



Bioenergetics
(فح ج 634)

Lecture 5

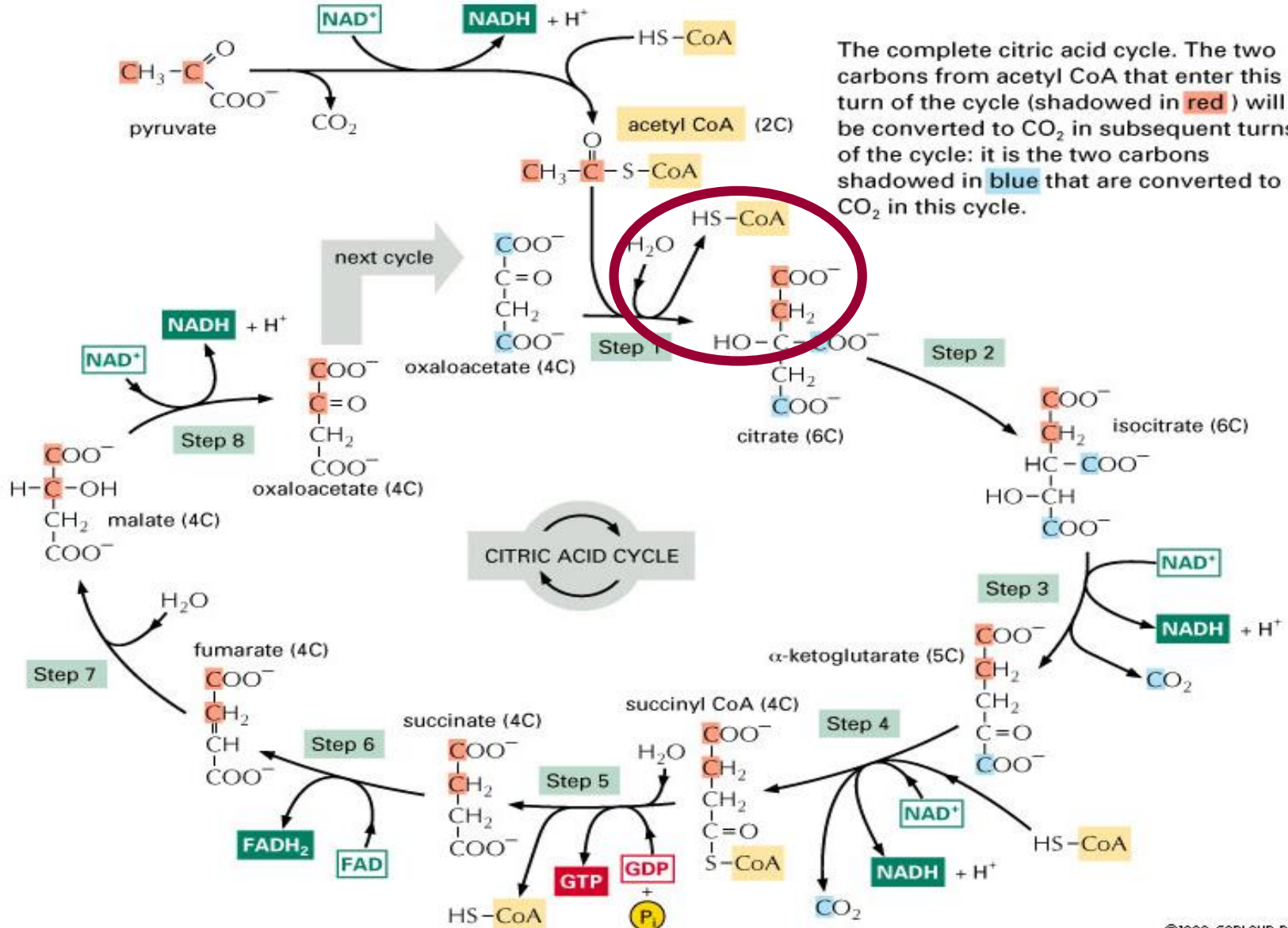
Prepared by:

Dr. Abdo A. Elfiky

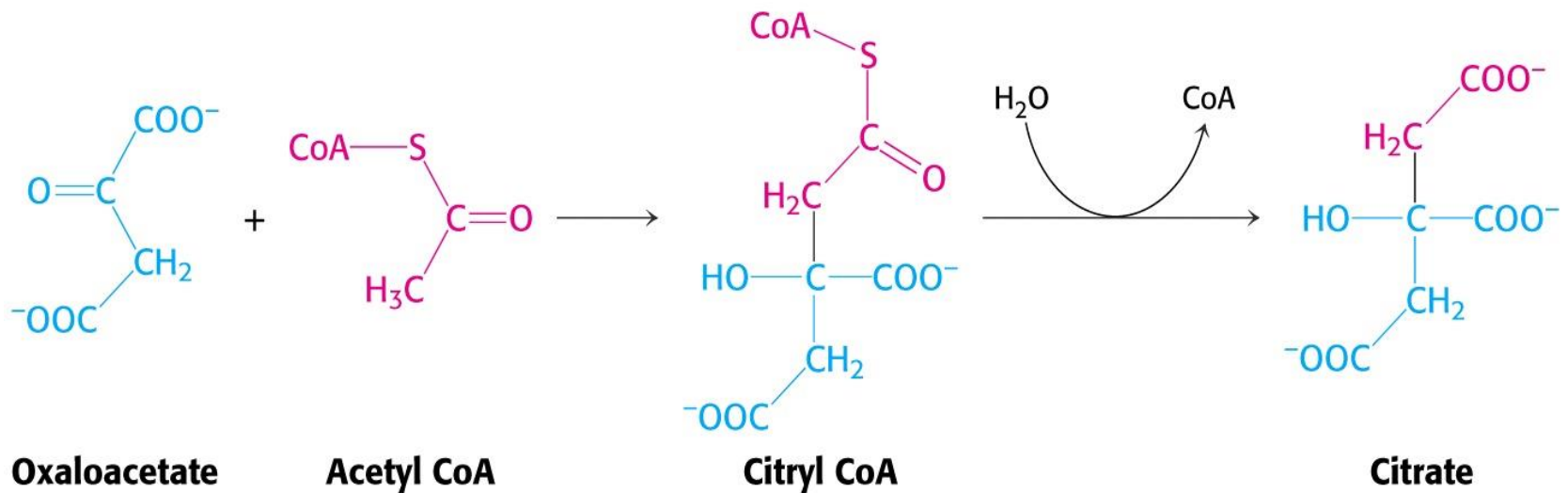


Citric acid cycle

Aerobic Respiration



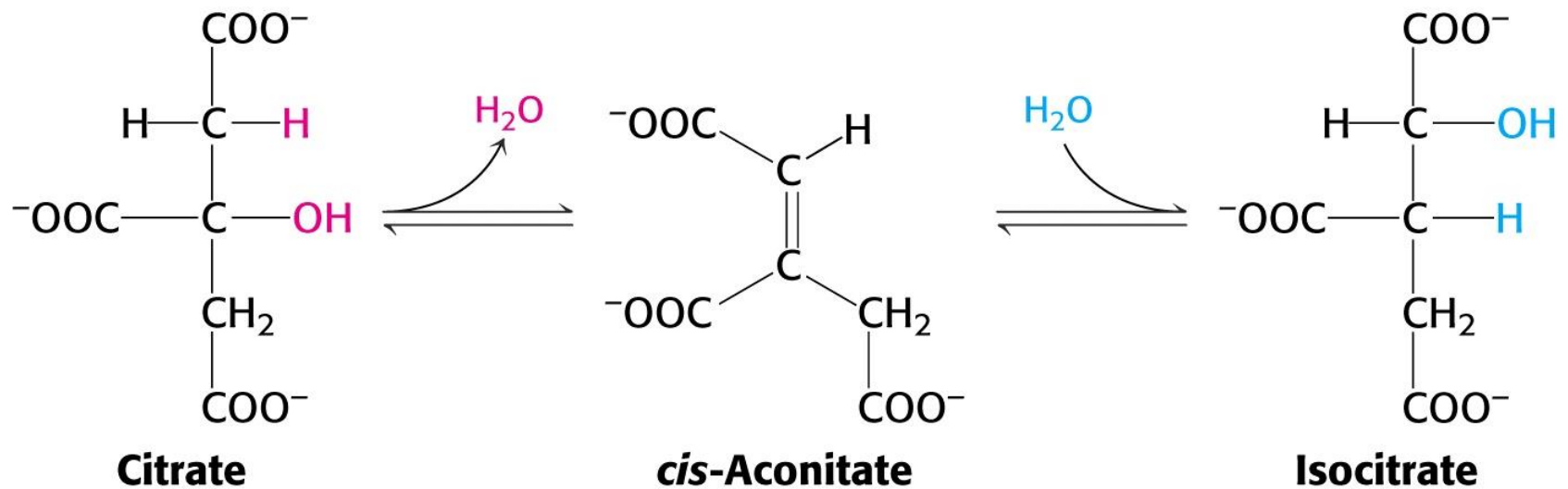
step 1 (Citrate synthase)



Condensation reaction

Hydrolysis reaction

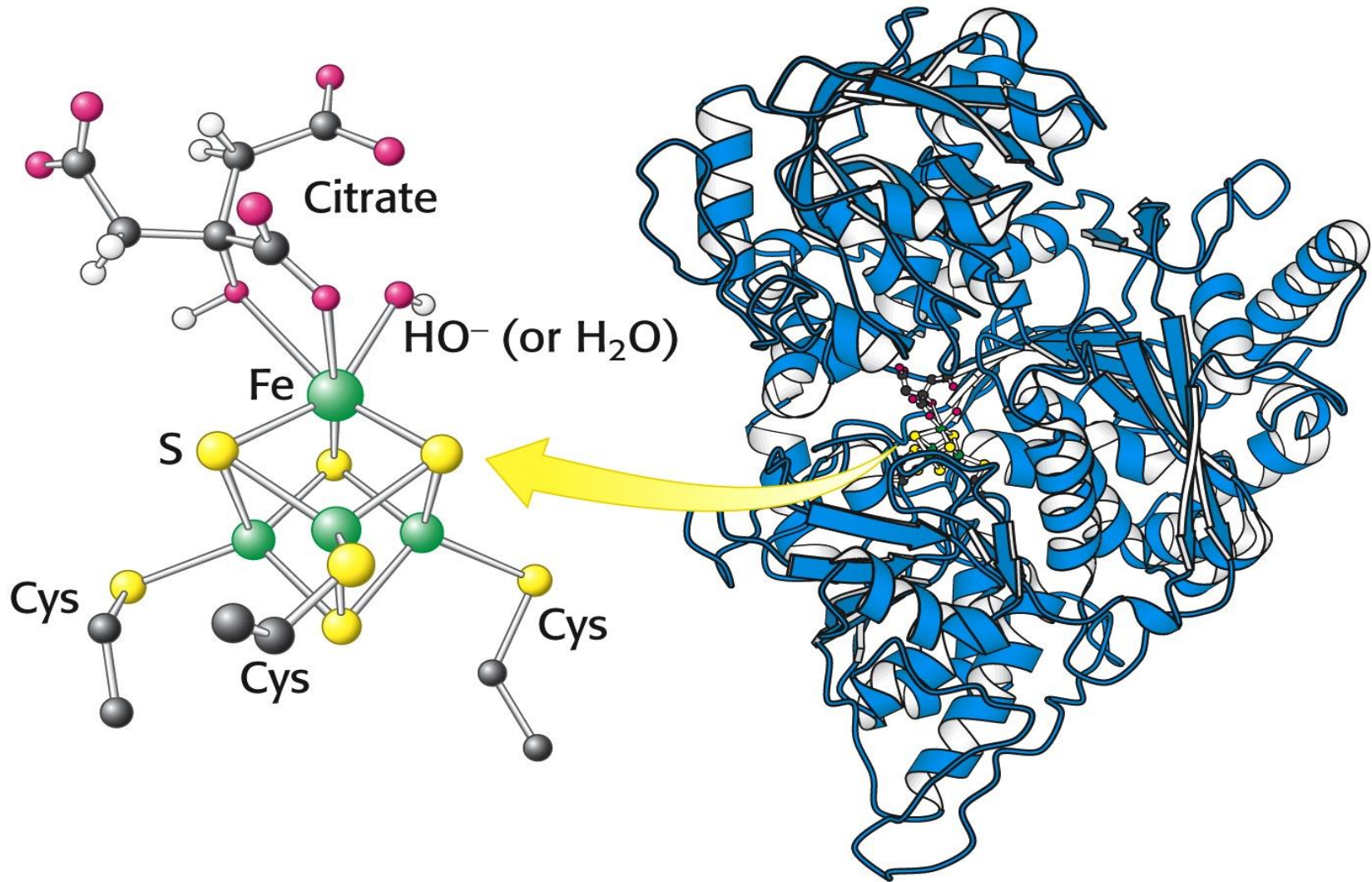
Step 2 (aconitase)



