Bohr effect, an increase in CO_2 has what effect on the Hb-O_2 dissociation curve:
  - A) Gives the curve a sigmoid shape
  - B) Shifts the curve up
  - C) Shifts the curve down
  - D) Shifts the curve left
  - E) Shifts the curve right



Question 8

- By binding 2,3-BPG with less affinity, fetal Hb has which characteristic change in its Hb-O_2 dissociation curve :
  - A) Gives the curve a sigmoid shape
  - B) Shifts the curve up
  - C) Shifts the curve down
  - D) Shifts the curve left
  - E) Shifts the curve right