M.SC Semester III
Core Course XI
Bio-Inorganic Chemistry

TOPIC:-Unit III, Oxygen dissociation curve (ODC)

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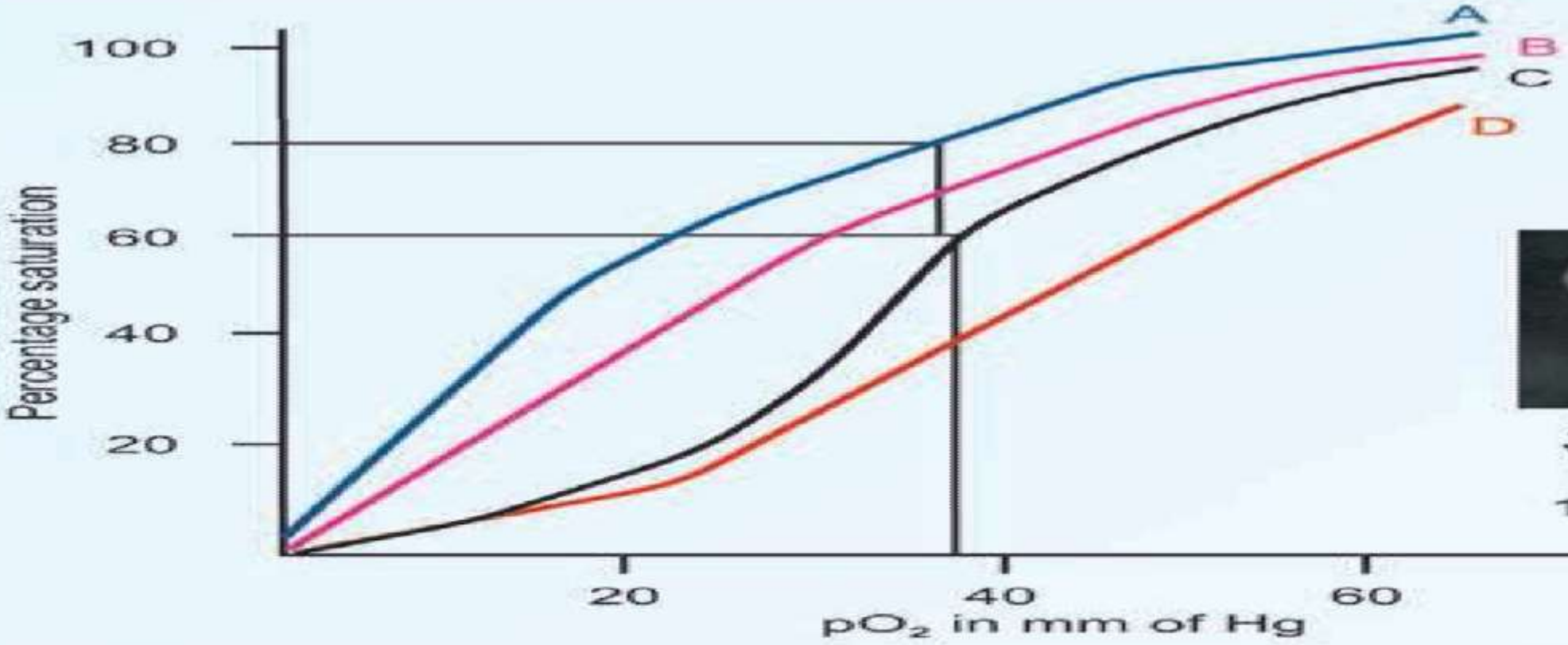
Oxygen dissociation curve (ODC)



Archibald Vivian Hill
NP 1922
1886-1977

A—Theoretical curve as per mass action. **B**—Sigmoid curve, due to heme-heme interaction (Hill effect). **C**—Further shift to right due to carbon dioxide (Bohr effect) and BPG. This curve represents the pattern under normal conditions. **D**—Further shift to right when temperature is increased to 42°C.

Christian Bohr
(1855-1911)

Factors affecting oxygen dissociation curve

- **Heme-heme Interaction & Cooperativity:**
- The oxygen dissociation curve (ODC) is sigmoid shape.
- The binding of O_2 to one heme residue increases the affinity of remaining heme residues for O_2.
- Thus the affinity of Hb for the last O_2 is about 100 times greater than the binding of the first O_2 to Hb.
- This is called positive cooperativity

- Release of O2 from one heme facilitates the release of O2 from others.
- The quaternary structure of oxy-Hb is described as R (relaxed) form; & deoxy- Hb is T(tight) form.

