Bioenergetics and Oxidative Phosphorylation

DENTAL BIOCHEMISTRY COURSE

CARLOS M. BASILIO, M.D.

2012-13

Laws of Thermodynamics

The first law is the principle of the conservation of energy: *"for any physical or chemical change, the total amount of energy in the universe remains constant"*.

The second law says that the universe always tends toward increasing disorder: *"in all natural processes, the entropy of the universe increases"*.

TABLE 13–1 Some Physical Constants and Units Used in Thermodynamics

Boltzmann constant, $\mathbf{k} = 1.381 \times 10^{-23}$ J/K

Avogadro's number, $N = 6.022 \times 10^{23}\ \text{mol}^{-1}$

Faraday constant, $\mathcal{F} = 96{,}480$ J/V · mol

Gas constant, $R = 8.315$ J/mol · K

(= 1.987 cal/mol · K)

Units of ΔG and ΔH are J/mol (or cal/mol)

Units of ΔS are J/mol · K (or cal/mol · K)

1 cal = 4.184 J

Units of absolute temperature, T, are Kelvin, K

25 °C = 298 K

At 25 °C, RT = 2.479 kJ/mol

(= 0.592 kcal/mol)

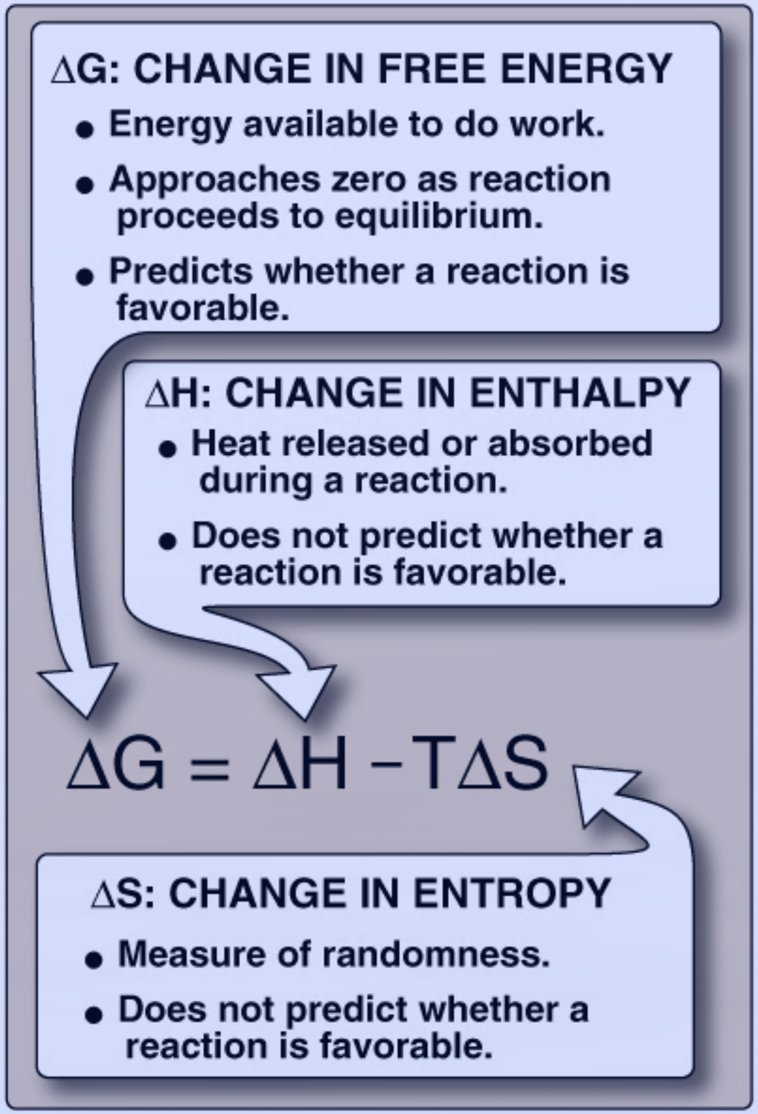


Figure 6.1

Relationship between changes in free energy (G), enthalpy (H), and entropy (S). T is the absolute temperature in degrees Kelvin (^oK): $^oK = ^oC + 273$.

Gibbs free energy, G:

Expresses the amount of energy capable of doing work during a reaction at constant temperature and pressure

Enthalpy, H:

Is the heat content of the reacting system. It reflects the number and kinds of chemical bonds in the reactants and products.