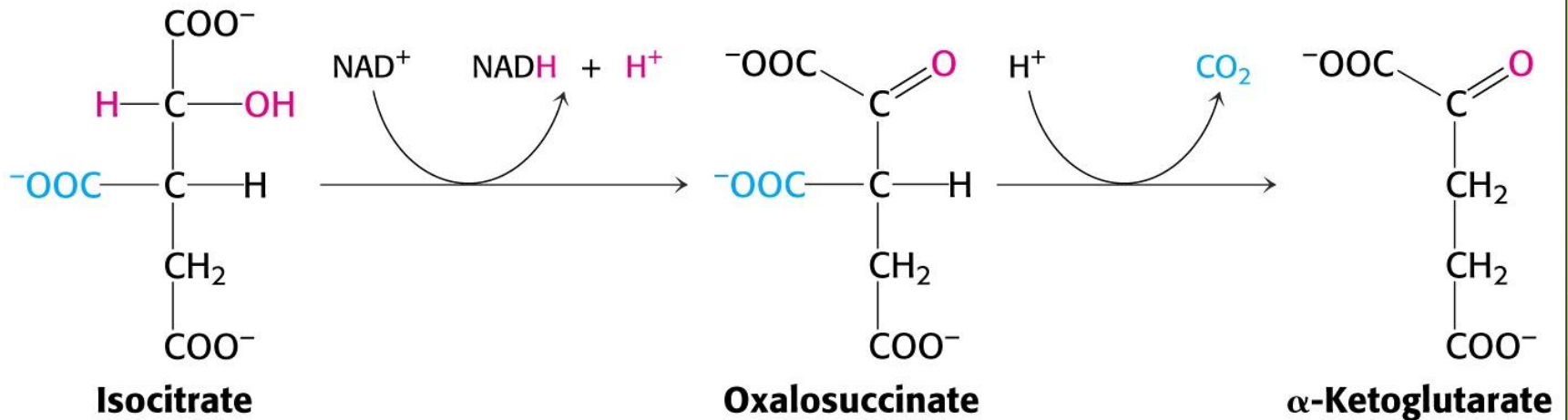
Dehydration

Hydration

Aconitase: citrate binding to iron-sulfur cluster



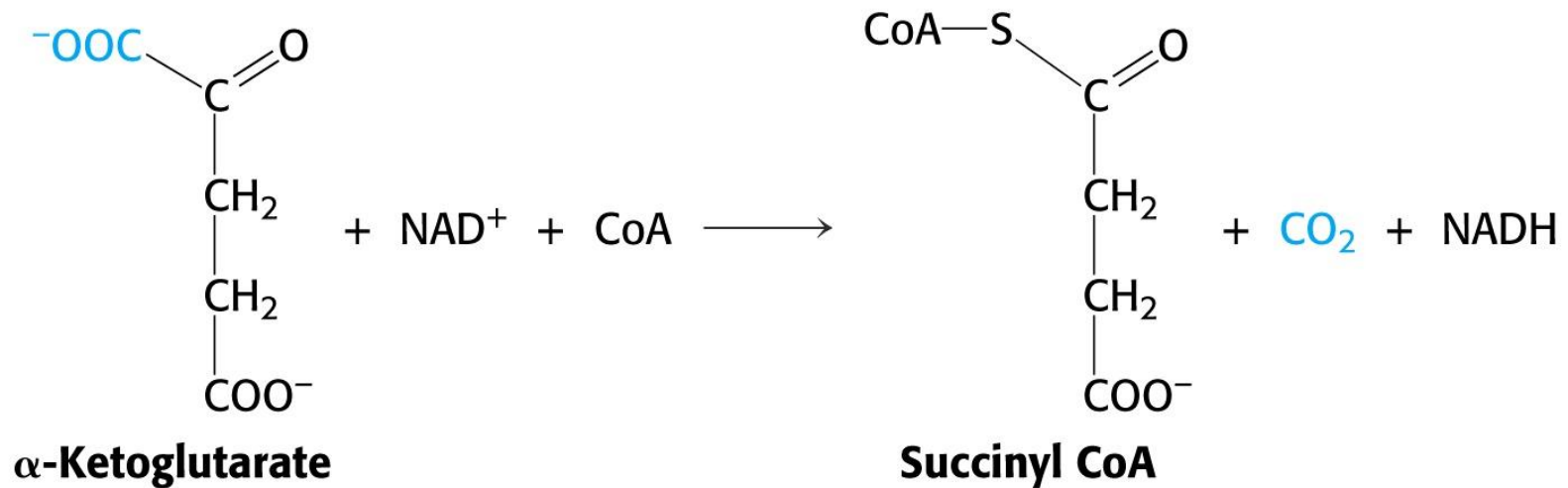
Step 3 (isocitrate dehydrogenase)



1st NADH
produced

1st CO_2
removed

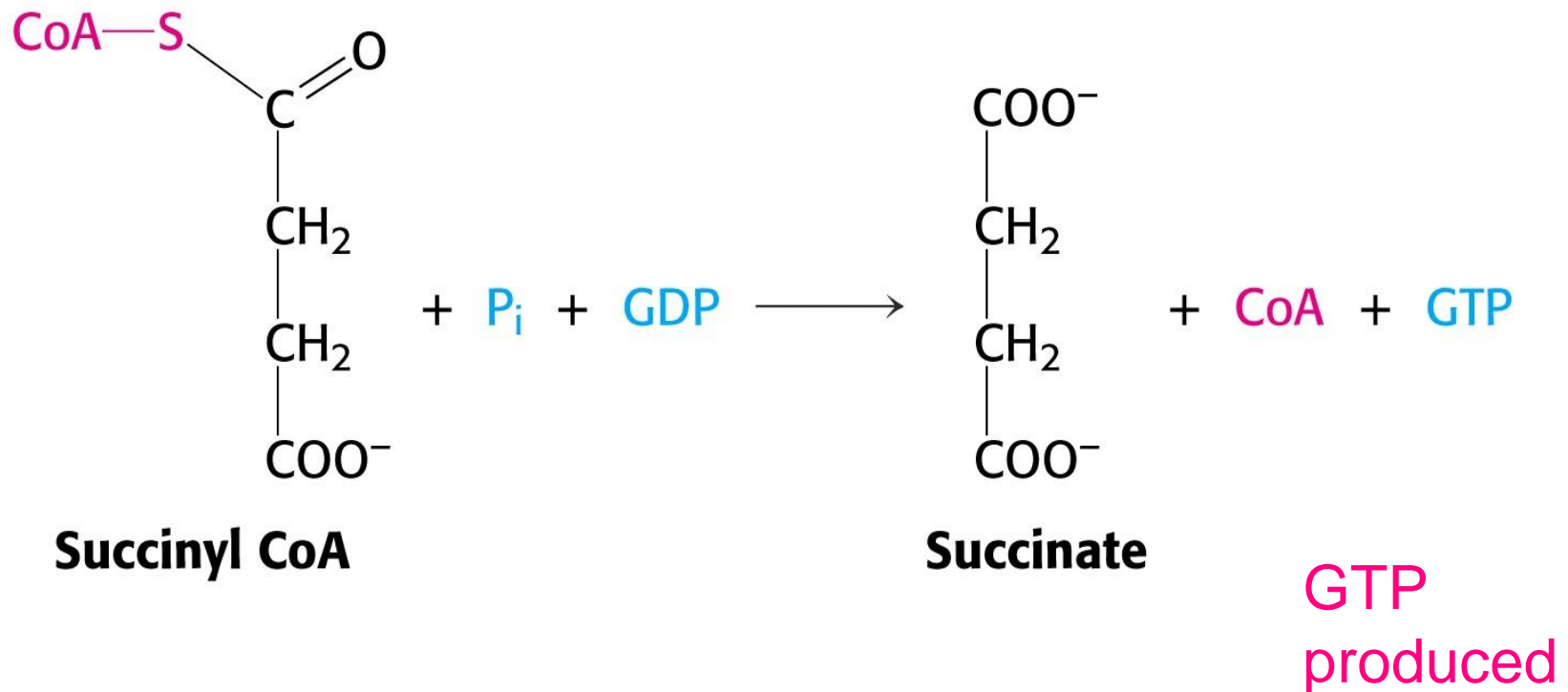
Step 4 (α-ketoglutarate dehydrogenase)



