Membrane Biochemistry

Lectures by

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jfallen.org/lectures

Queen Mary
University of London

Lectures in Membrane Biochemistry

- The endomembrane system - endocytosis and exocytosis (Acrobat, .pdf file)
- The endomembrane system - vesicular transport and protein trafficking (Acrobat, .pdf file)
- Transport across membranes 1 - Proteins (Acrobat, .pdf file)
- Transport across membranes 2 - Small molecules and ions (Acrobat, .pdf file)

Course web pages

Membrane Biochemistry web pages

General reference

Cell and Molecular Biology: Concepts and Experiments
Gerald Karp. Fifth Edition 2008. John Wiley & Sons Inc.

Further reading

- Chemiosmotic coupling: The cost of living. By Peter Rich. (.pdf file, 80 kb)
- Power for Life. Review of Nick Lane's book "Power Sex Suicide...." (.pdf file, 416 kb)
- N,K-ATPase. Page of Mark Hilge at Protein Biophysics, Nijmegen
- ATP Synthase. Group Pages of John Walker at the MRC Mitochondrial Biology Unit, Cambridge

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Animations

- The pump cycle of Na,K-ATPase. By Mark Hilge at Protein Biophysics, Nijmegen
- Animation. From Light to ATP. By O. Fritsche and W. Junge, University of Osnabruck. (.avi file, 17.7 mb)
- Molecular animations of ATP synthase. From the research group of John Walker at the MRC Mitochondrial Biology Unit, Cambridge
- Animation. Powering the Cell: Mitochondria. From BioVisions at Harvard University

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Relevant Nobel prizes

- 1906 Nobel Prize in Physiology or Medicine to Camillo Golgi and Santiago Ramón y Cajal
- 1974 Nobel Prize in Physiology or Medicine to Albert Claude, Christian de Duve and George E. Palade
- 1978 Nobel Prize in Chemistry to Peter Mitchell
- 1988 Nobel Prize in Chemistry to Johann Deisenhofer, Robert Huber and Hartmut Michel
- 1997 Nobel Prize in Chemistry to Paul D. Boyer, John E. Walker and Jens C. Skou
- 1999 Nobel Prize in Physiology or Medicine to Günter Blobel

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Membrane Biochemistry

Oxidative phosphorylation and respiratory control

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Photosynthetic phosphorylation in chloroplasts

How do plants convert light energy into ATP?

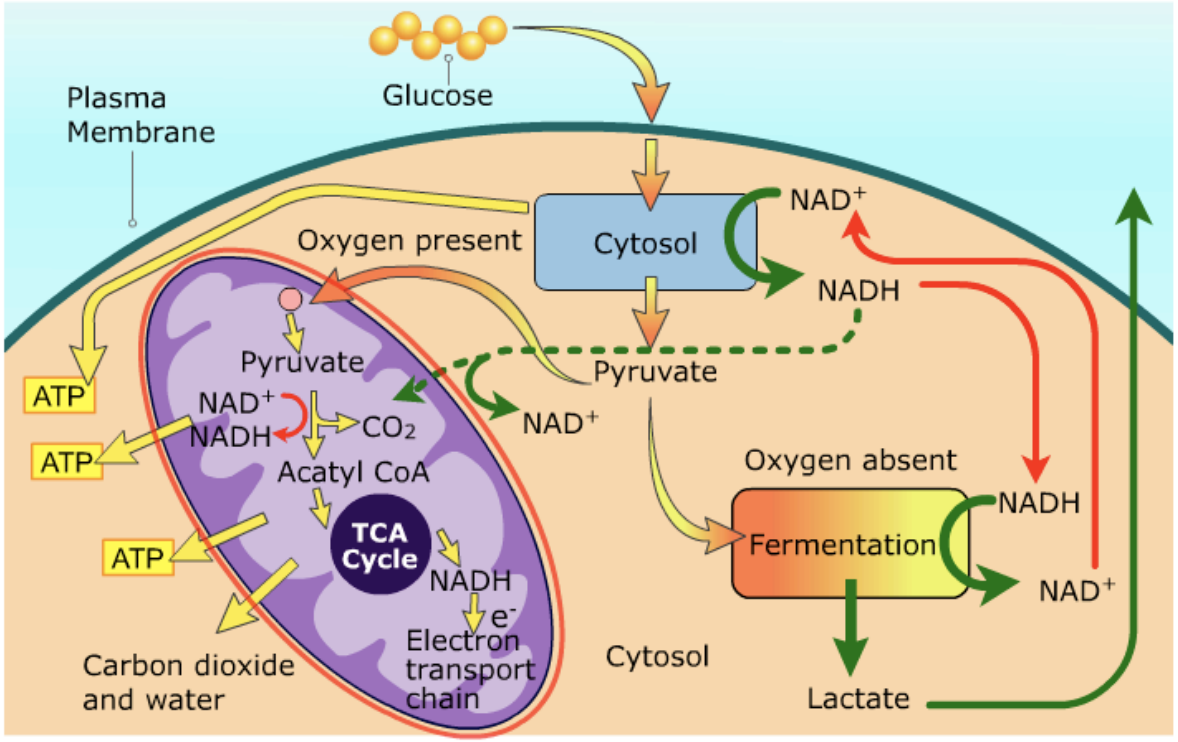
Leaves are shaped so as to optimize their exposure to sunlight.

Click the leaf to view its cell layers.

Oxidative phosphorylation in mitochondria

Aerobic Respiration

Glycolysis converts glucose (C6) into two molecules of pyruvate (C3). If oxygen is present, pyruvate enters mitochondria and its free energy is utilized to make ATP via the TCA cycle and oxidative phosphorylation.



Click the mitochondrion to examine the TCA cycle and oxidative phosphorylation.