Entropy, S:

Is a quantitative expression for the randomness or disorder in a system

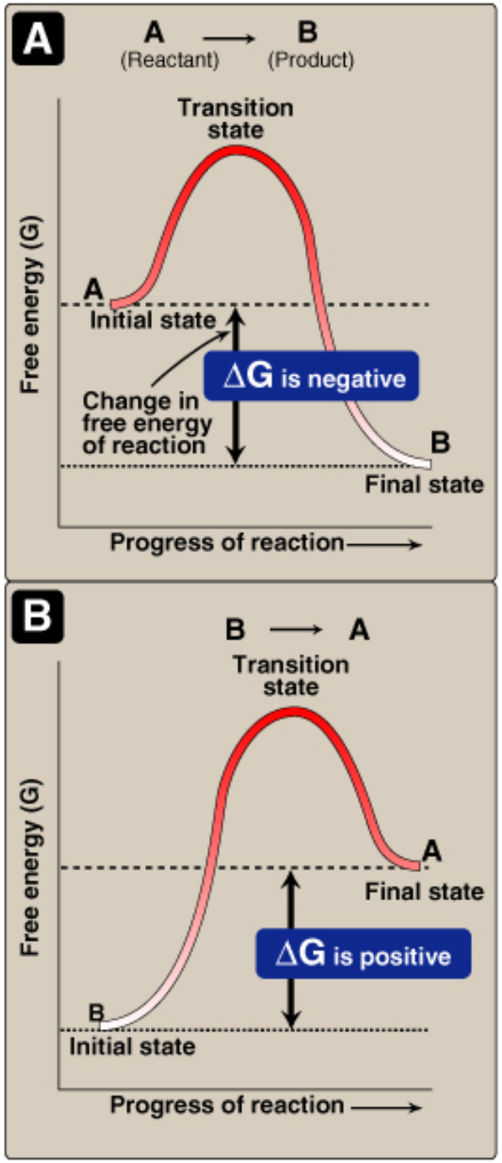


Figure 6.2

Change in free energy (DG) during a reaction. A. The product has a lower free energy (G) than the reactant. B. The product has a higher free energy than the reactant.

Variations of Reaction Spontaneity (Sign of ΔG) with the signs of ΔH and ΔS

ΔH	ΔS	$\Delta G = \Delta H - T\Delta S$
-	+	Spontaneous (exergonic)
-	-	Spontaneous below T= $\Delta H/\Delta S$
+	+	Spontaneous above T= $\Delta H/\Delta S$
+	-	Unspontaneous (endergonic)

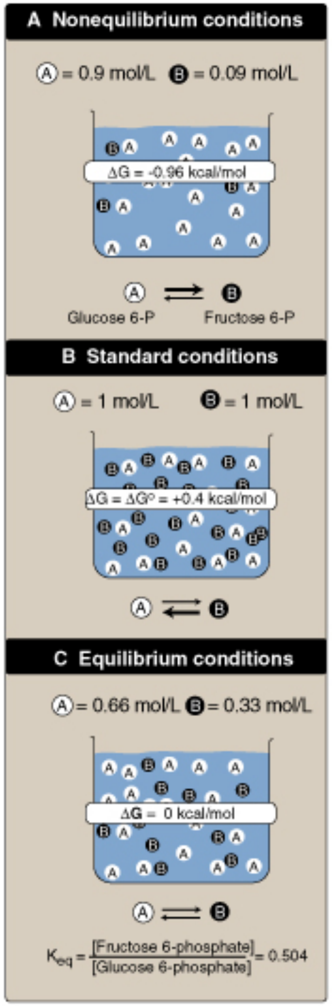


Figure 6.3

ΔG of a reaction depends on the concentration of reactant (A) and product (B). For the conversion of glucose 6-P to fructose 6-P, ΔG is negative when the ratio of reactant (A) to product (B) is large (top, panel A); is positive under standard conditions (middle, panel B); and is zero at equlibrium (bottom, panel C).

$$\Delta G = \Delta G_0' + RT \ln \frac{B}{A}$$

$$\Delta G = 0 = \Delta G_0' + RT \ln \frac{B}{A}$$

$$\Delta G_0' = -RT \ln K_{eq}$$

TABLE 13–2 Relationship between the Equilibrium Constants and Standard Free-Energy Changes of Chemical Reactions