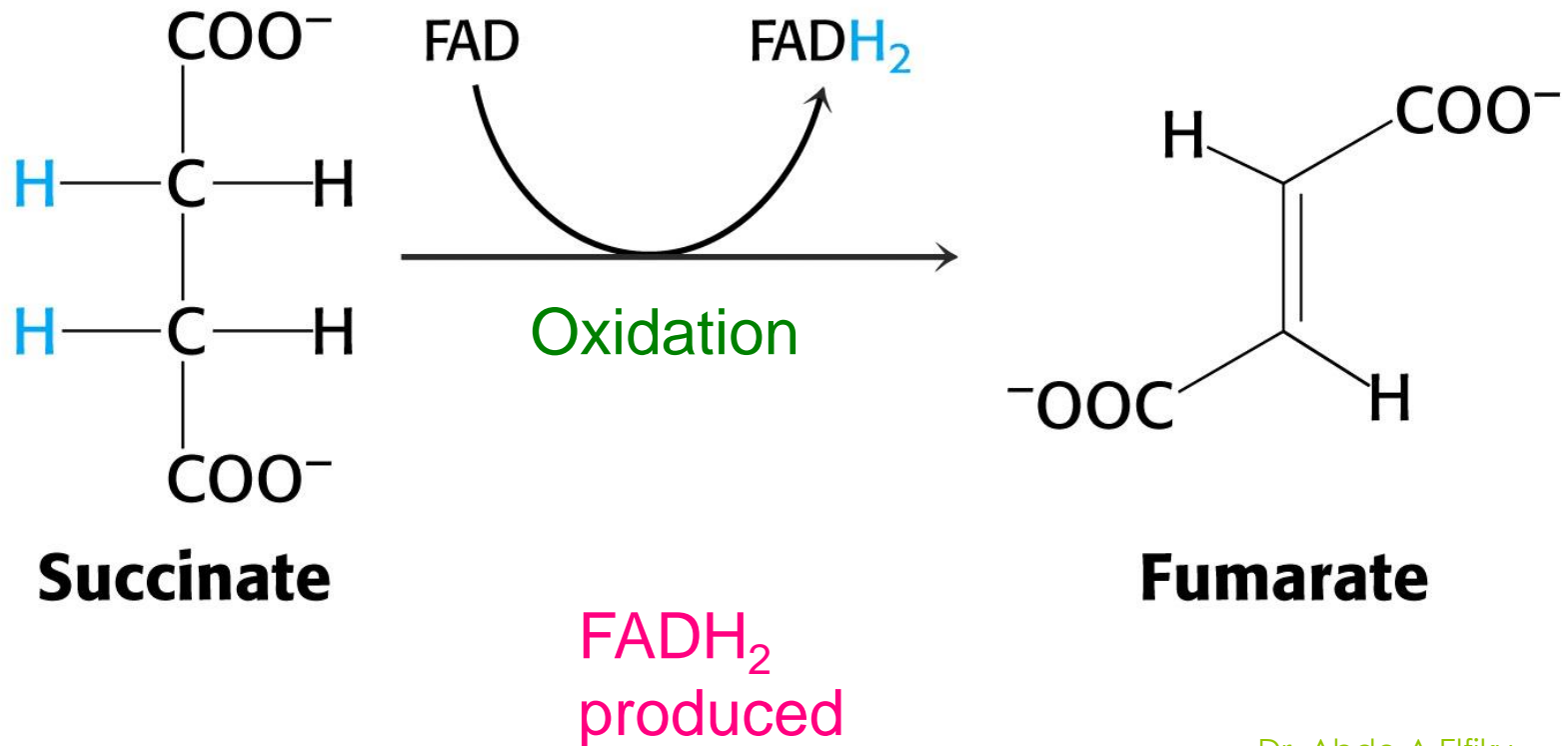
2nd NADH
produced

2nd CO₂
removed

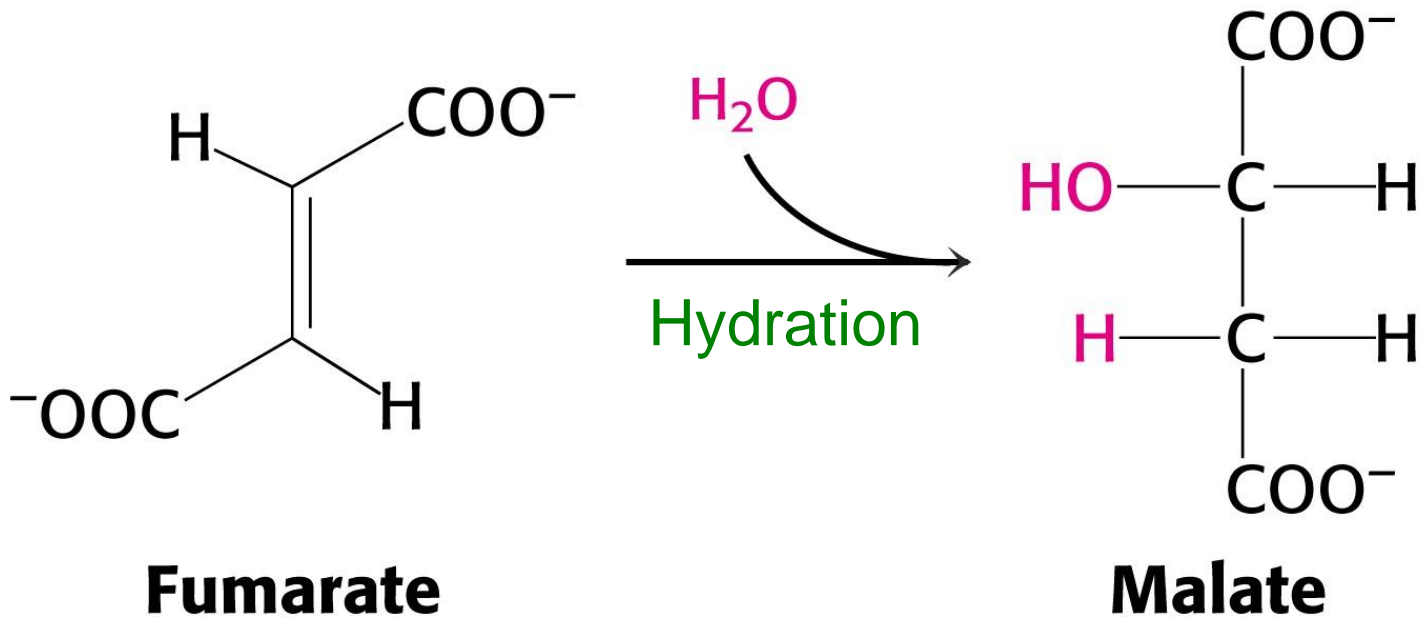
Step 5 (succinyl CoA synthetase)

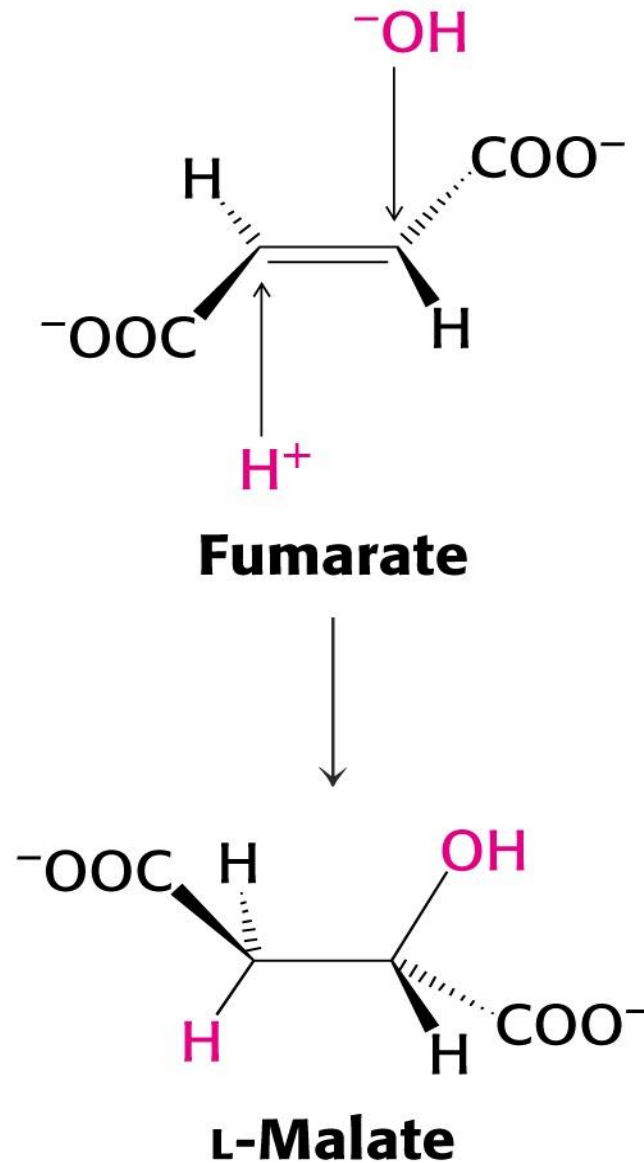


Step 6 (succinate dehydrogenase)



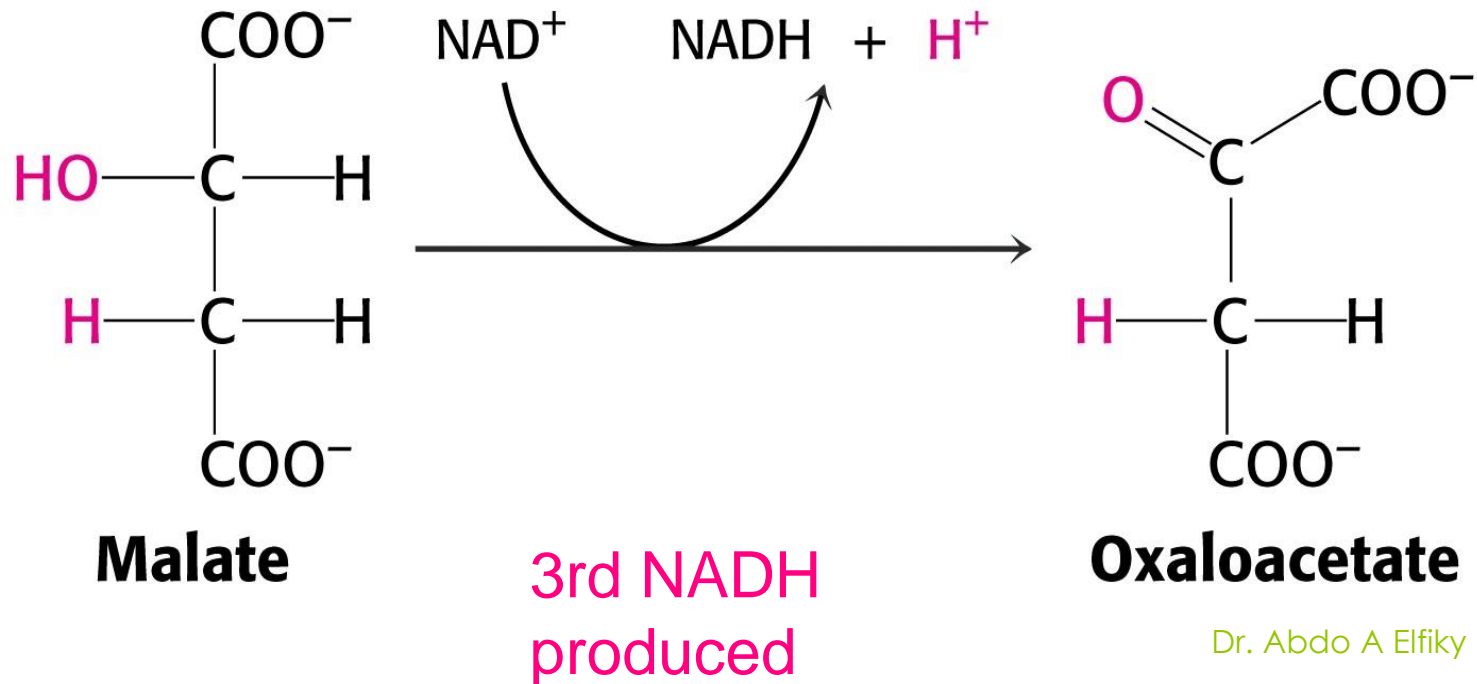
Step 7 (fumarase)

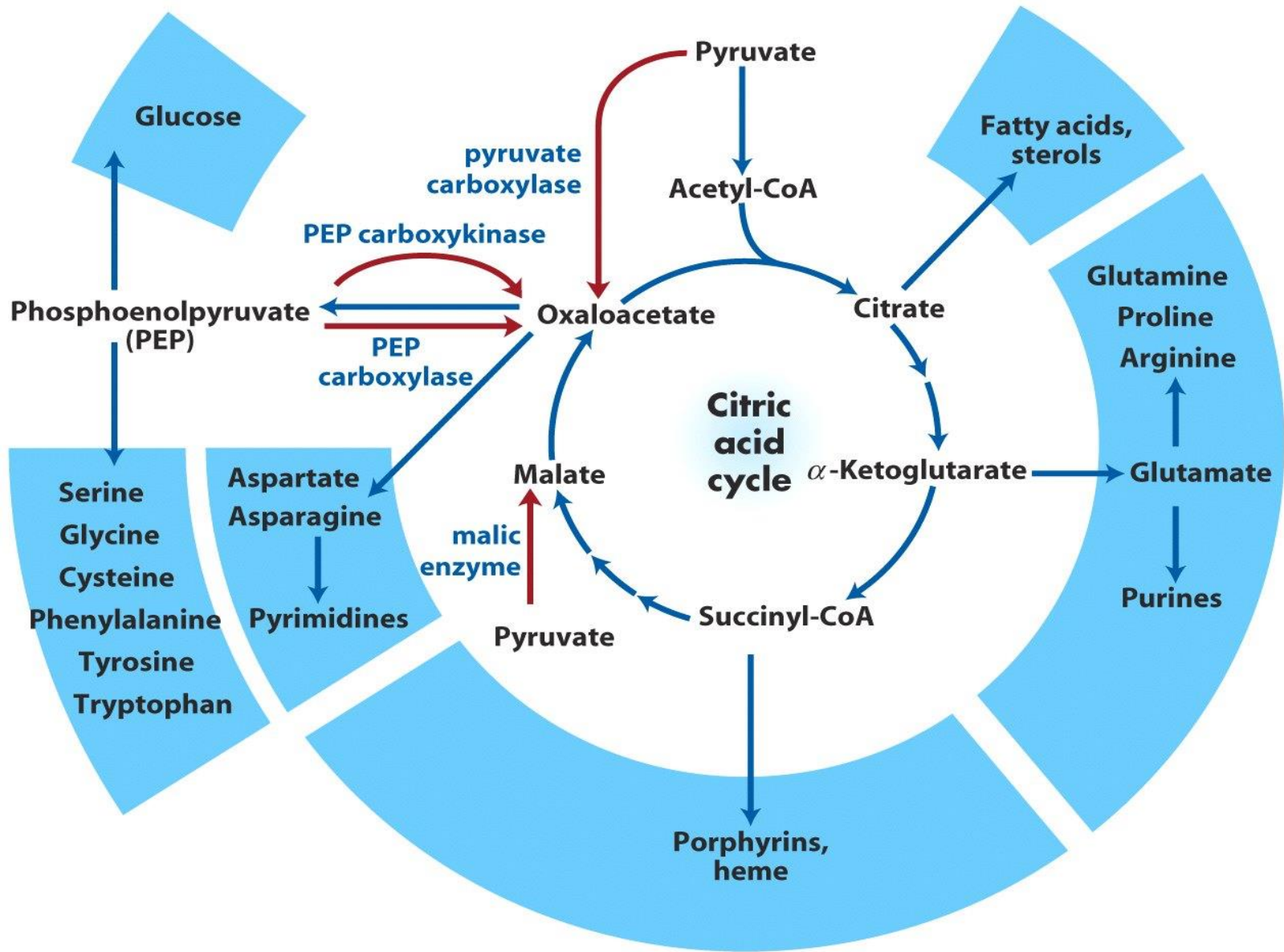




Hydroxyl group to one side only of fumarate double bond; hence, only L isomer of malate formed