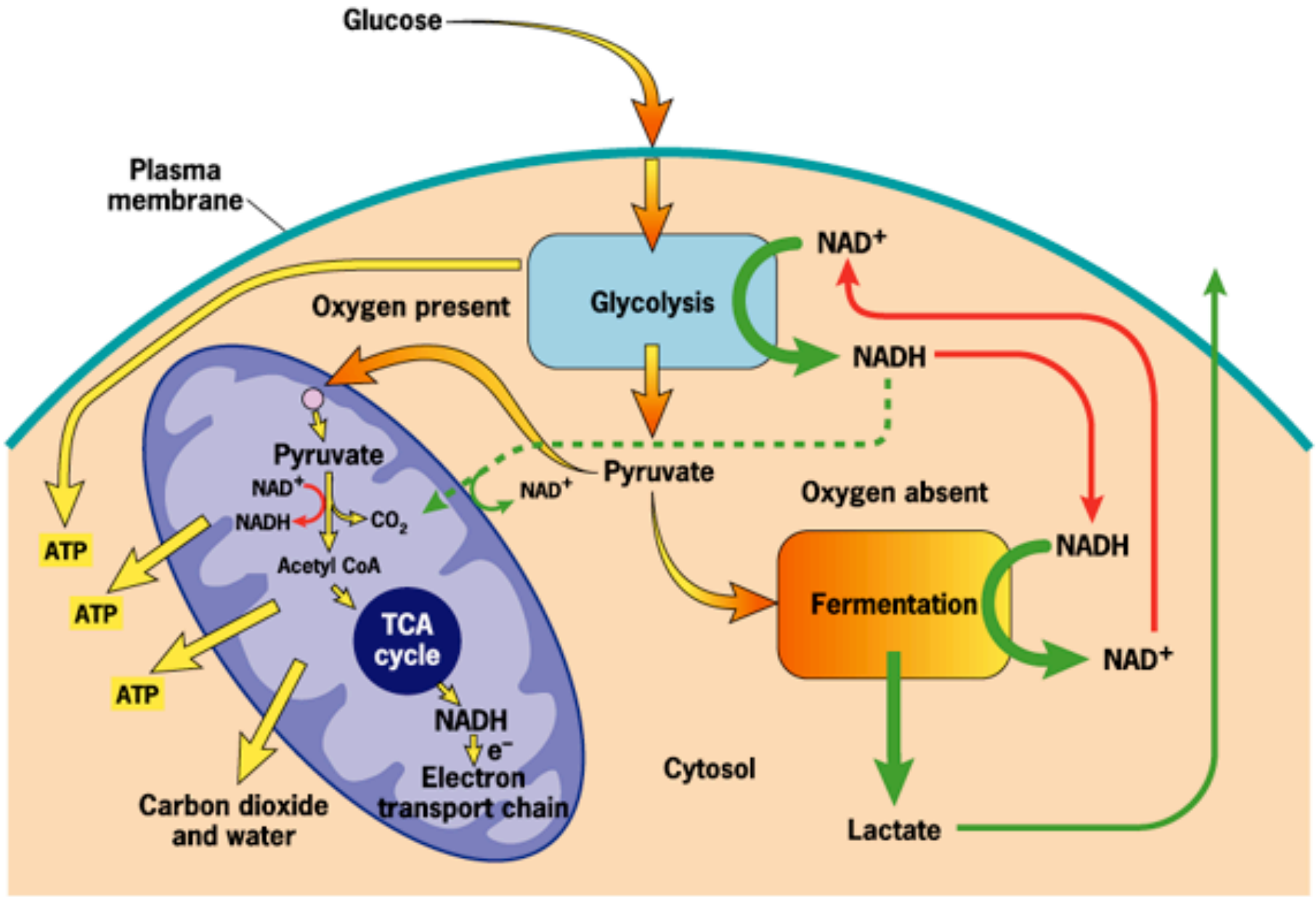


Figure 5.5 An overview of carbohydrate metabolism in eukaryotic cells.

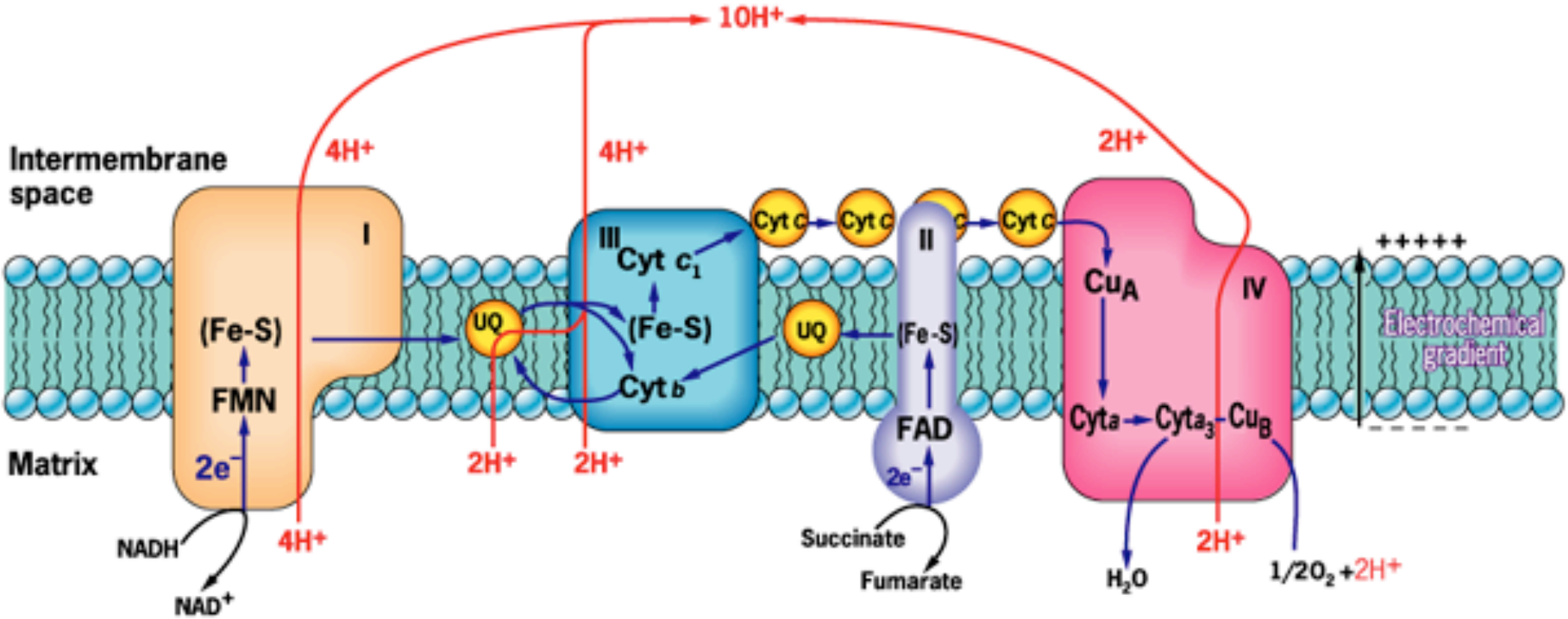
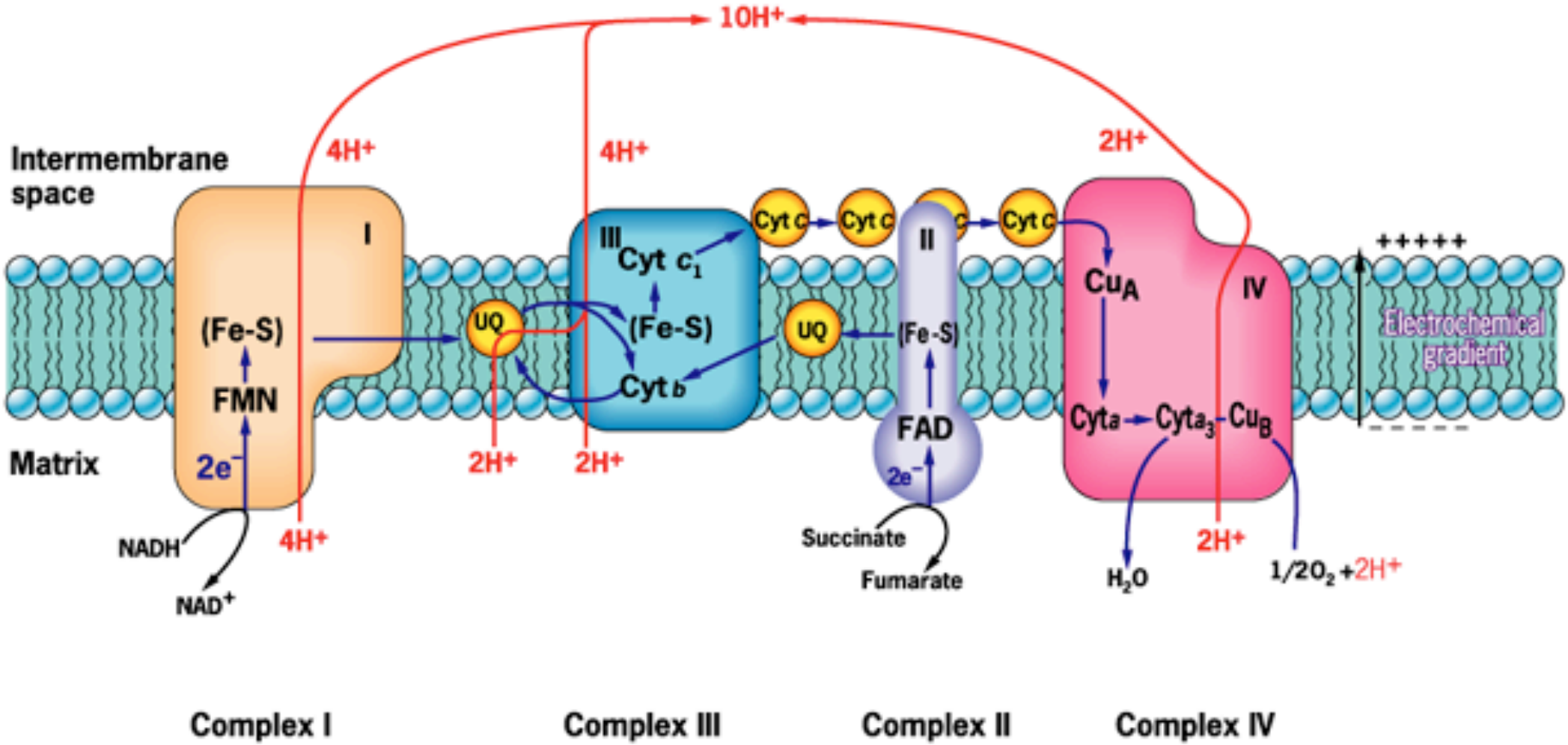