	$\Delta G'^\circ$	
K'_{eq}	(kJ/mol)	(kcal/mol)*
10^3	−17.1	−4.1
10^2	−11.4	−2.7
10^1	−5.7	−1.4
1	0.0	0.0
10^{-1}	5.7	1.4
10^{-2}	11.4	2.7
10^{-3}	17.1	4.1
10^{-4}	22.8	5.5
10^{-5}	28.5	6.8
10^{-6}	34.2	8.2

*Although joules and kilojoules are the standard units of energy and are used throughout this text, biochemists sometimes express $\Delta G'^\circ$ values in kilocalories per mole. We have therefore included values in both kilojoules and kilocalories in this table and in Tables 13–4 and 13–6. To convert kilojoules to kilocalories, divide the number of kilojoules by 4.184.

TABLE 13–3 **Relationships among K'_{eq}, $\Delta G'^{\circ}$, and the Direction of Chemical Reactions under Standard Conditions**

When K'_{eq} is . . .	$\Delta G'^{\circ}$ is . . .	Starting with all components at 1 M, the reaction . . .
>1.0	negative	proceeds forward
1.0	zero	is at equilibrium
<1.0	positive	proceeds in reverse

TABLE 13–4 **Standard Free-Energy Changes of Some Chemical Reactions at pH 7.0 and 25 °C (298 K)**

Reaction type	$\Delta G'^{\circ}$ *(kJ/mol)*	$\Delta G'^{\circ}$ *(kcal/mol)*
Hydrolysis reactions		
Acid anhydrides		
Acetic anhydride + $H_2O \longrightarrow$ 2 acetate	−91.1	−21.8
ATP + $H_2O \longrightarrow$ ADP + P_i	−30.5	−7.3
ATP + $H_2O \longrightarrow$ AMP + PP_i	−45.6	−10.9
PP_i + $H_2O \longrightarrow 2P_i$	−19.2	−4.6
UDP-glucose + $H_2O \longrightarrow$ UMP + glucose 1-phosphate	−43.0	−10.3
Esters		
Ethyl acetate + $H_2O \longrightarrow$ ethanol + acetate	−19.6	−4.7
Glucose 6-phosphate + $H_2O \longrightarrow$ glucose + P_i	−13.8	−3.3
Amides and peptides		
Glutamine + $H_2O \longrightarrow$ glutamate + NH_4^+	−14.2	−3.4
Glycylglycine + $H_2O \longrightarrow$ 2 glycine	−9.2	−2.2

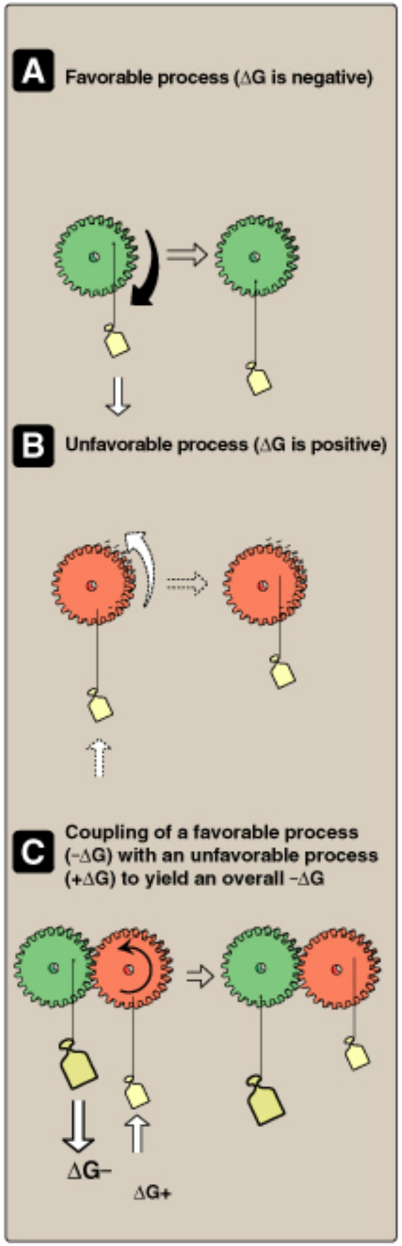


Figure 6.4
Mechanical model of coupling of favorable and unfavorable processes.