Step 8 (malate dehydrogenase)





Citric acid cycle regulation

- Because the TCA cycle is central to many pathways of metabolism, there must always be a large supply of the intermediates. For example, oxaloacetate is the direct precursor of the amino acid aspartate, with the alpha-keto group being replaced by an amino group. Likewise, alpha-ketoglutarate is the direct precursor to glutamate. These two amino acids are important, not only for protein synthesis, but even more so for maintaining nitrogen balance and eliminating toxic ammonia.

Citric acid cycle regulation

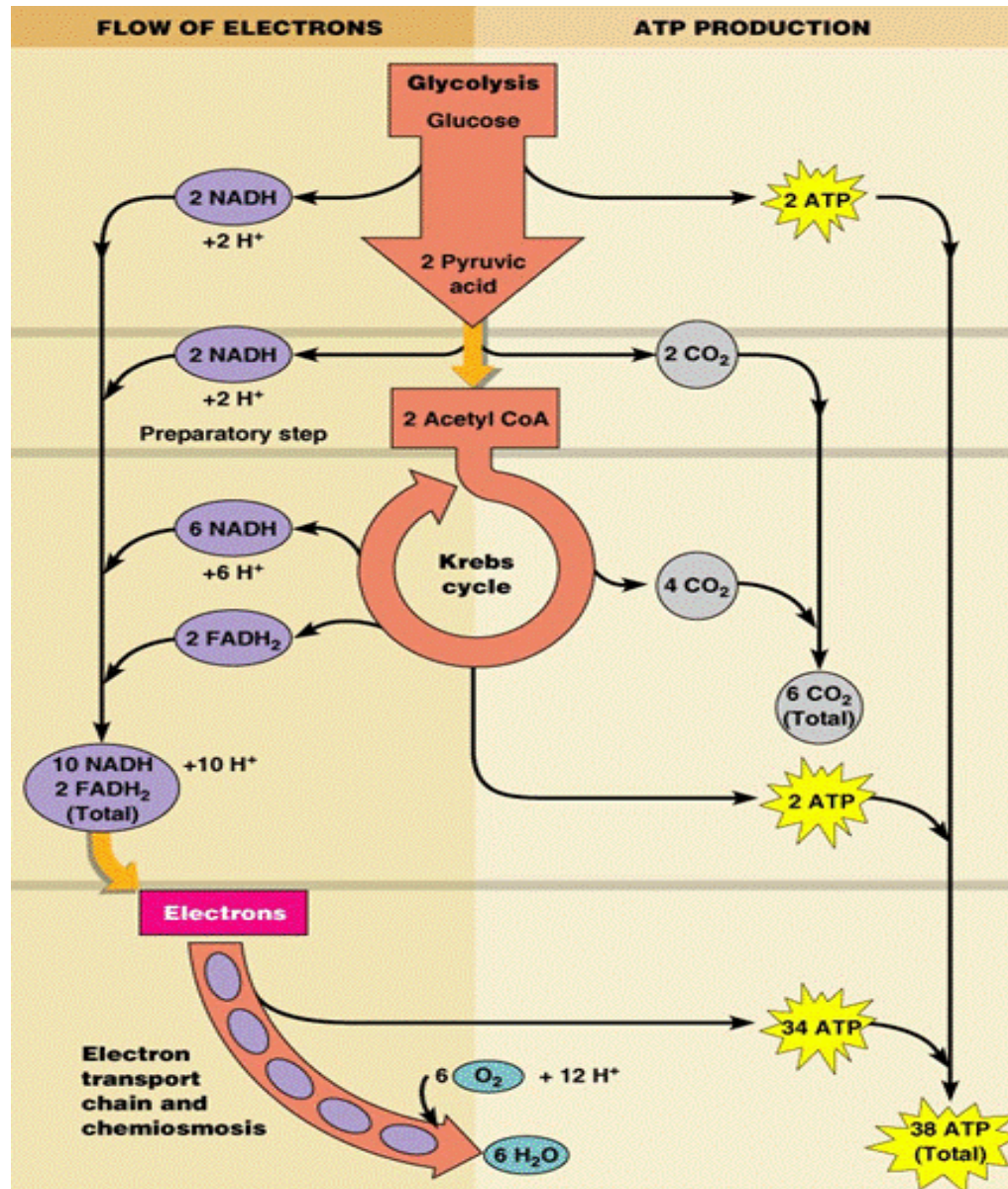
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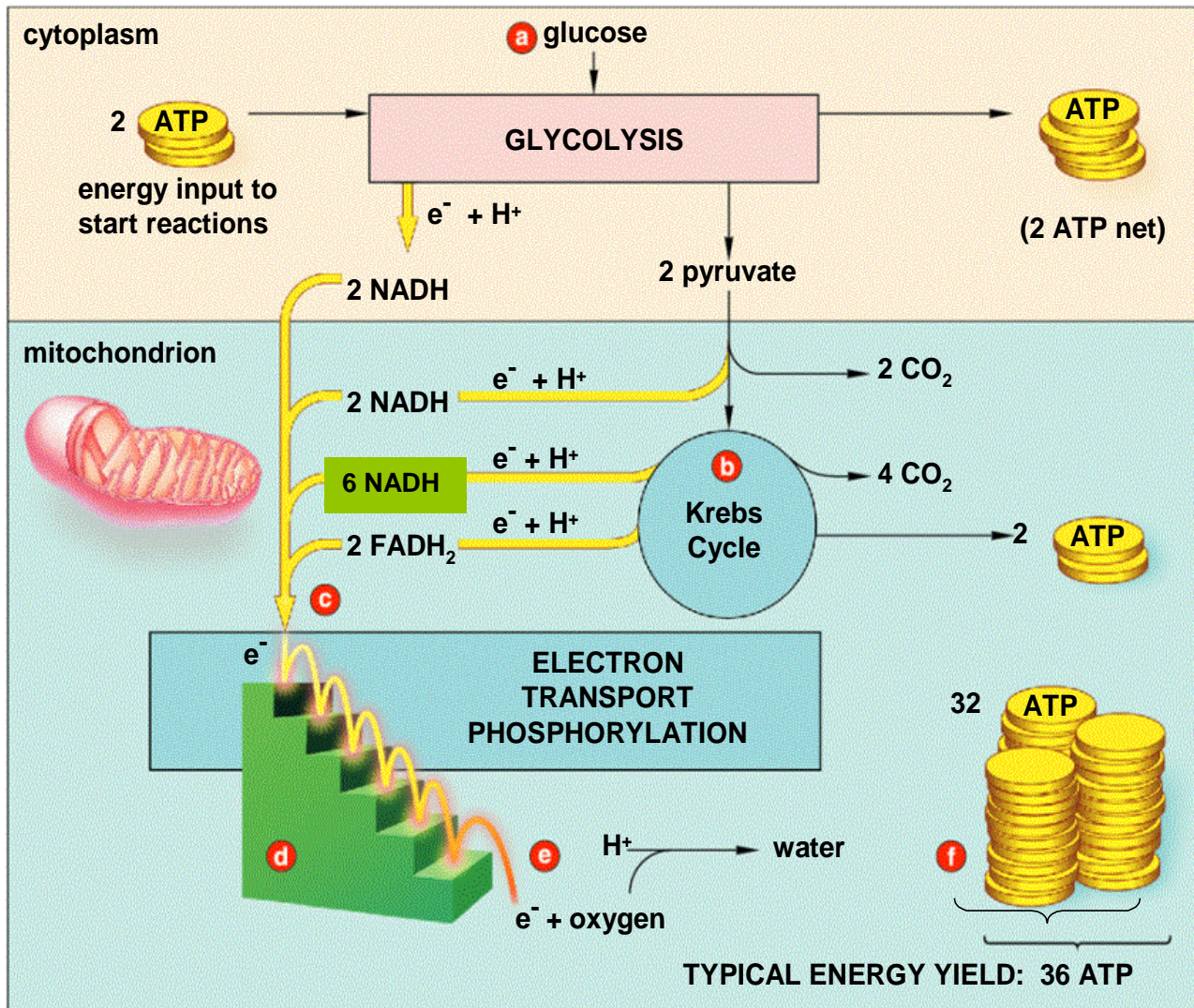
- Therefore, there are a variety of pathways that serve to regenerate TCA cycle intermediates if the supply falls low. For example, the breakdown of amino acids leads to TCA cycle intermediates.
- If the supply of intermediates falls low, for example, during even short periods of starvation, muscle can be broken down and the carbon skeletons of the amino acids used to build up the supply of 4-carbon dicarboxylic acids. Oxaloacetate and malate can be synthesized from pyruvate by carboxylation using bicarbonate.