Figure 5.16 Schematic diagram of the components of the electron-transport chain within the inner mitochondrial membrane.



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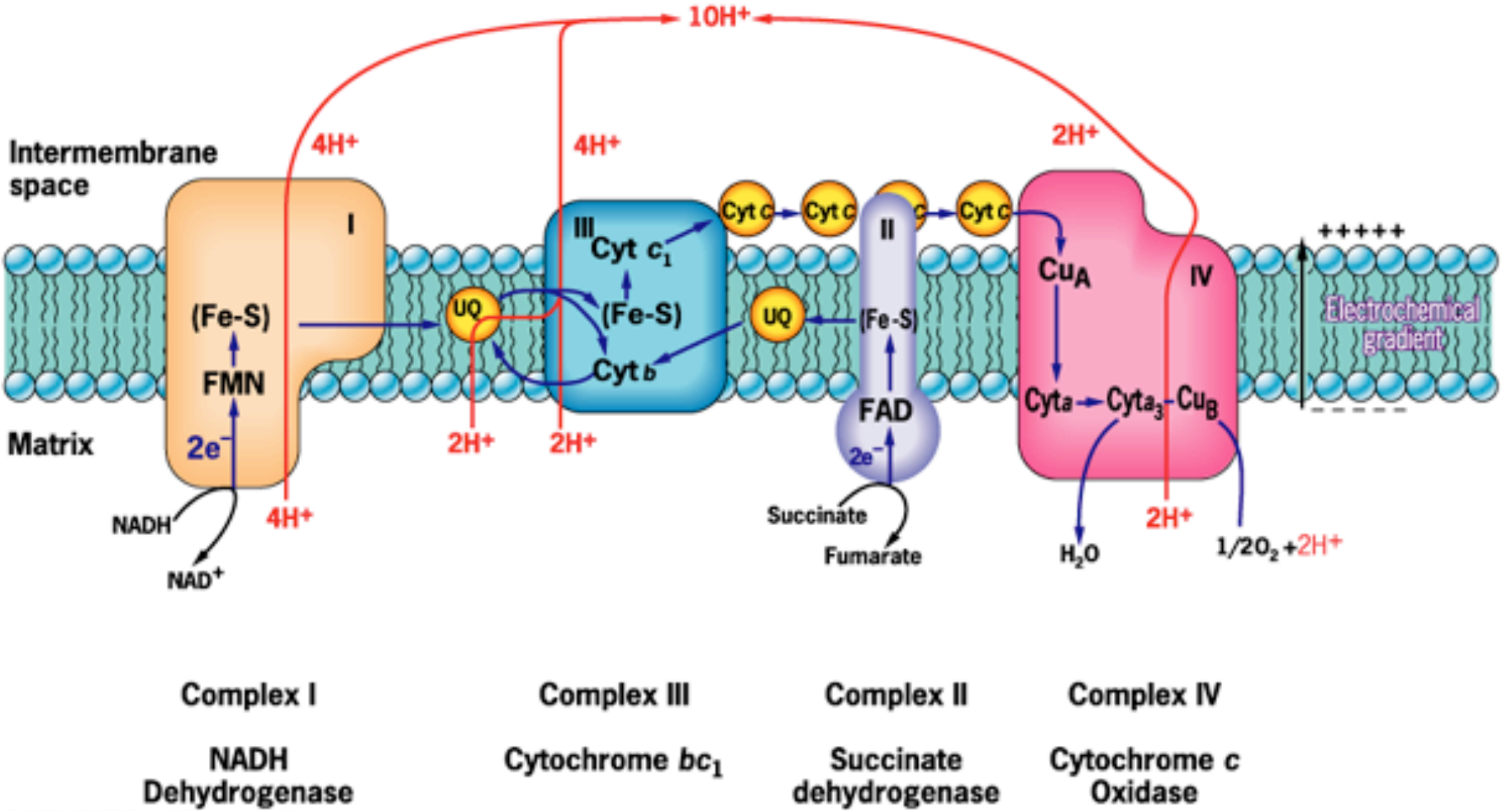
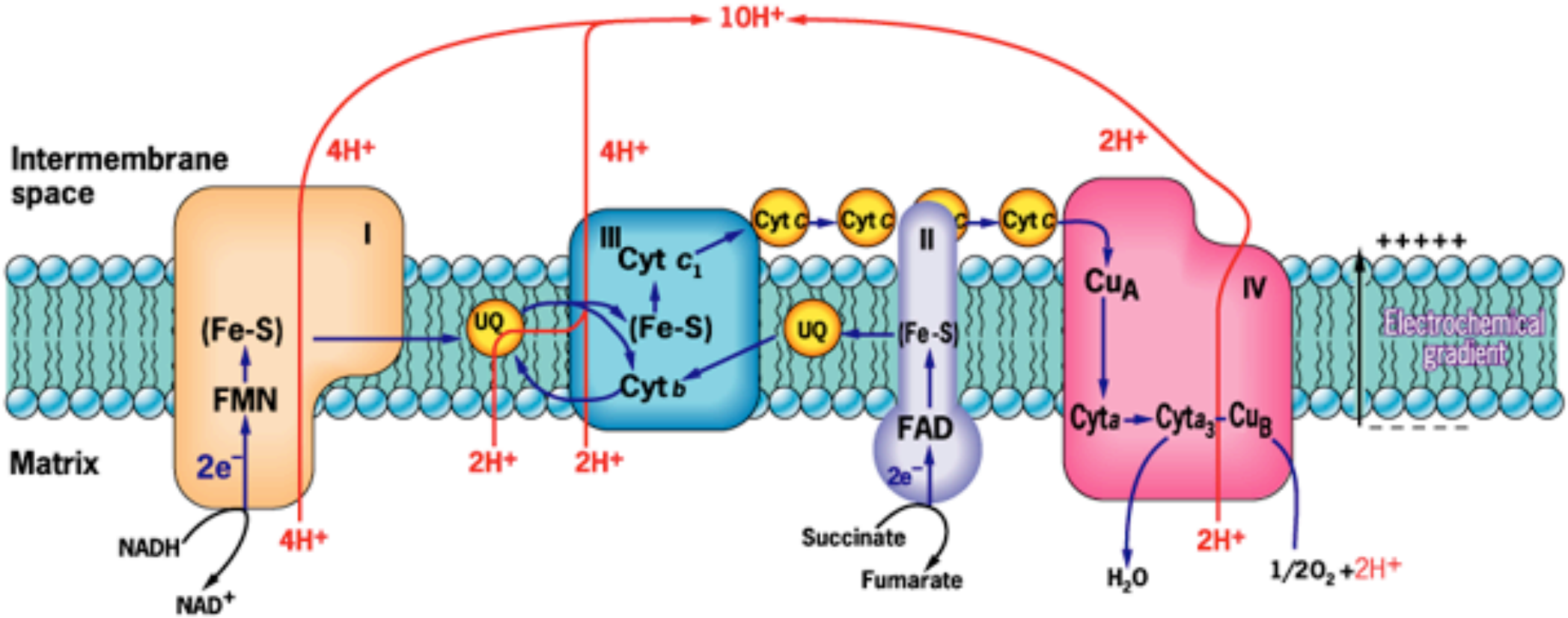


Figure 5.16 Schematic diagram of the components of the electron-transport chain within the inner mitochondrial membrane.