$2\alpha + 2\beta$ (Deoxy-Hb – T-form) $\longrightarrow$ $2\alpha,\beta$ (Oxy-Hb – R-form)

T and R forms of hemoglobin

- The four subunits ($\alpha_2\beta_2$) of hemoglobin are held together by weak forces.
- The relative position of these subunits is different in oxyhemoglobin compared to deoxyhemoglobin.
- **T-form of Hb:**
- The deoxy form of Hb exists in T or taut (tense) form.
- The H & ionic bonds limit the movement of monomers.
- The T-form of Hb has low oxygen affinity.

R-form of Hb

- The binding of O2 destabilizes some of the hydrogen & ionic bonds particularly between αβ dimers.
- This results in a relaxed form or R-form of Hb
- Therefore, the R-form has high oxygen affinity.

Transport of CO_2 by hemoglobin

- In aerobic metabolism, for every molecule of O_2 utilized, one molecule of CO_2 is liberated.
- Hemoglobin actively participates in the transport of CO_2 from the tissues to the lungs.
- About 15% of CO_2 carried in blood directly binds with Hb.
- The rest of the tissue CO_2 is transported as bicarbonate (HCO_3).

- CO_2 molecules are bound to the uncharged α-amino acids of hemoglobin to form carbamyl hemoglobin.
- The oxyHb can bind 0.15 moles CO_2/mole heme, whereas deoxyHb can bind 0.40 moles CO_2/mole heme.
- The binding of CO_2 stabilizes the T(taut) form of hemoglobin structure, resulting in decreased O_2 affinity for Hb.

Hemoglobin also helps in the transport of CO_2 as bicarbonate

- CO_2 enters the blood from tissues, the enzyme carhonic anhydrase present in erythrocytes catalyses the formation of carbonic acid (H_2CO_3).
- Bicarbonate (HCO_3^-) & proton (H^+) are released on dissociation of carbonic acid
- Hb acts as a buffer & immediately binds with protons

- Every 2protons bound to Hb, 4oxygen molecules are released to the tissues.
- In the lungs, binding of O_2 to Hb results in the release of protons.
- The bicarbonate & protons combine to form carbonic acid.
- Acted upon by carbonic anhydrase to release CO_2, which is exhaled

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TOPIC:-Unit III, The Bohr Effect

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The Bohr Effect

- The binding of O_2 to hemoglobin decreases with increasing H^+ concentration (lower pH) or when the hemoglobin is exposed to increased partial pressure of CO_2 (pCO_2).
- This phenomenon is known as Bohr effect.
- It is due to a change in the binding affinity of O_2 to hemoglobin
- Bohr effect causes a shift in the oxygen dissociation curve to the right

- **Bohr effect is primarily responsible for the release of O_2 from the oxyhemoglobin to the tissue.**
- **This is because of increased pCO_2 & decreased pH in the actively metabolizing cells**
- ***Binding of CO_2 forces the release of O_2.***