Electron transport chain

Aerobic Respiration



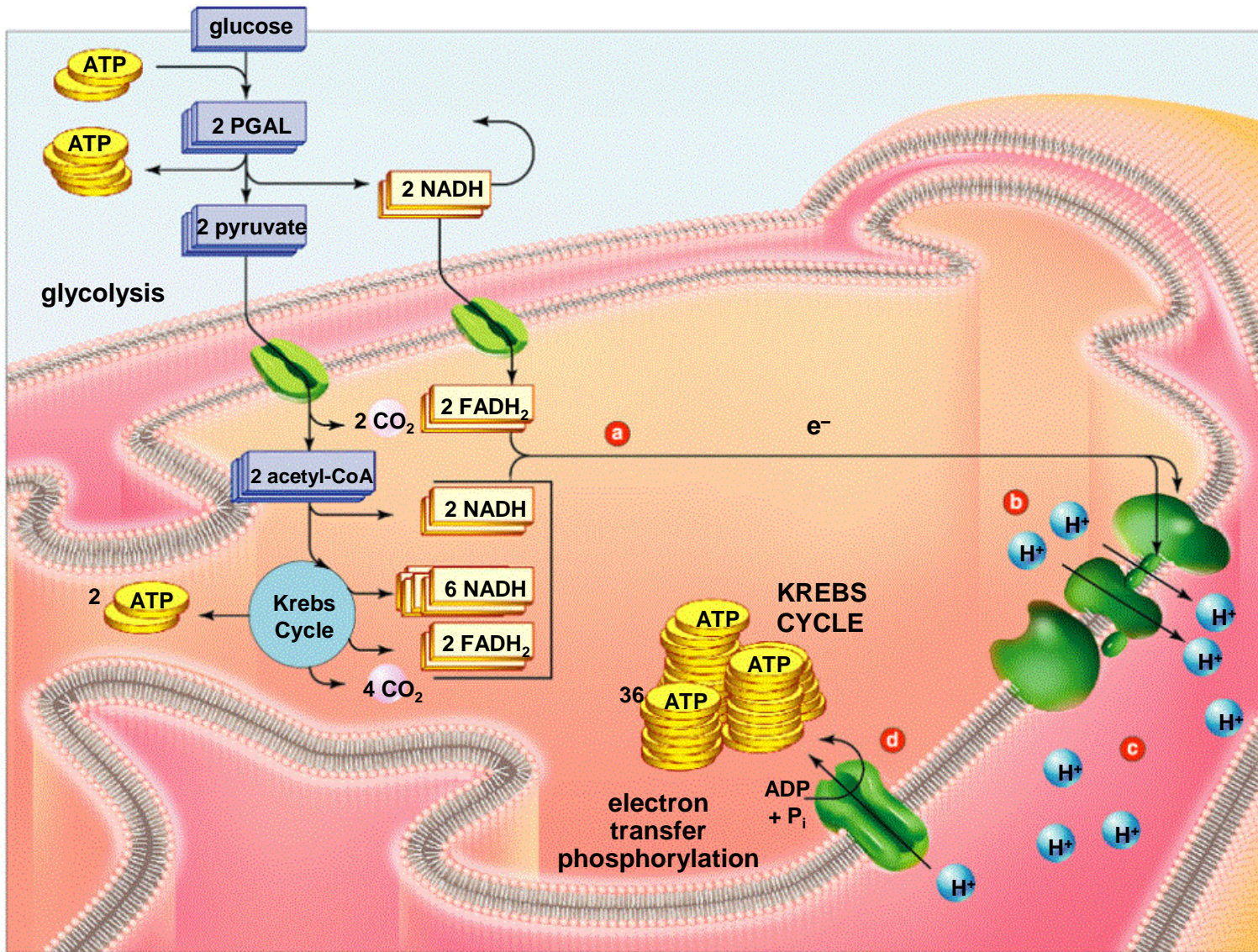


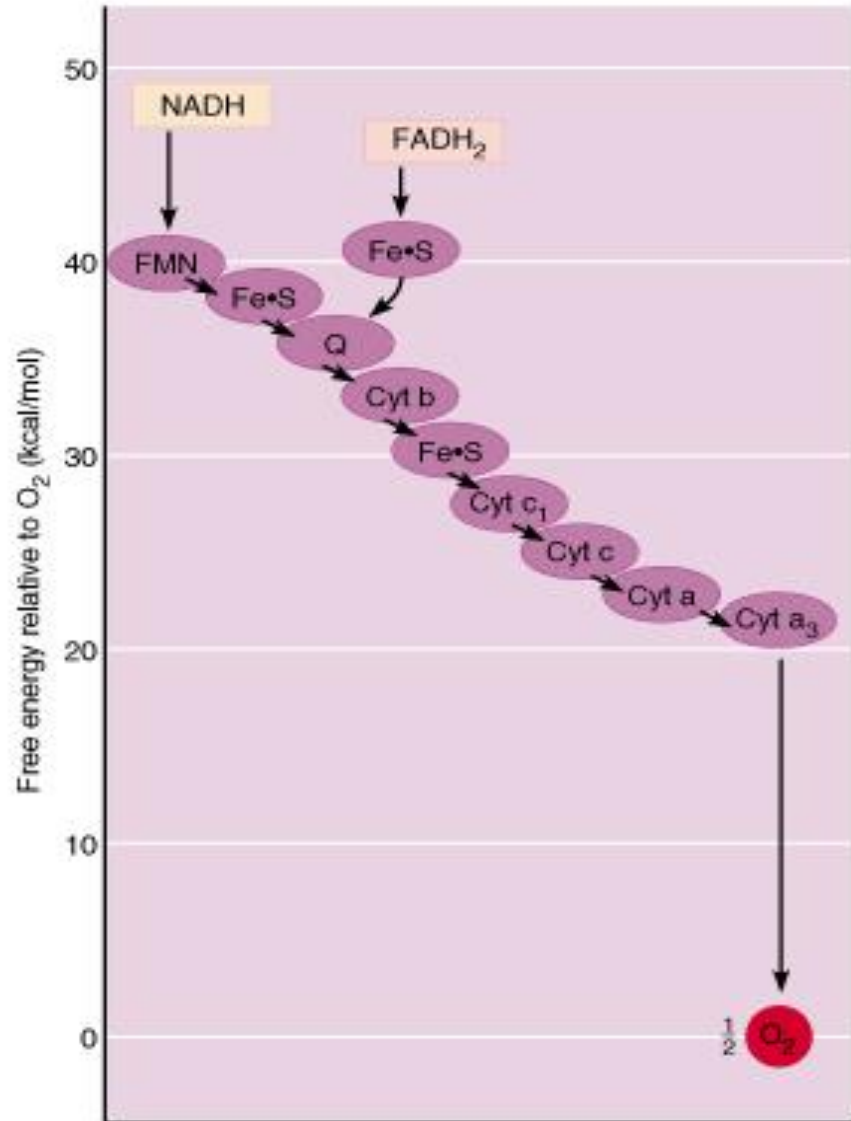
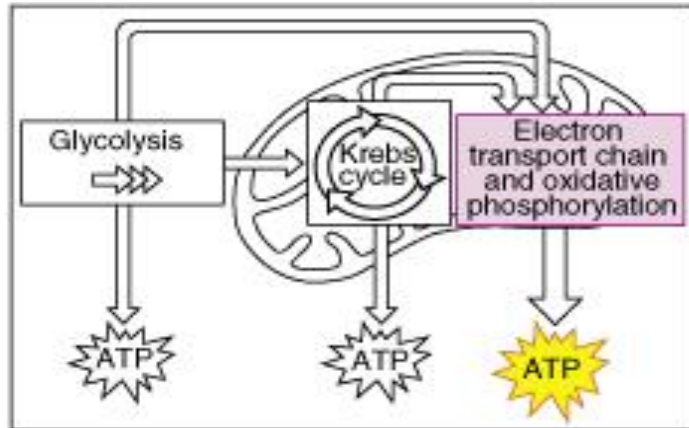
Electron transport chain

- Resides in the inner mitochondrial membrane – also called respiratory chain
- 15 proteins involved in the chain – grouped in 3 large respiratory enzyme complexes
- NADH dehydrogenase complex
- Cytochrome b-c1 complex
- Cytochrome oxidase complex
- Pumps protons across the membrane as e- are transferred thru them

Chemiosmotic mechanism

- The electron transport chain, consisting of several molecules (primarily proteins), is built into the inner membrane of a mitochondrion.
- NADH shuttles electrons from food to the “top” of the chain.
- At the “bottom”, oxygen captures the electrons and H^+ to form water.
- Electrons are passed by increasingly electronegative molecules in the chain until they are caught by oxygen, the most electronegative.
- This model for ATP synthesis is called the **chemiosmotic mechanism**





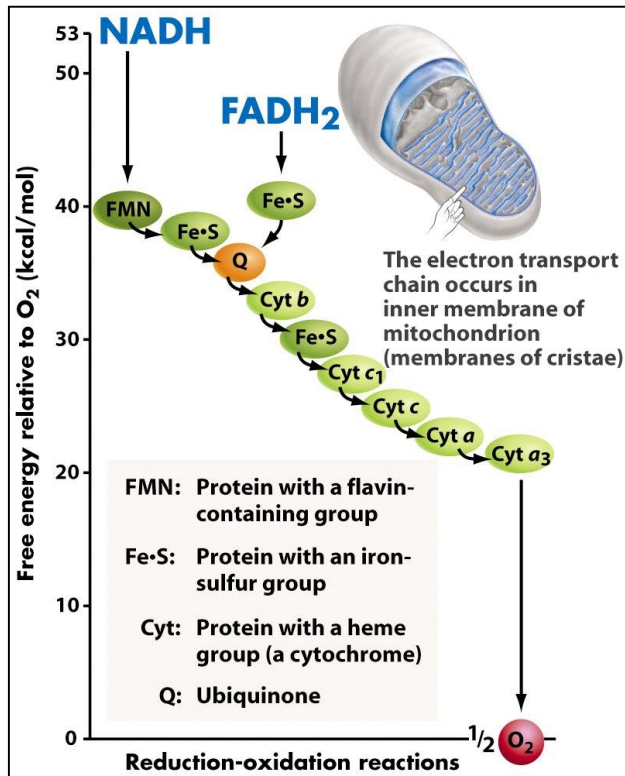
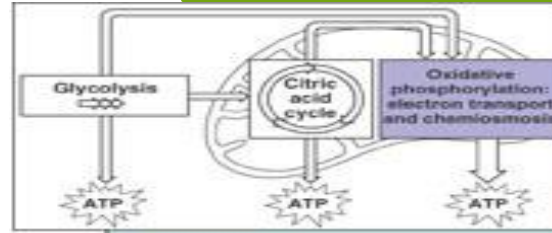
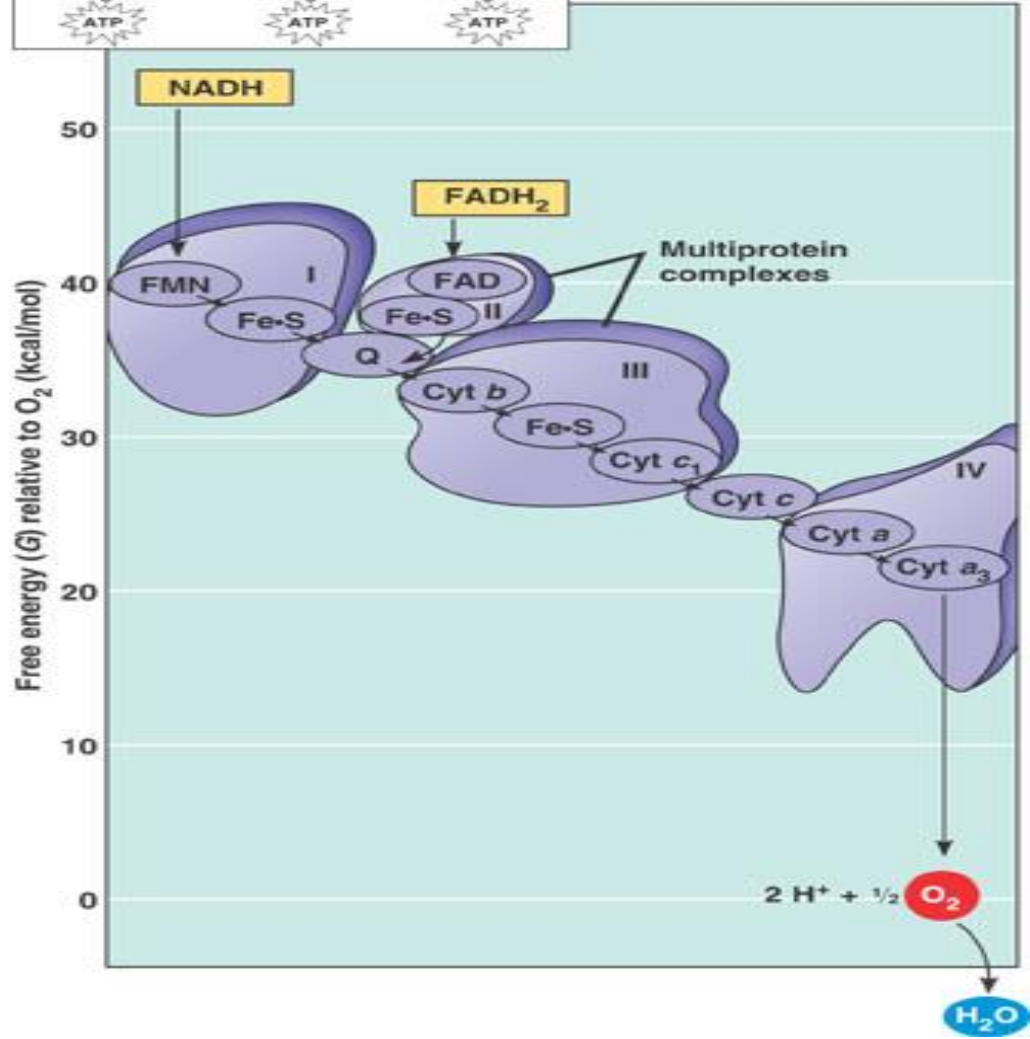
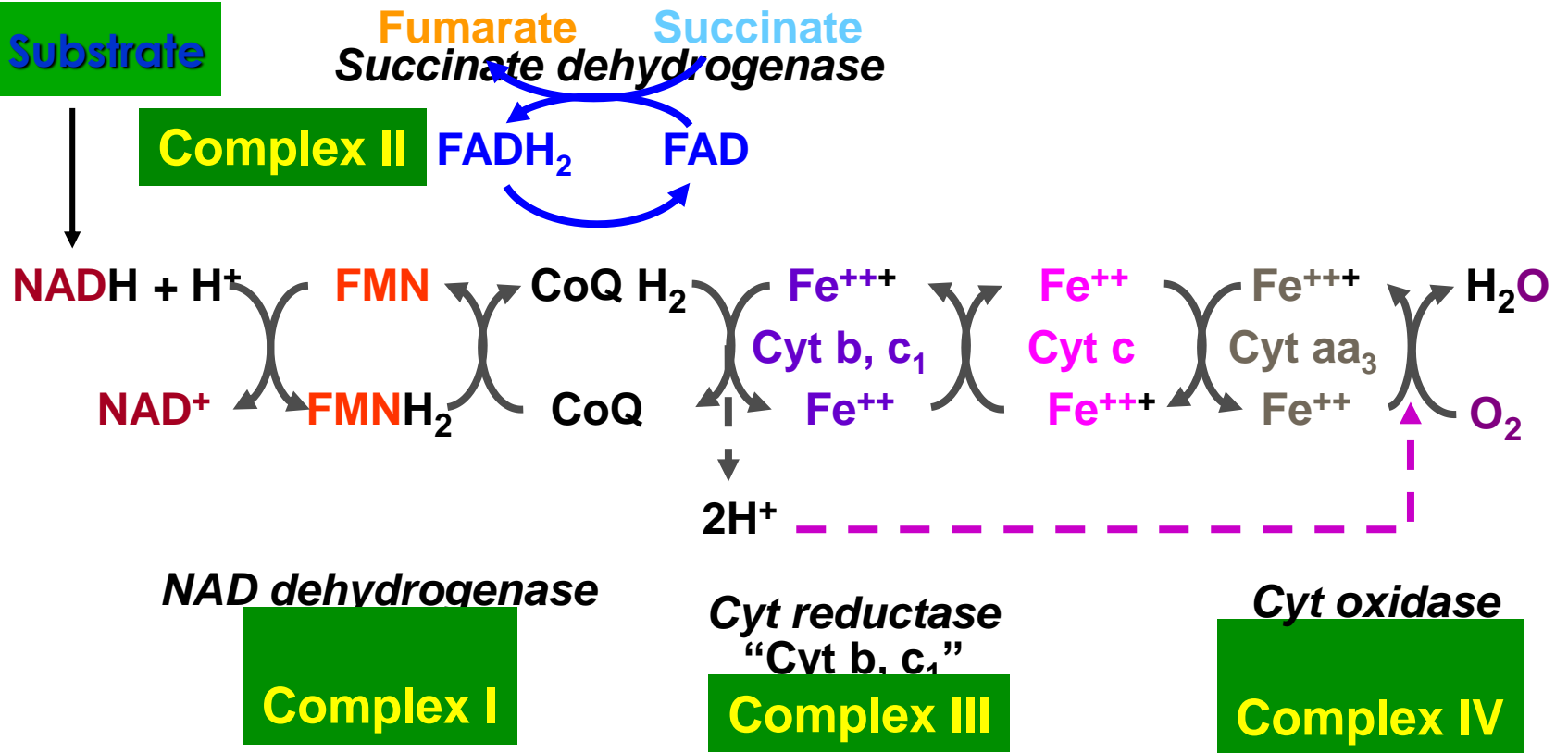