	Complex I	Complex III	Complex II	Complex IV
	NADH Dehydrogenase	Cytochrome bc_1	Succinate dehydrogenase	Cytochrome *c* Oxidase
SUBUNITS				
mtDNA				
nDNA				
TOTAL				

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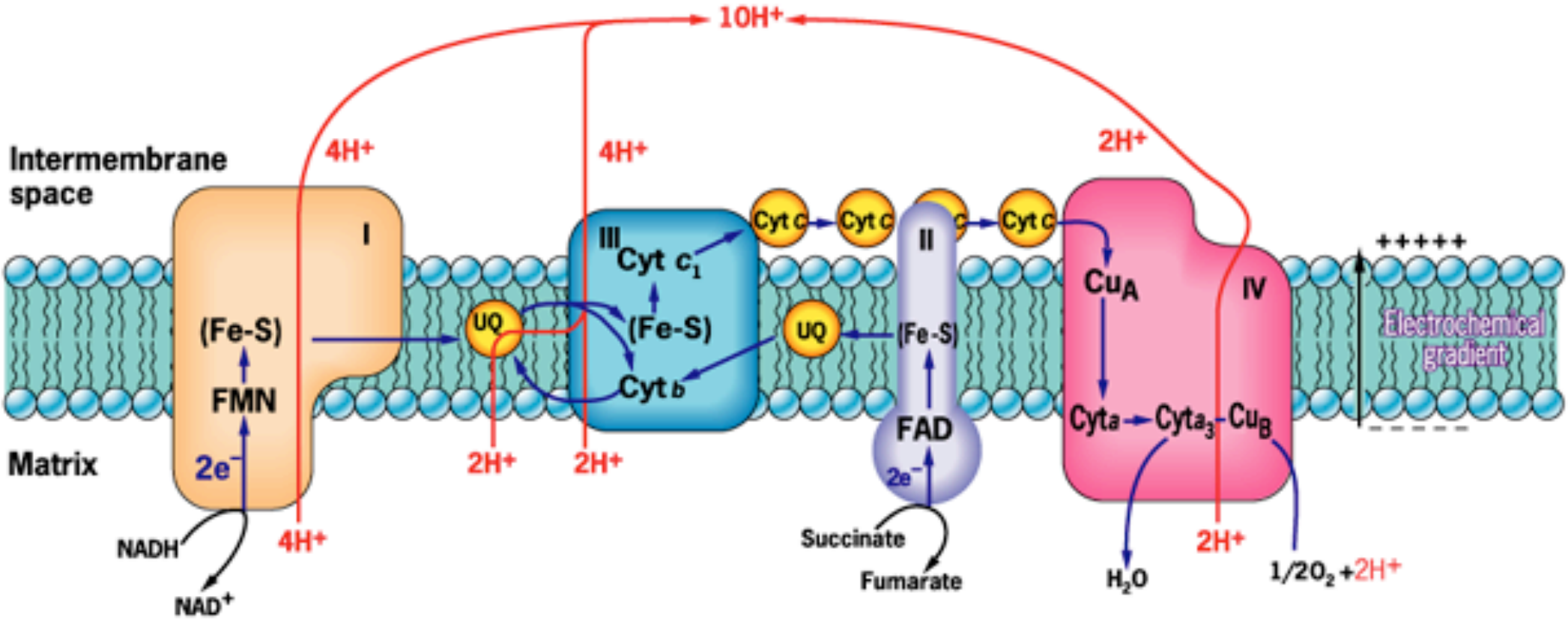

	Complex I	Complex III	Complex II	Complex IV
	NADH Dehydrogenase	Cytochrome bc_1	Succinate dehydrogenase	Cytochrome *c* Oxidase
SUBUNITS	Mammalian			
mtDNA	7			
nDNA	35			
TOTAL	42			

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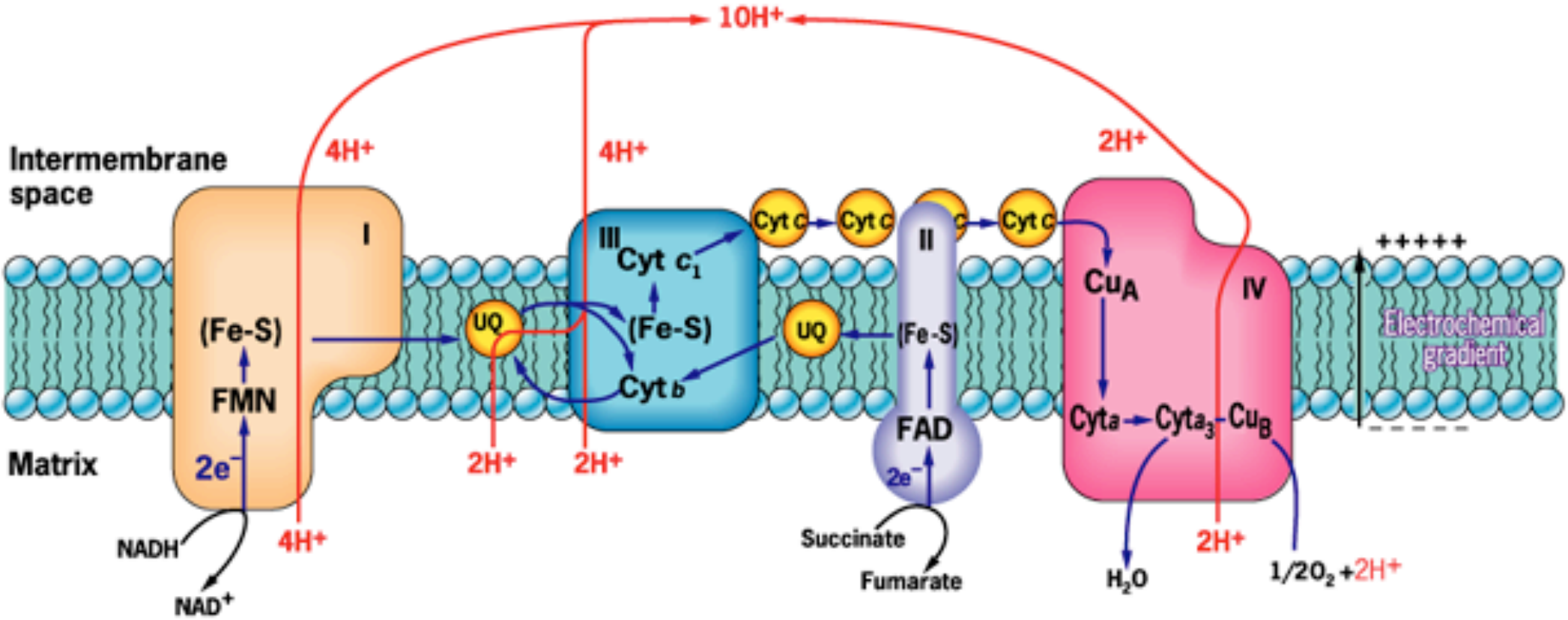