Carbonic anhydrase

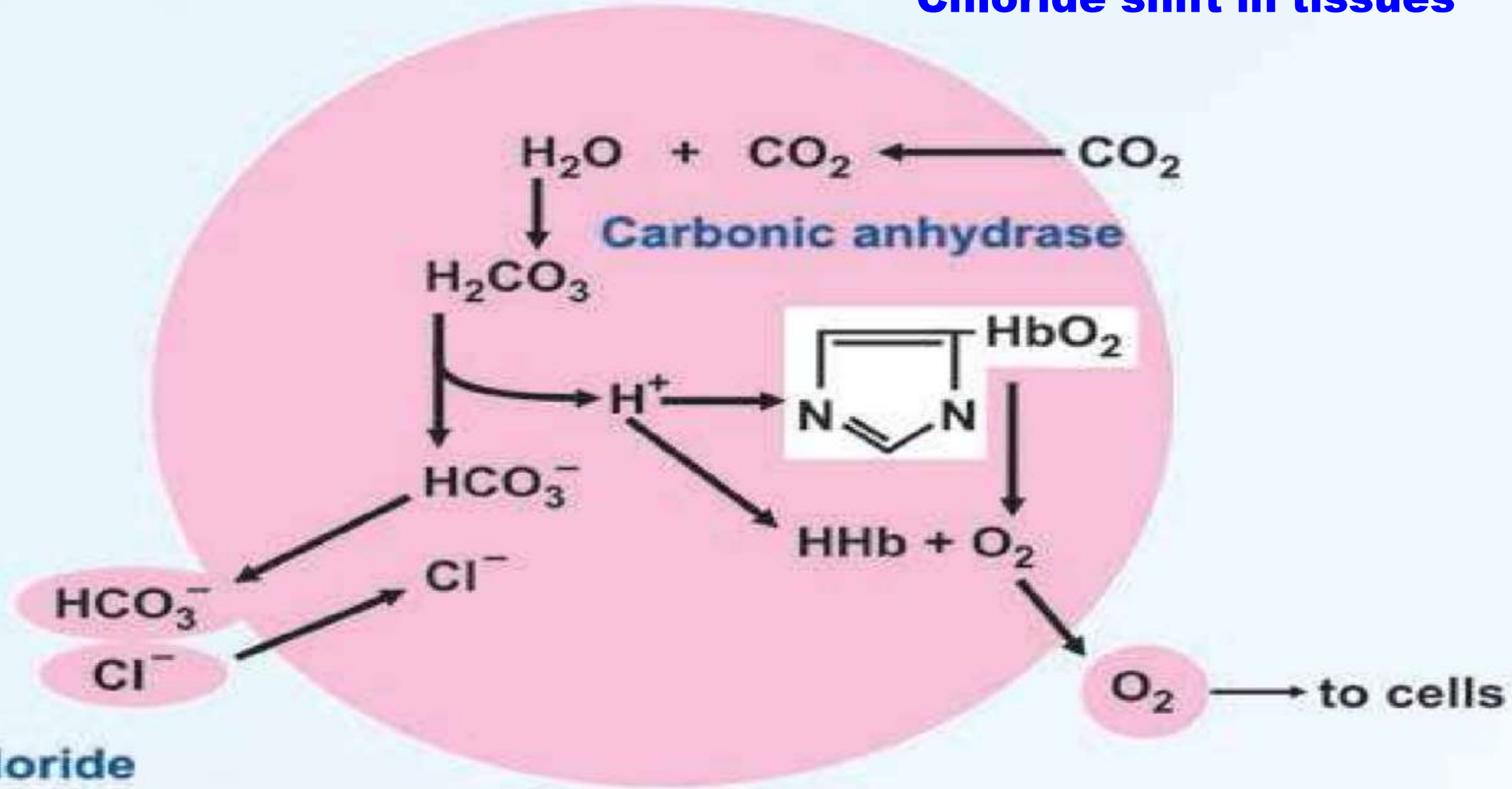
$$CO_2 + H_2O \longrightarrow H_2CO_3 \longrightarrow H^+ + HCO_3$$

- When carbonic acid ionizes, the intracellular pH falls.
- The affinity of Hb for O2 is decreased & O2 is unloaded to the tissues.

The Chloride Shift

- When CO_2 is taken up, the HCO_3^- concentration within the cell increases.
- This would diffuse out into the plasma.
- Chloride ions from the plasma enter into cell to establish electrical neutrality.
- This is called chloride shift or Hamburger effect.
- RBCs are slightly bulged due to the increased chloride ions