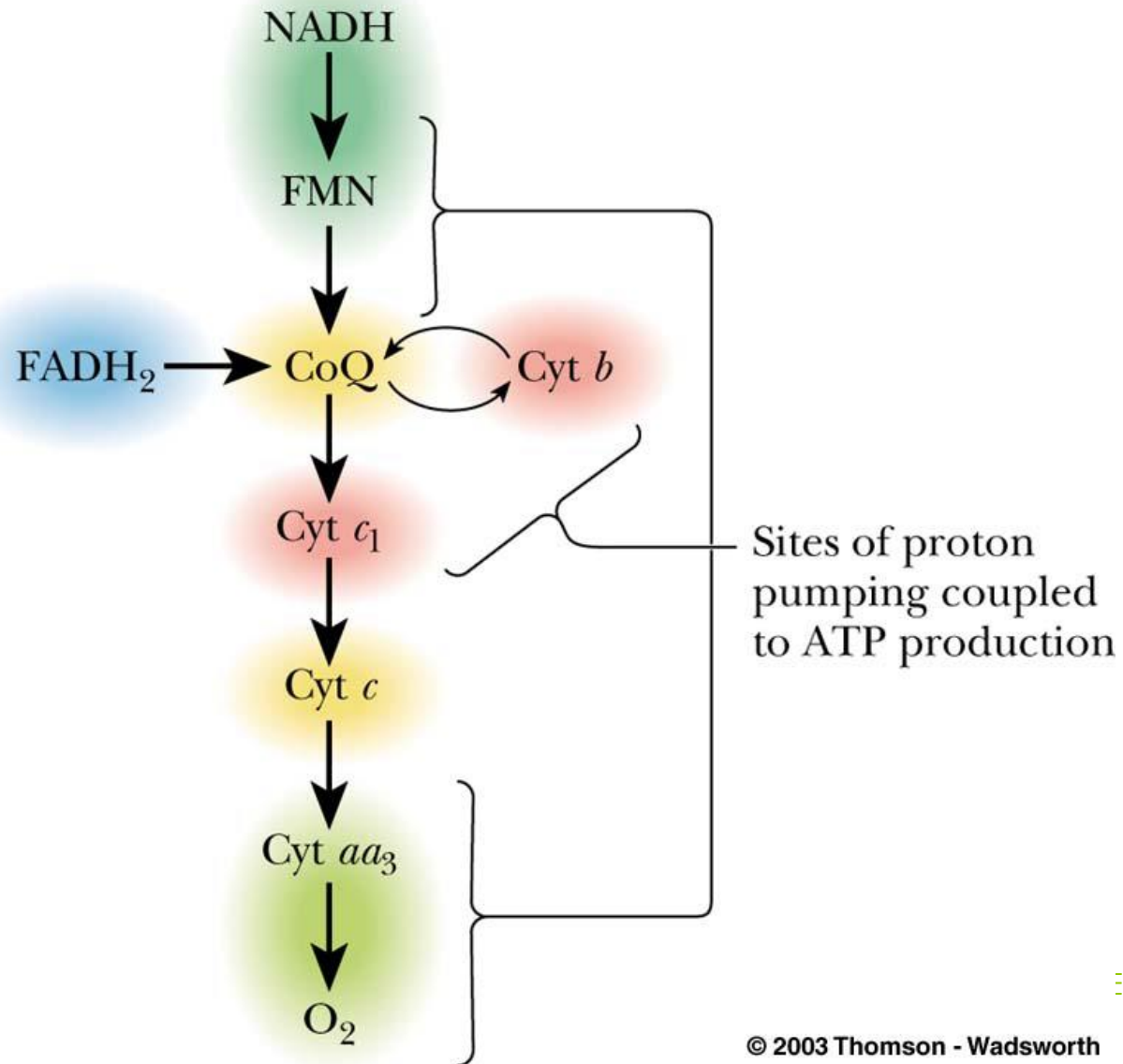
Figure 9-17 Biological Science, 2/e © 2005 Pearson Prentice Hall, Inc.



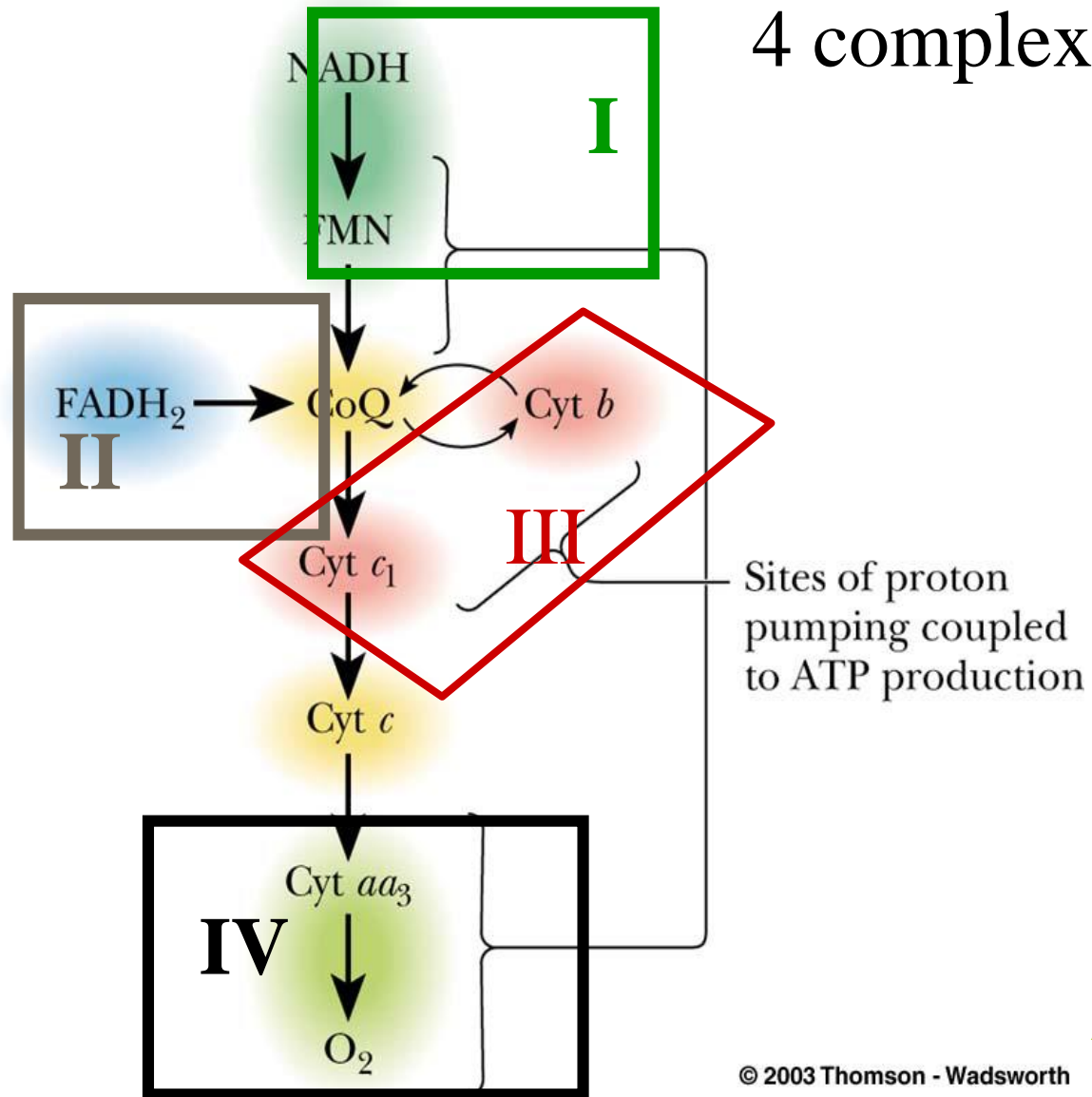
Composition of Respiratory Chain Complexes