SUBUNITS	Complex I NADH Dehydrogenase Mammalian	Complex III Cytochrome bc_1	Complex II Succinate dehydrogenase	Complex IV Cytochrome *c* Oxidase
mtDNA	7	1		
nDNA	35	10		
TOTAL	42	11		

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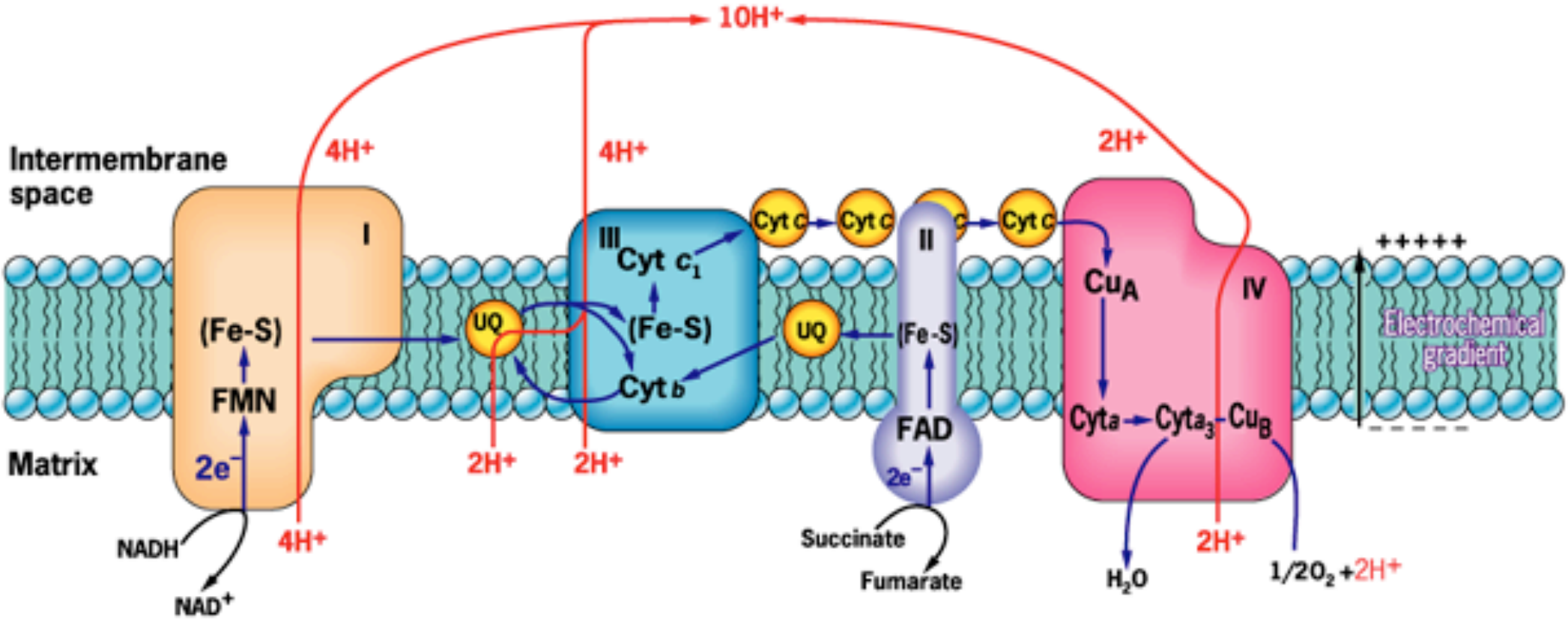

SUBUNITS	Complex I NADH Dehydrogenase Mammalian	Complex III Cytochrome bc_1	Complex II Succinate dehydrogenase	Complex IV Cytochrome *c* Oxidase
mtDNA	7	1	0	
nDNA	35	10	4	
TOTAL	42	11	4	

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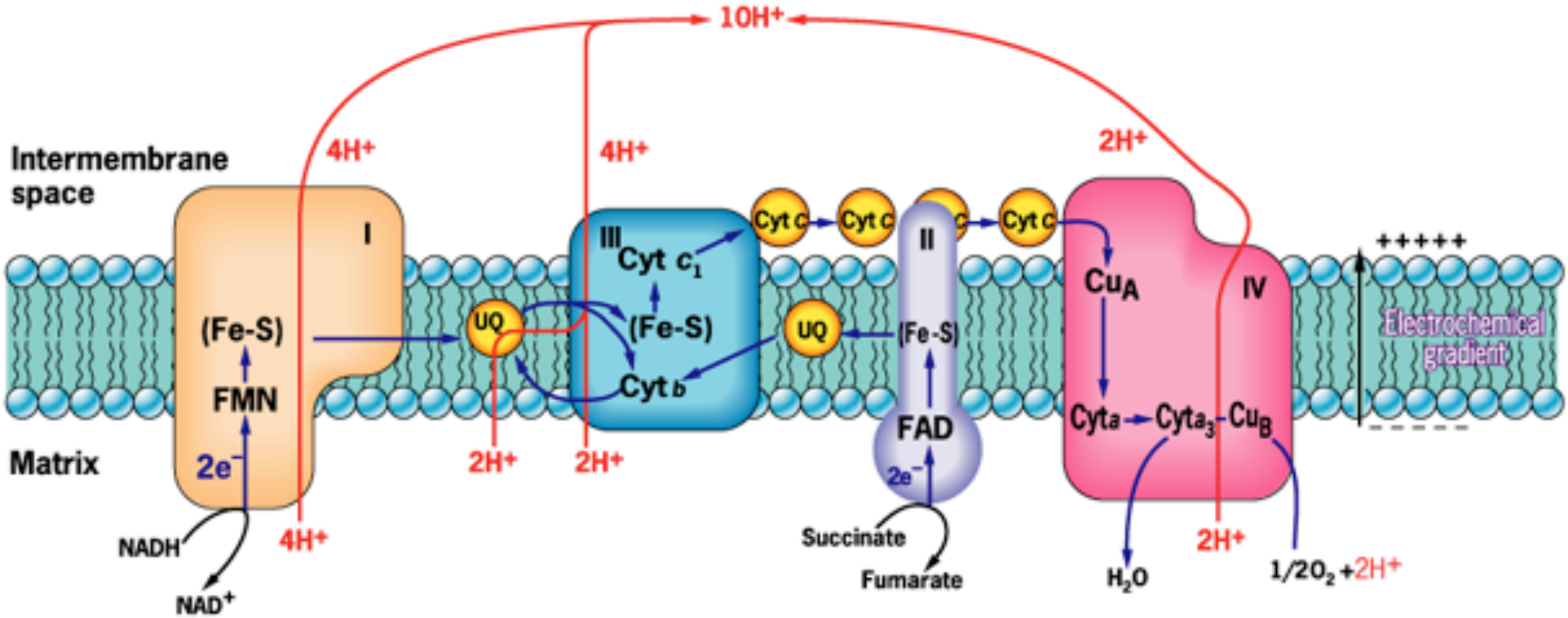

SUBUNITS	Complex I NADH Dehydrogenase Mammalian	Complex III Cytochrome bc_1	Complex II Succinate dehydrogenase	Complex IV Cytochrome *c* Oxidase
mtDNA	7	1	0	3
nDNA	35	10	4	10
TOTAL	42	11	4	13

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Characteristics of oxidative phosphorylation

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By early 1960's researchers had determined certain observed characteristics of oxidative phosphorylation linked to respiratory electron transfer in animal mitochondria, that had to be explained by any theory proposed for the mechanism of this energy transduction (transducing redox energy of electron transfer into chemical energy of ATP).

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a) the rate of electron transport – the number of electrons transferred along the chain in unit time – by measuring the rate at which oxygen is consumed (1 0 atom = $2e^-$)

b) the amount of ATP synthesised (or amount of ADP or Pi converted into ATP)

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2] Respiratory control

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You will observe 1-4 in the laboratory classes.