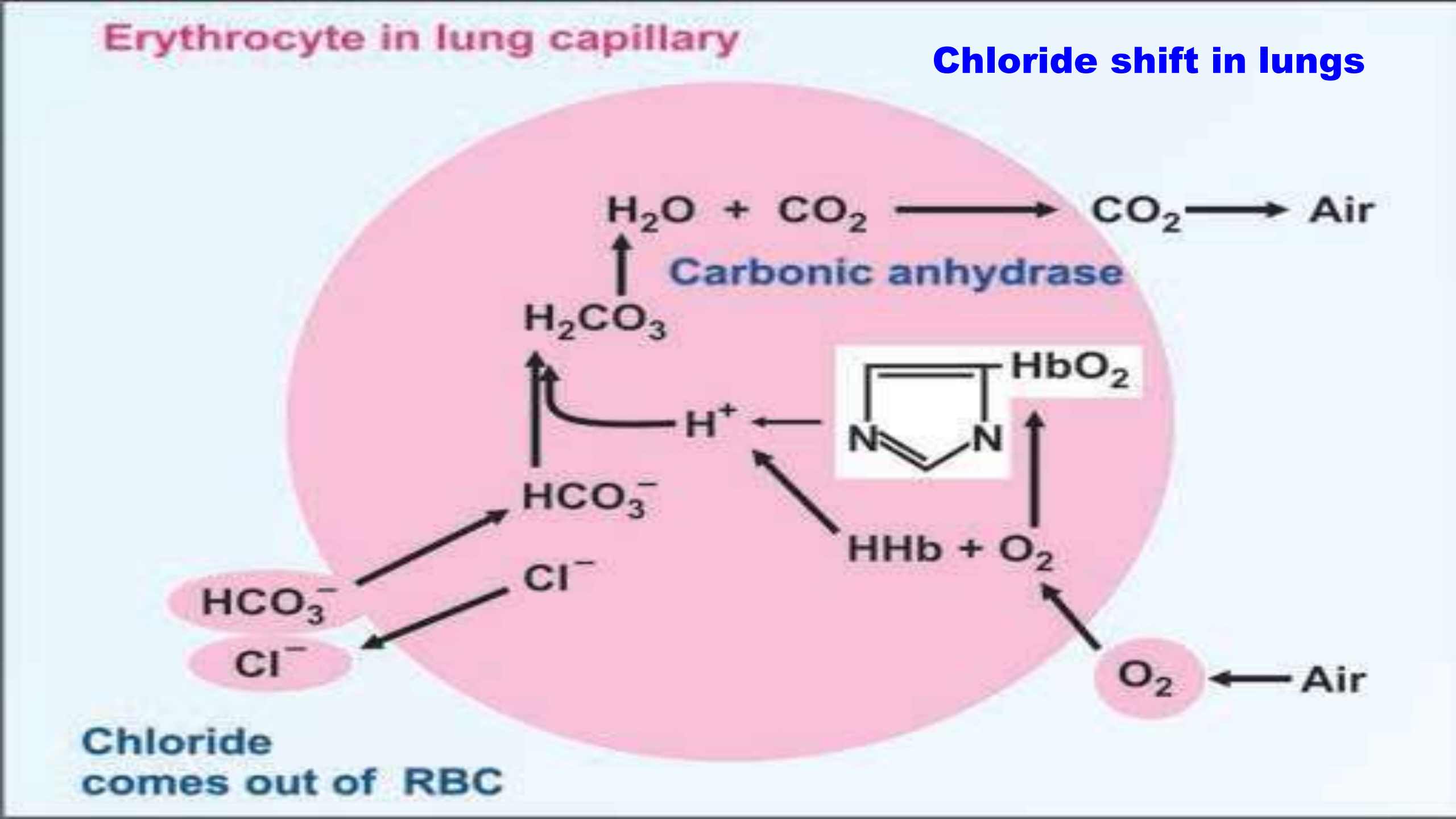
Chloride shift in tissues



When the blood reaches the lungs, the reverse reaction takes place.

- The deoxyhemoglobin liberates protons (H^+).
- These H^+ combine with HCO_3^- to form H_2CO_3.
- H_2CO_3 dissociated to CO_2 & H_2O by the carbonic anhydrase.
- The CO_2 is expelled.
- HCO_3^- binds H^+, more HCO_3^- from plasma enters the cell & Cl^- gets out (reversal of chloride shift)