Complex	Name	No. of Proteins	Prosthetic Groups
Complex I	NADH Dehydrogenase	46	FMN, 9 Fe-S cntrs.
Complex II	Succinate-CoQ Reductase	5	FAD, cyt b₅₆₀, 3 Fe-S cntrs.
Complex III	CoQ-cyt c Reductase	11	cyt b_H, cyt b_L, cyt c₁, Fe-S
Complex IV	Cytochrome Oxidase	13	cyt a, cyt a₃, Cu_A, Cu_B



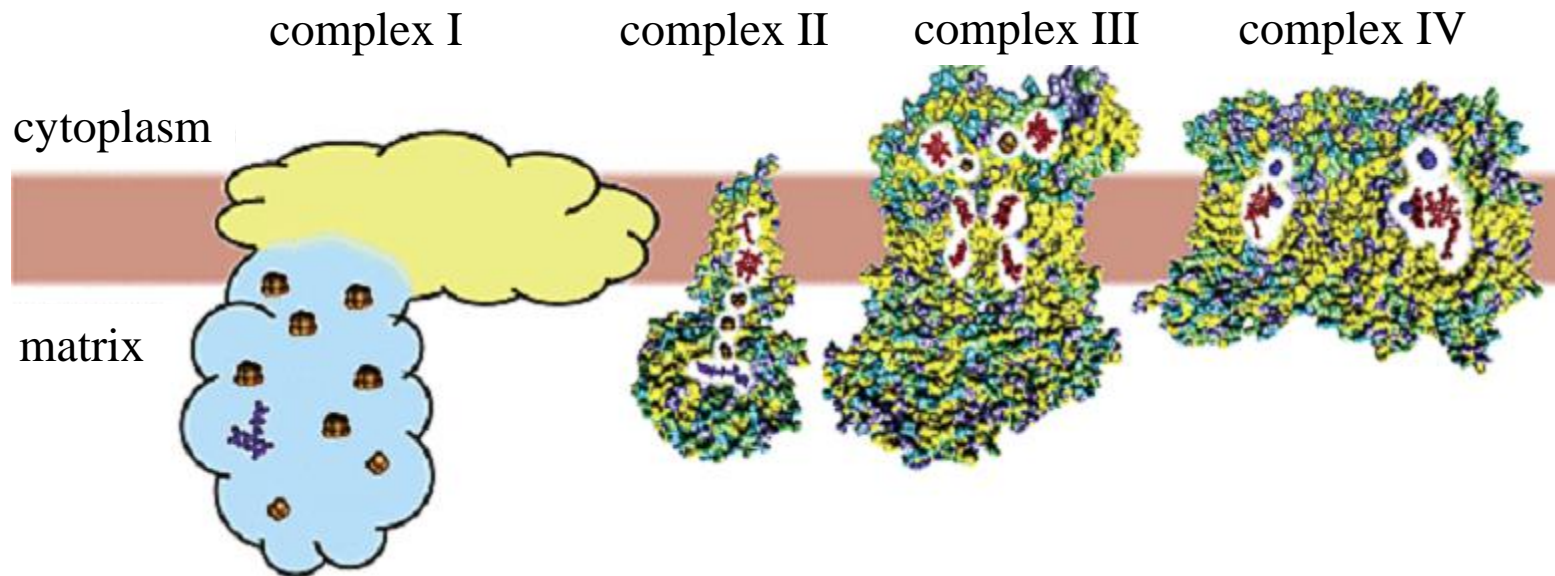


4 complexes



A Elfiky

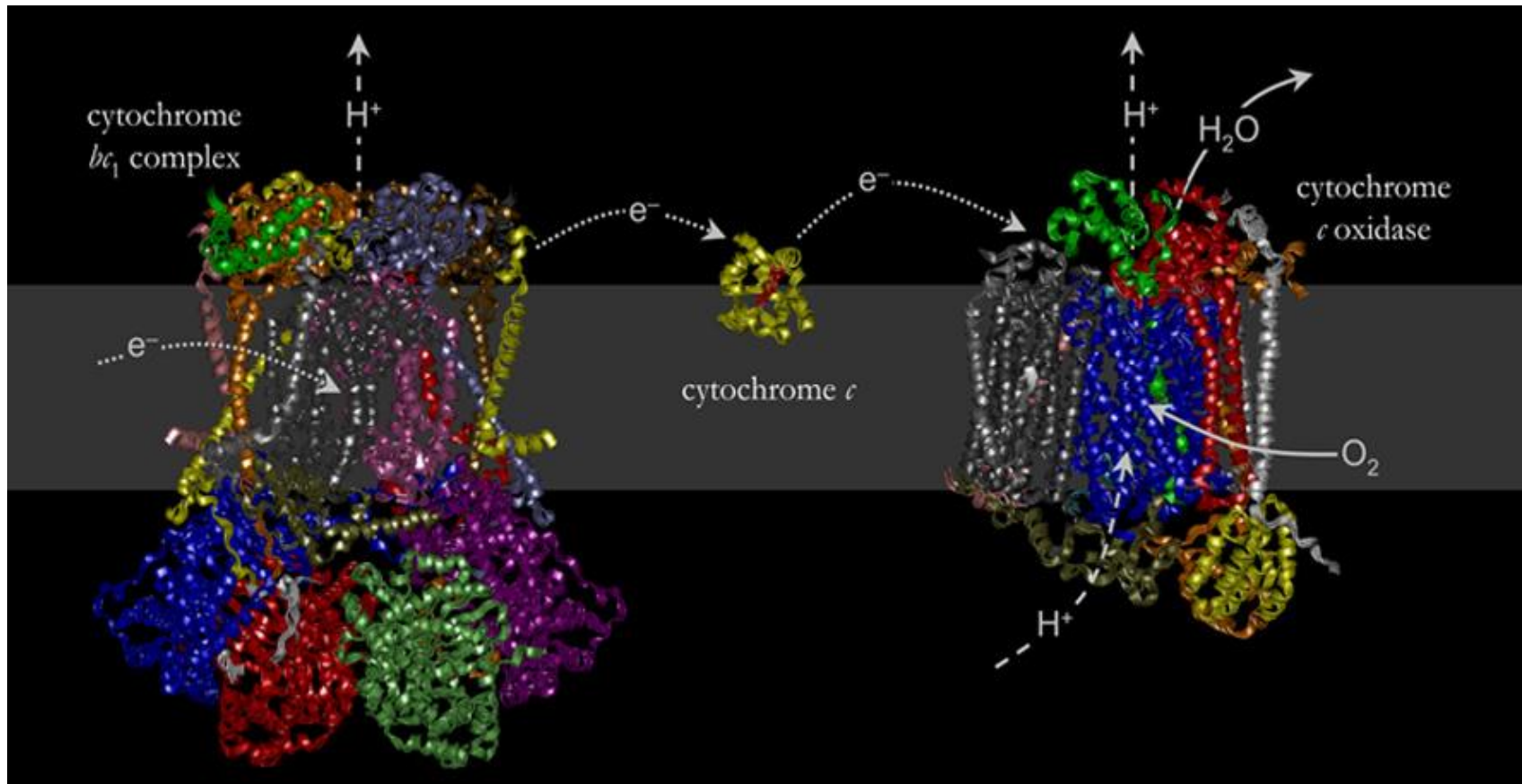
Each of the complexes possesses multiple bound redox cofactors



from: *Biochemistry*, **42** (8), 2266 -2274, 2003

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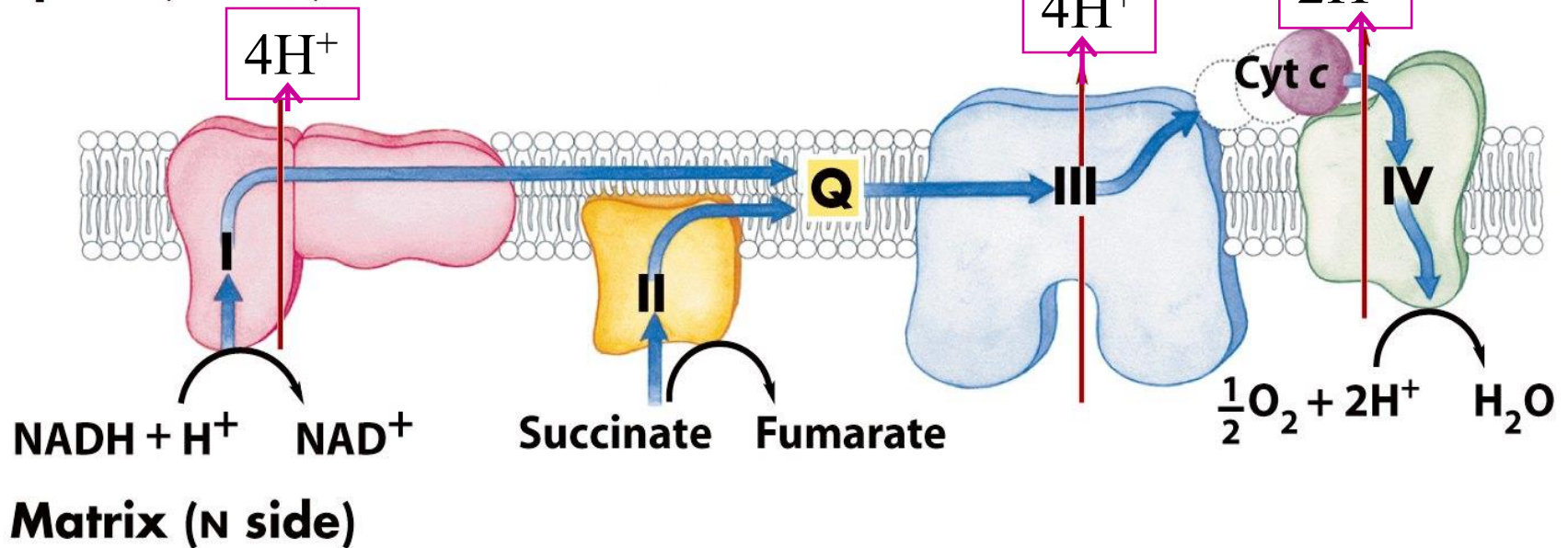
3D structure of cytochromes



How is energy captured?