Characteristics of oxidative phosphorylation

1] Energy coupling sites

2] Respiratory control

3] Uncoupling agents

4] Phosphorylation inhibitors

1] Energy Coupling Sites

It became apparent that the amount of ATP formed (or ADP/Pi converted into ATP) was stoichiometric with amount of oxygen consumed

This stoichiometry is called

P/O or P/$2e^-$ quotient

ATP/O or ATP/$2e^-$ quotient

ADP/O or ADP/$2e^-$ quotient

The value obtained reflects several parameters

1) the nature of the substrate undergoing oxidation
2) the integrity of coupling membrane
3) the redox carrier composition of respiratory chain

In late 1940s and early 1950s several labs showed that oxidation of NADH (in fact oxidation of substrates like βHOB that feed into resp. chain via NADH) leads to production of 3 molecules of ATP for every oxygen atom consumed, that is, for every pair of electrons ($2e^-$) transferred through the chain (ATP/O quotient of 3).

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It is possible to isolate particular sections of the respiratory chain with different electron donors and acceptors, together with electron transfer inhibitors to inhibit other parts of the chain.

Reductant	Oxidant	Inhibitor	ATP/O ATP/2e$^-$

Reductant	**Oxidant**	**Inhibitor**	**ATP/O** **ATP/2e$^-$**
β-hydroxybutyrate (NADH)	O_2	None	3

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Succinate	O_2	Rotenone	2

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An increased ATP/$2e^-$ quotient is observed if it is measures with ADP and Pi already inside (endogeneous) mitochondria. About 25% of energy released by electron transfer is used for this active transport of ATP, ADP and Pi.

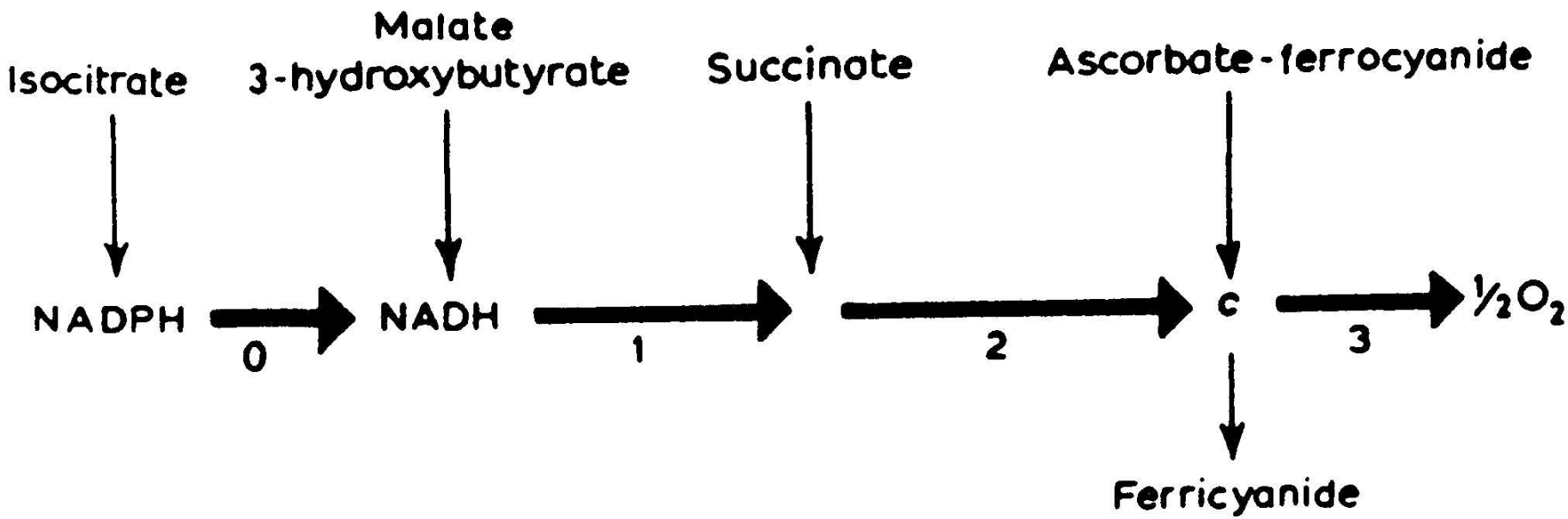

Fig. 4.1 Energy coupling sites.

Characteristics of oxidative phosphorylation

1] Energy coupling sites

2] Respiratory control

3] Uncoupling agents

4] Phosphorylation inhibitors

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a) In the absence of ADP, the rate of electron transfer is low, reflecting a low rate at which energy for ATP synthesis (provided by electron transfer) is dissipated in the absence of ATP synthesis. The state is called the “controlled state” or *state IV*