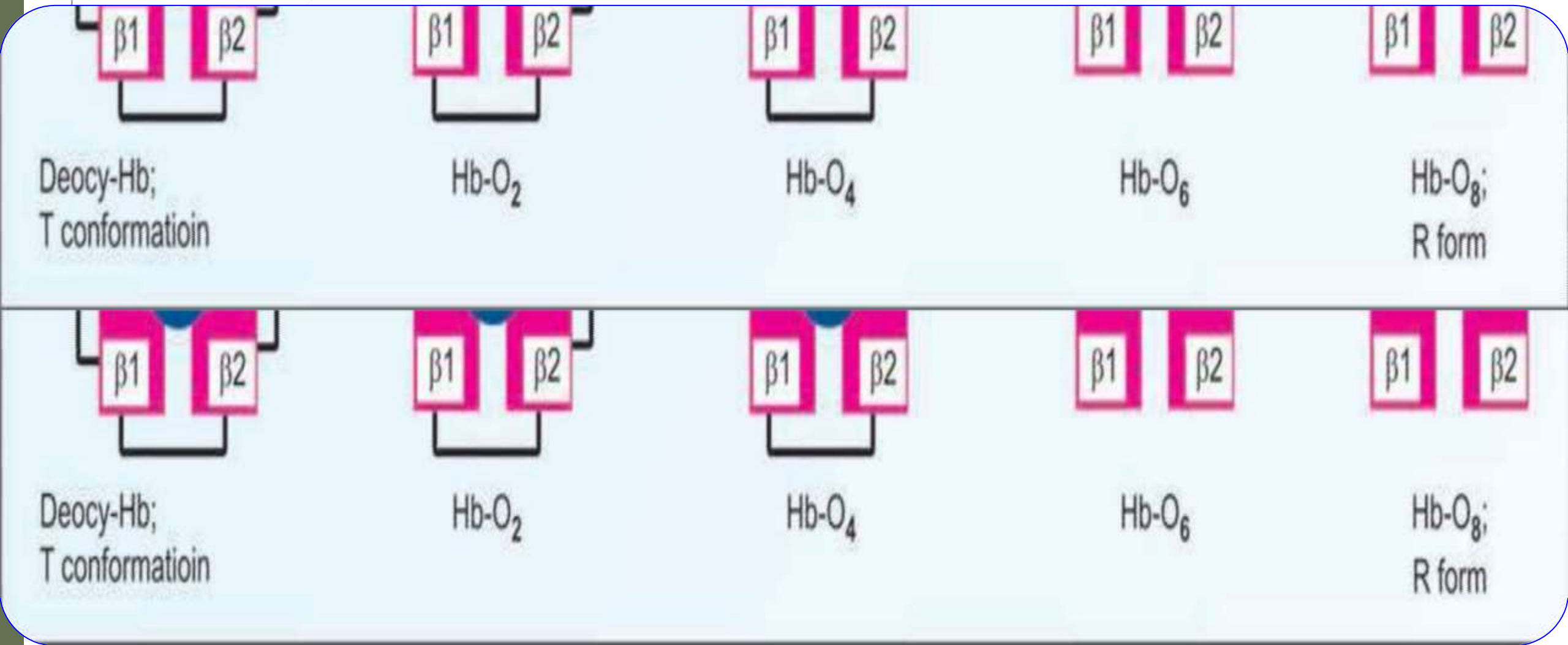
Chloride shift in lungs



Effect of 2,3-BPG

- 2,3-Bisphosphoglycerate is the most abundant organic phosphate in the erythrocyte.
- The 2,3-BPG is produced from 1,3-BPG, an intermediate of glycolytic pathway
- This short pathway, referred to as Rapaport-Leubering cycle
- The 2,3-BPG, binds to deoxy-Hb (and not to oxyhemoglobin) & decreases the O2 affinity to Hb & stabilizes the T conformation.

As oxygen is added, salt bridges are successively broken and finally 2,3-BPG is expelled. Simultaneously the T(taught) confirmation of deoxy-Hb is changed into R(relaxed) confirmation of oxy-Hb.
Blue circle represents 2,3-bisphosphoglycerate (BPG)



- When the Tform reverts to the Rconformation, the 2,3-BPG is ejected.
- The reduced affinity of O2 to Hb facilitates the release o f O2 at the partial pressure found in the tissues.
- 2,3-BPC shifts the oxygen dissociation curve to the right
- The high oxygen affinity of fetal blood (HbF) is due to the inability of gamma chains to bind 2,3-BPG.

Mechanism of action of 2,3-BPG

- One molecule of 2,3-BPG binds with one molecule (tetramer) of deoxyhemoglobin in the central cavity of the four subunits.
- This central pocket has positively charged (e.g. histidine, lysine) two β-globin chains.
- *Ionic bonds (salt bridges) are formed between the positively charged amino acids (of β-globins) with the negatively charged phosphate groups of 2,3-BPG*

- Binding of 2,3-BPG stabilizes the deoxygenated hemoglobin (T-form) by crosslinking the β -chains
- On oxygenation of hemoglobin, 2,3-BPG is expelled from the pocket and the oxyhemoglobin attains the R-form of structure

Clinical significance of 2,3-BPG

- In hypoxia:
- The 2,3-BPG in erythrocytes is elevated in chronic hypoxic conditions associated with difficulty in O2 supply.
- These include adaptation to high altitude, obstructive pulmonary emphysema
- In anemia:
- 2,3-BPC levels are increased in severe anemia in order to cope up with the oxygen demands of the body.

- This is an adaptation to supply as much O2 as possible to the tissue, despite the low hemoglobin levels.
- In blood transfusion:
- Storage of blood in acid citrate-dextrose medium results in the decreased concentration of 2,3-BPG.
- Such blood when transfused fails to supply O2 to the tissues immediately.

- Addition of inosine (hypoxanthine-ribose) to the stored blood prevents the decrease of 2,3-BPG.
- The ribose moiety of inosine gets phosphorylated & enters the hexose monophosphate pathway and finally gets converted to 2.3-BPG