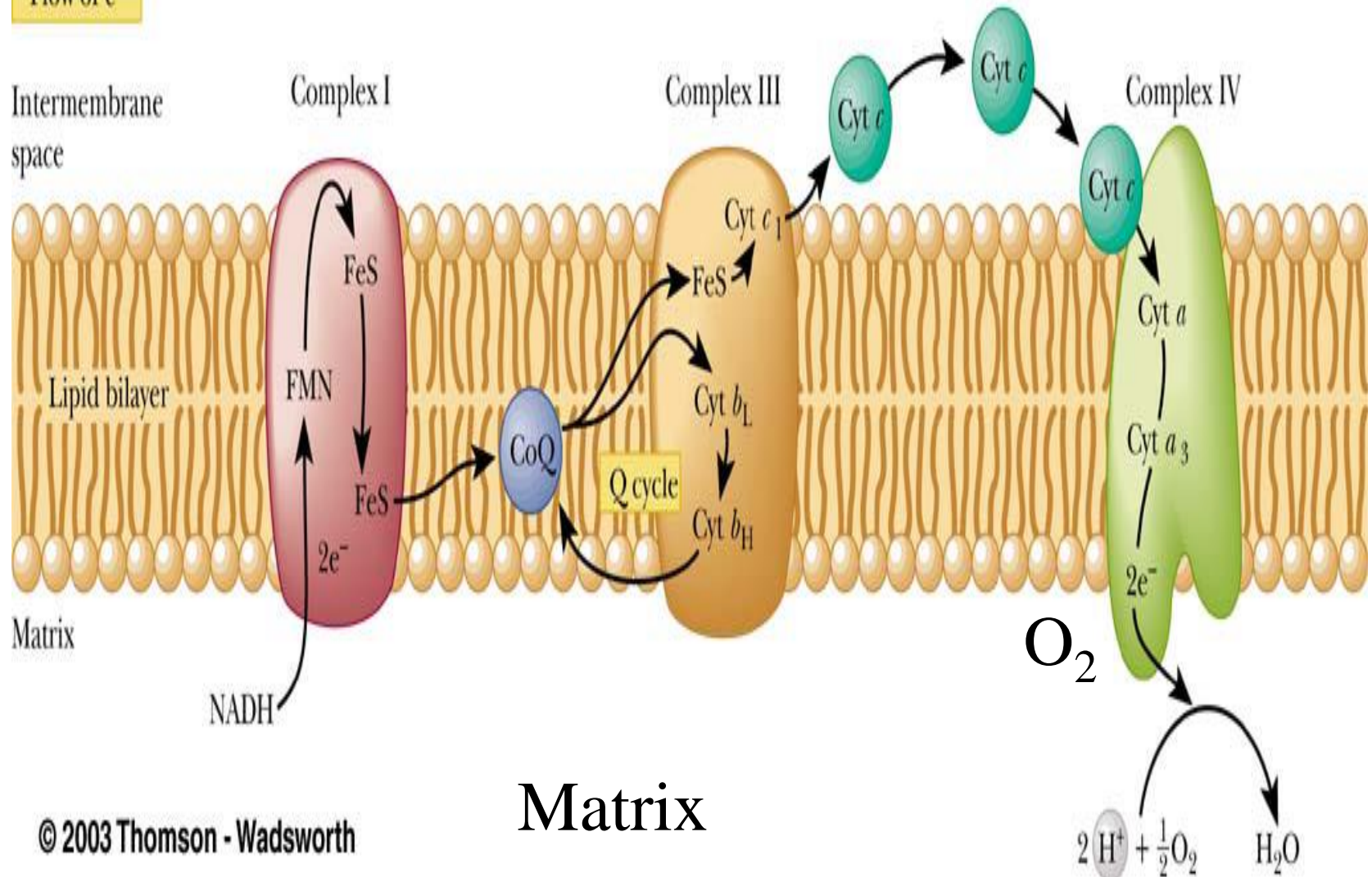
- As a proton gradient:

**Intermembrane
space (P side)**





Intermembrane space



Complex I: NADH dehydrogenase

- It has a tightly bound molecule of flavin mono- nucleotide (FMN) that accepts 2 hydrogen atoms ($2 e^- + 2 H^+$) becoming FMNH₂.
- It also contains iron-sulfur centers (composed of several iron atoms paired with sulfur atoms) that are necessary for the transfer of hydrogen atoms to the next member of the chain, coenzyme Q.

Complex II: FADH₂ dehydrogenase

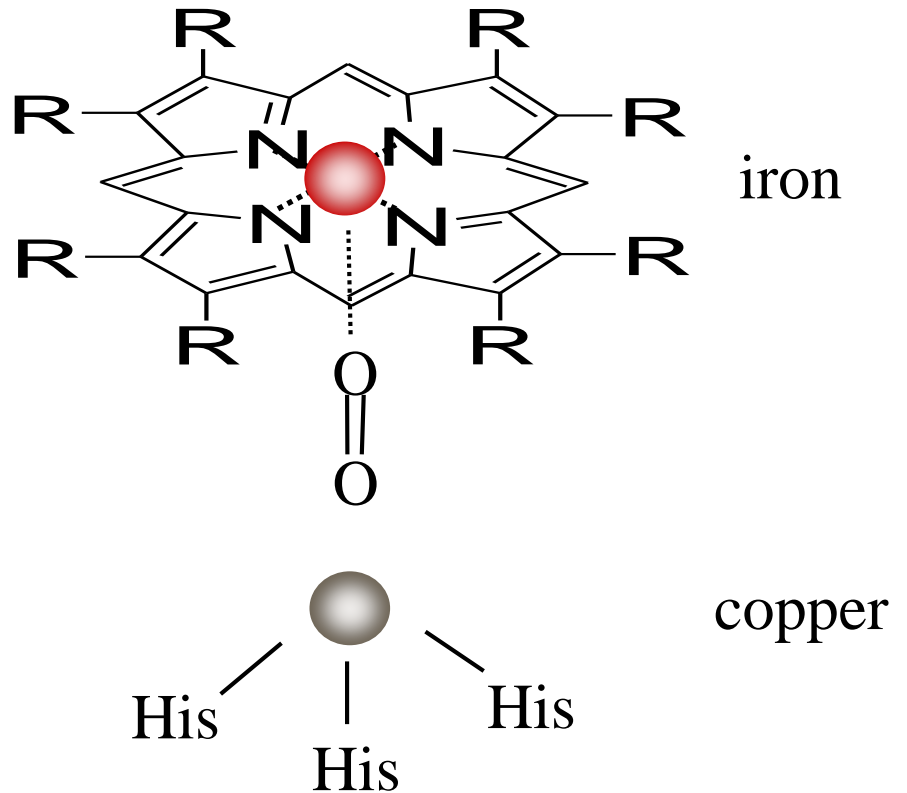
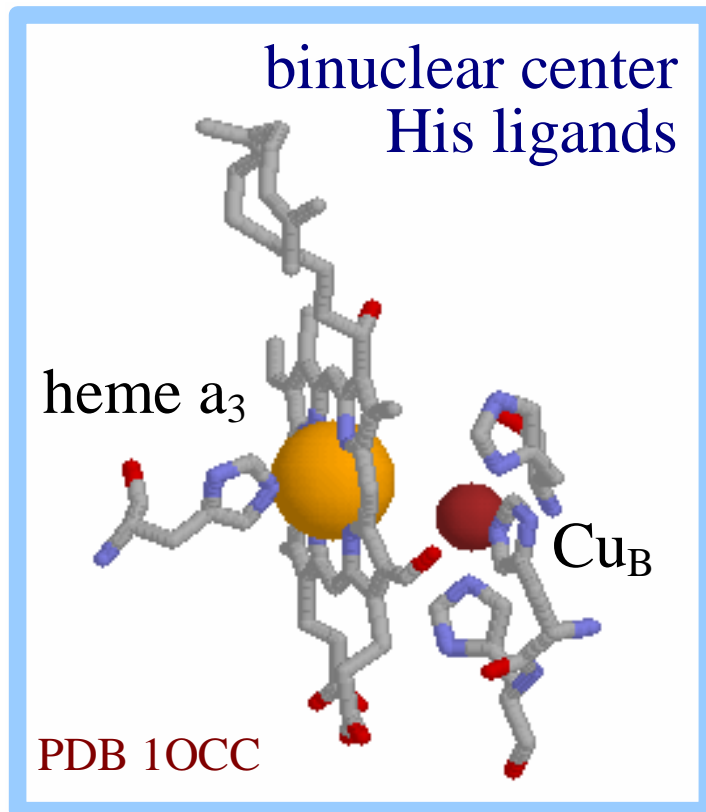
- It is produced by succinate dehydrogenase and acyl CoA dehydrogenase.

Complex III: Cytochromes b and c (cytochrome reductase)

- Each contains a heme group made of a porphyrin ring containing an iron atom.
- The iron atom acts as a reversible carrier of electrons since it can be reversibly converted from the ferric (Fe^{3+}) to the ferrous (Fe^{2+}) form
- It accepts electrons from coenzyme Q.

Complex IV: Cytochrome a+a₃ (Cytochrome oxidase)

- Metal centers of cytochrome oxidase are heme a & heme a₃, Cu_A (2 adjacent Cu atoms) & Cu_B.
- It is the only electron carrier in which the heme iron has a free ligand that can react with molecular oxygen. It also contains a copper atoms that are required for this complex reaction to occur.



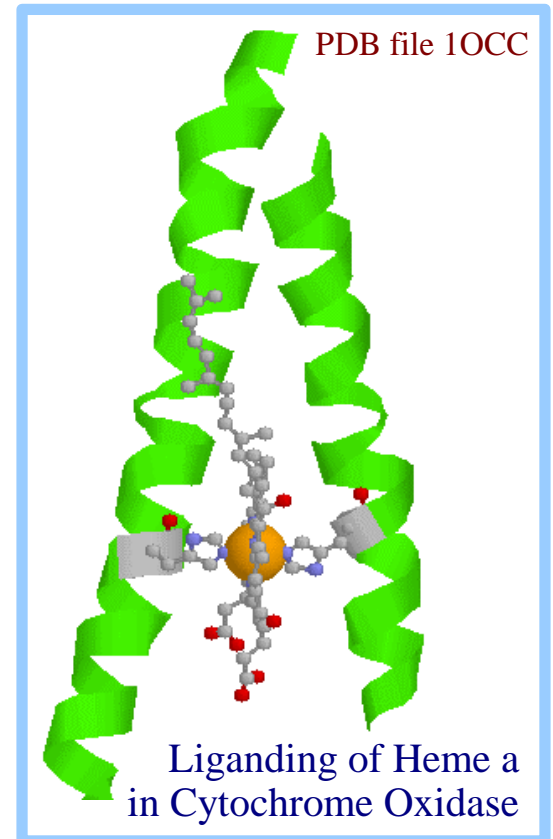
Metal center ligands in complex IV

Heme a in which heme axial ligands are His N atoms.

Heme a is held in place between 2 transmembrane α -helices by its axial His ligands.

Heme a₃, which sits adjacent to Cu_B, has only one axial ligand.

Cu ligands consist of His N, & in the case of Cu_A also Cys S, Met S, & a Glu backbone O.



Metal center ligands in complex IV (Continued)

Electrons enter complex IV one at a time from cyt c to **Cu_A**. They then pass via **heme a** to the **binuclear center** (heme a₃/Cu_B) where the chemical reaction takes place.



O₂ binds at the open axial ligand position of **heme a₃**, adjacent to **Cu_B**.

Complex V: (ATP Synthase Complex)

- It synthesizes ATP, using the energy of the proton gradient generated by the ETC.
- It is also called ATPase, because it also catalyzes the hydrolysis of ATP to ADP and inorganic phosphate (Pi).

Respiratory chain inhibitors

- **Rotenone** (a rat poison) blocks complex I.
- **Antimycin A** blocks electron transfer in complex III.
- **CN⁻** & **CO** inhibit complex IV.

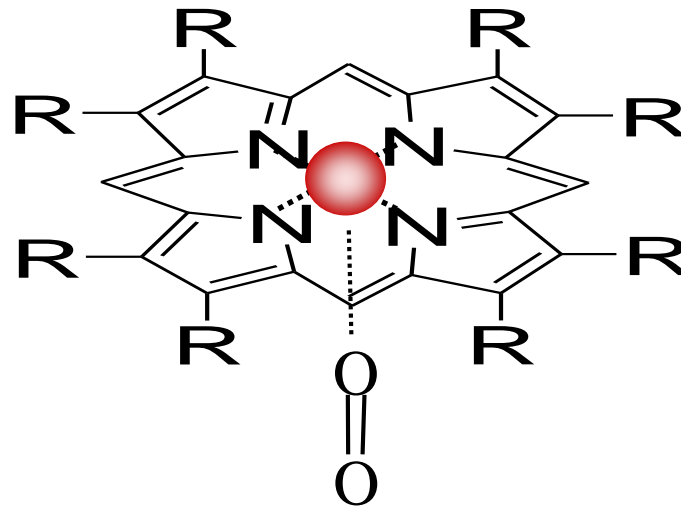
- The open axial ligand position makes heme a₃ susceptible to binding each of the following inhibitors:

CN⁻, **CO**, and the radical signal molecule **·NO**

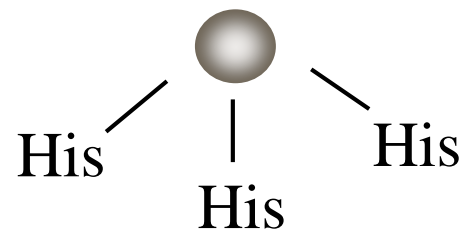
- Inhibition at any of these sites will block e⁻ transfer from NADH to O₂.

Respiratory chain inhibitors

(continued)



iron



copper