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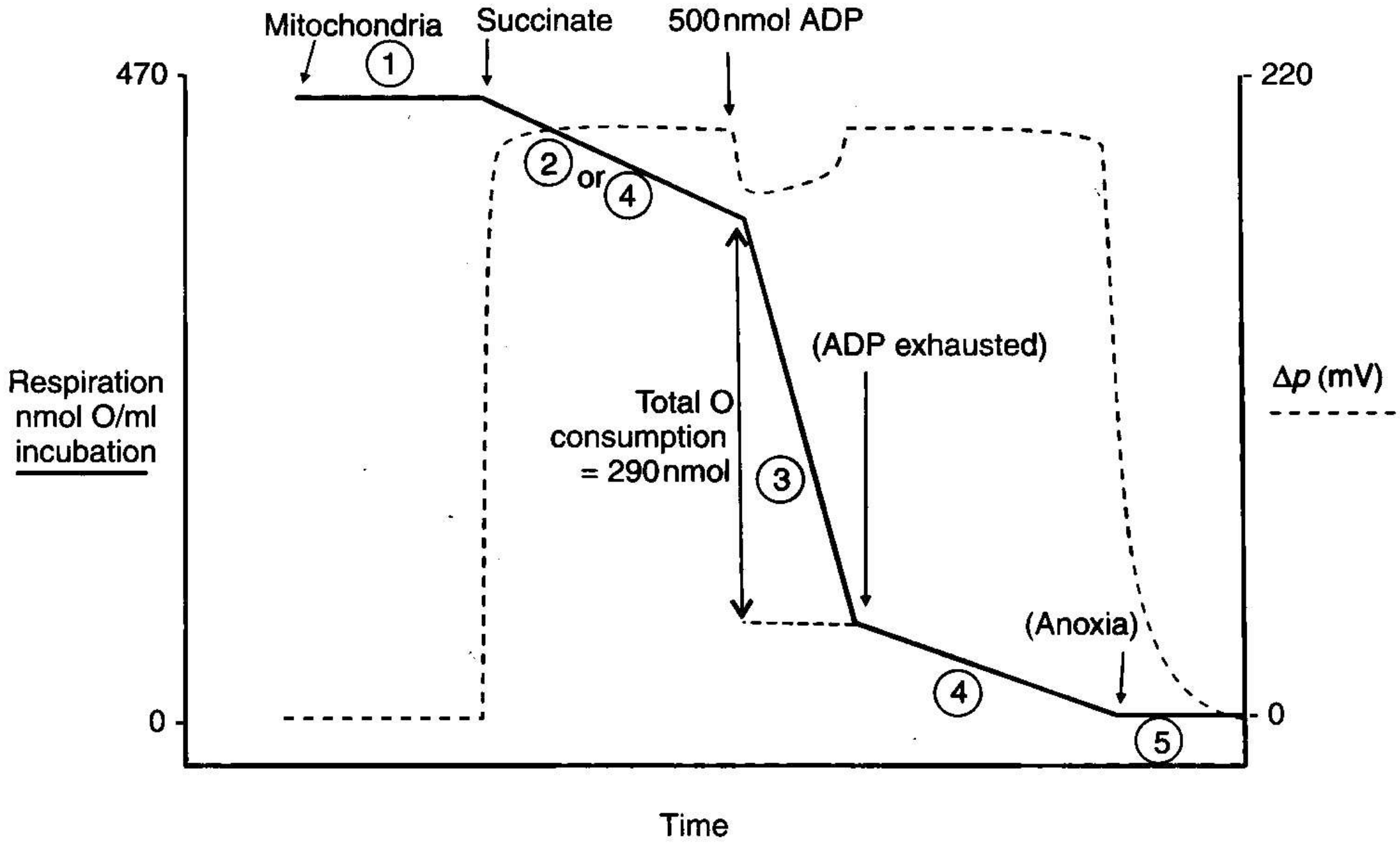
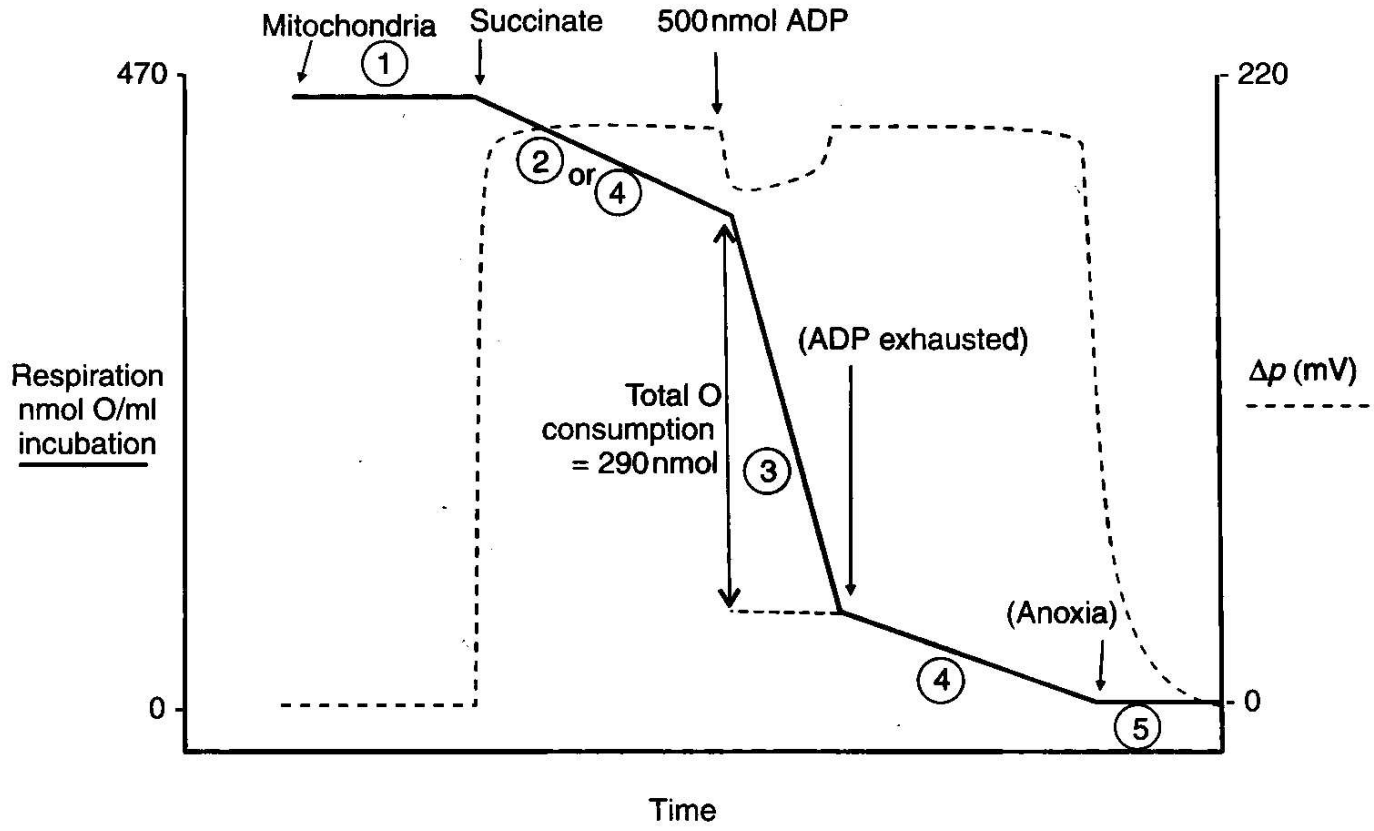
c) The rate then remains high until all the ADP has been phosphorylated to give ATP. At this point the rate declines again to state IV


Mitochondria
Succinate
500 nmol ADP
470
220
1
2
or
4
Respiration
nmol O/ml
incubation
Total O
consumption
= 290 nmol
3
(ADP exhausted)
Δp (mV)
(Anoxia)
4
0
0
5
Time


Mitochondria
Succinate
500 nmol ADP
470
220
1
2
or
4
(ADP exhausted)
Respiration
nmol O/ml
incubation
Total O
consumption
= 290 nmol
3
Δp (mV)
(Anoxia)
4
0
0
5
Time

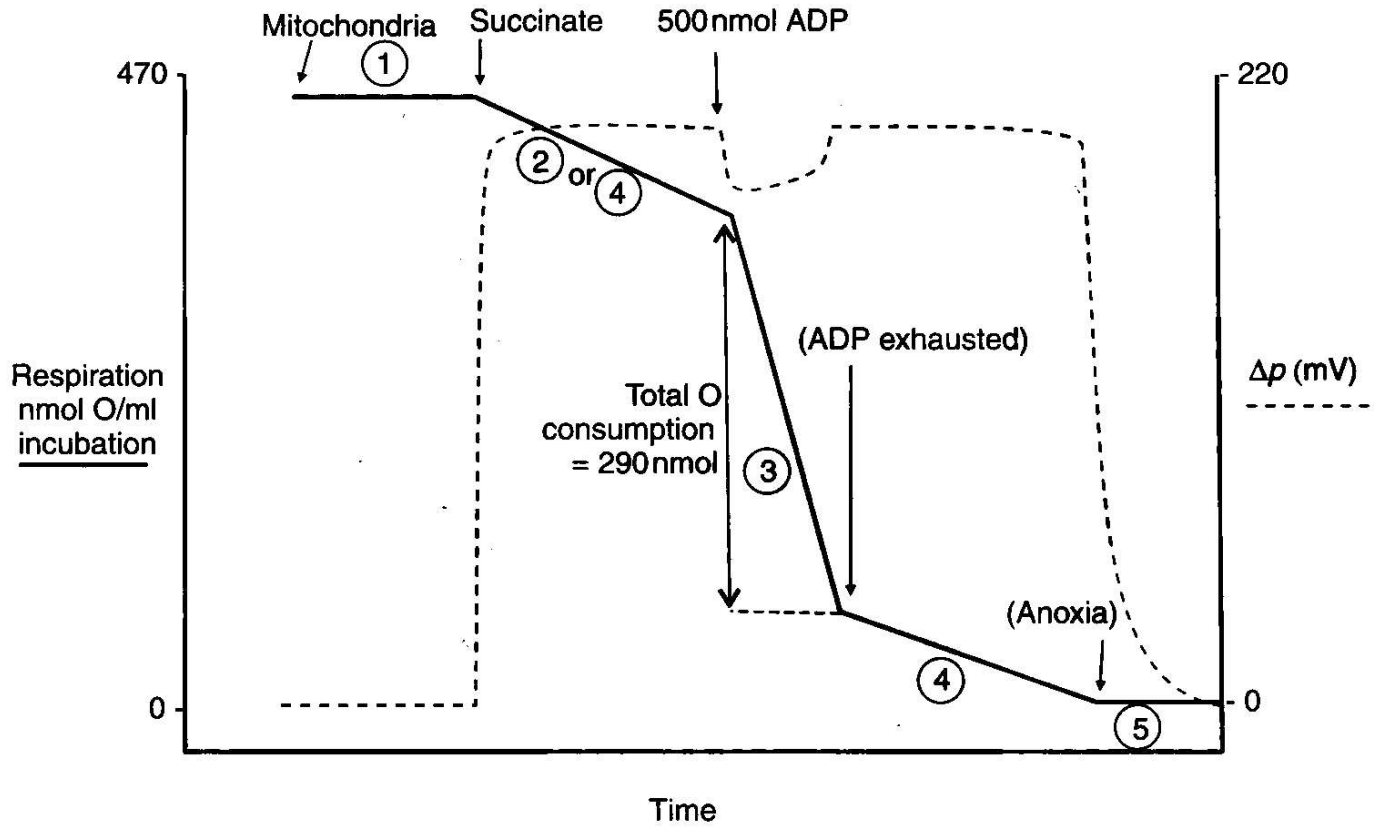


Figure 4.9 Respiratory 'states' and the determination of P/O ratios.
In this experiment mitochondria were added to an oxygen electrode chamber, followed by succinate as substrate. Respiration is slow as the proton circuit is not completed by H^+ re-entry through the ATP synthase. That there is any respiration at all is because of a slow proton leak across the membrane. A limited amount of ADP is added, allowing the ATP synthase to synthesize ATP coupled to proton re-entry across the membrane, 'state 3' (Section 4.5). When this is exhausted, respiration slows and finally anoxia is attained. The circled numbers refer to the respiratory 'states'. If the amount of ADP is known, the oxygen uptake during the accelerated 'state 3' respiration can be quantified allowing a P/O ratio to be calculated (moles ATP synthesized per mol O). Since the proton leak is almost negligible in 'state 3' (Section 4.6.2), the total oxygen uptake during 'state 3' is effectively used for ATP synthesis. In this example, the ADP/O ratio for the substrate is found to be 500/290 = 1.72. Note the bioenergetic convention of referring to 'O', i.e. $\frac{1}{2}O_2$, which is equivalent to $2e^-$. Also, the controlled respiration prior to addition of ADP, which is strictly termed 'state 2' is functionally the same as state 4, and the latter term is usually used for both states. The dotted trace reports the values of Δp during the experiment.

Characteristics of oxidative phosphorylation

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Uncouplers dissipate this energised state as heat, and so no ATP synthesis takes place. Electron transfer then proceeds at a maximal rate because it is no longer controlled by back-pressure from the energised state – respiratory control has been abolished.

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They have the following effects:-

• Phosphorylation inhibitors cause the ADP-induced state III rate to decrease back to state IV, and further additions of ADP have no effect

• Phosphorylation inhibitors have no effect on the rate of uncoupled electron transfer

4] Phosphorylation inhibitors

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They have the following effects:-

• Phosphorylation inhibitors cause the ADP-induced state III rate to decrease back to state IV, and further additions of ADP have no effect

• Phosphorylation inhibitors have no effect on the rate of uncoupled electron transfer

• If mitochondria are already inhibited to state IV by phosphorylation inhibitor, added uncoupler will stimulate rate of electron transfer.

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This evidence indicates that uncouplers act between electron transfer and ATP synthesis, that is, on the energised state.

A view of mitochondrial electron transfer as a series of redox (oxidation-reduction) carriers in the inner mitochondrial membrane. This view concentrates on redox centres, substrates, and inhibitors, and neglects the significance of the proteins to which they bind, and of the mitochondrial inner membrane to which the proteins are bound.

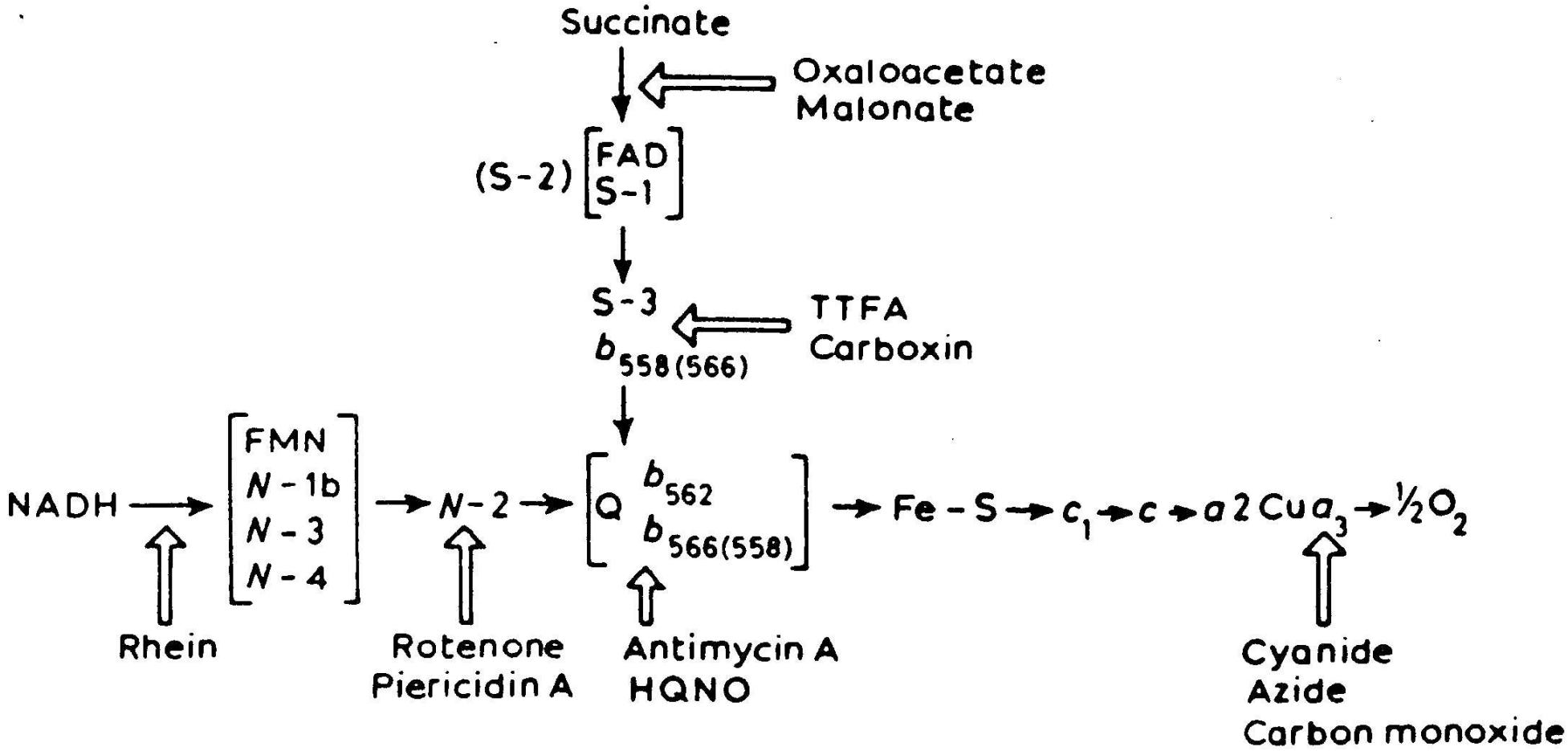

Fig. 2.19 The mitochondrial respiratory chain.

Membrane Biochemistry

Next lecture....

ATP Synthase – Coupling ATPase

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