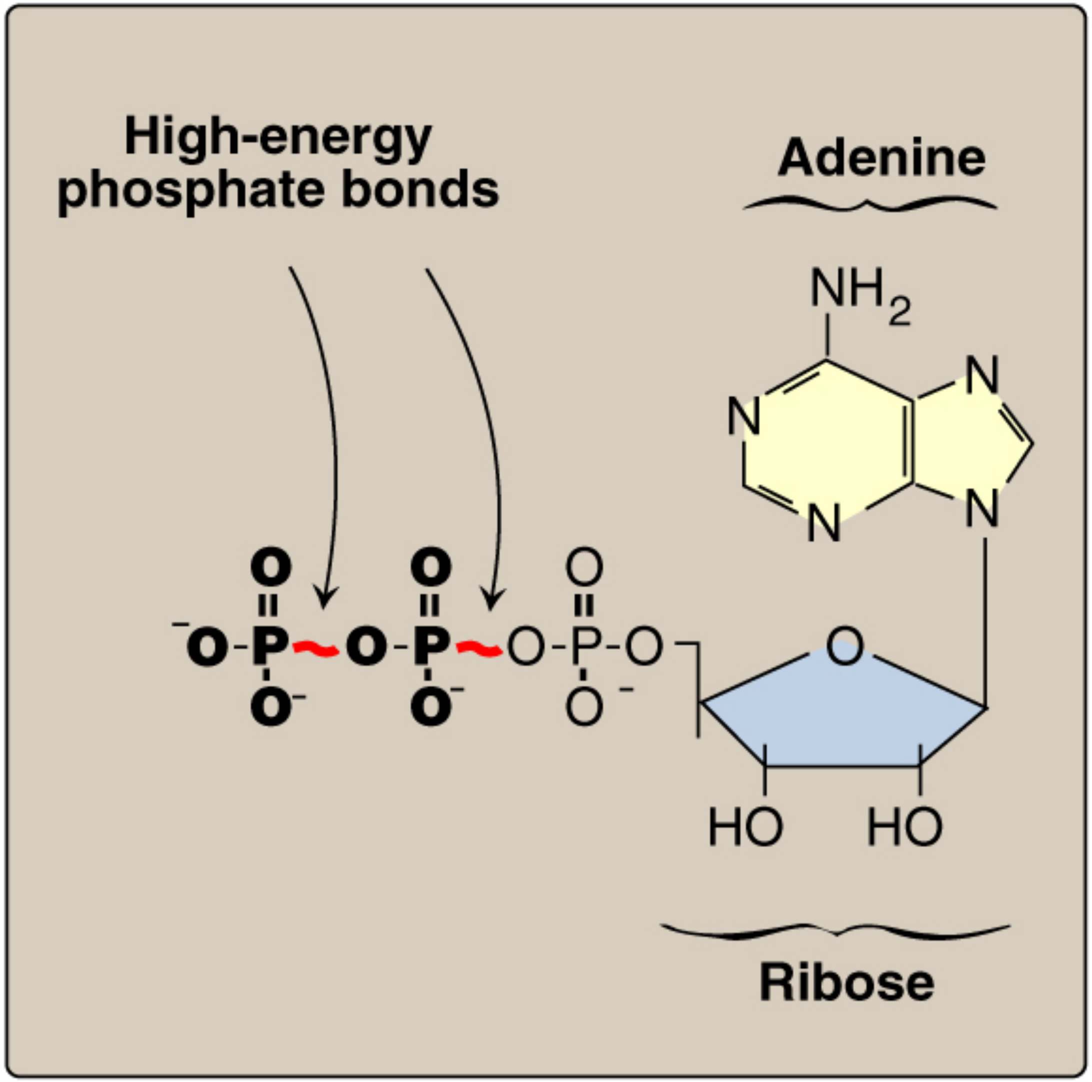


Figure 6.5
Adenosine triphosphate.

TABLE 13–5 Adenine Nucleotide, Inorganic Phosphate, and Phosphocreatine Concentrations in Some Cells

	Concentration (mM)*				
	ATP	ADP†	AMP	P_i	PCr
Rat hepatocyte	3.38	1.32	0.29	4.8	0
Rat myocyte	8.05	0.93	0.04	8.05	28
Rat neuron	2.59	0.73	0.06	2.72	4.7
Human erythrocyte	2.25	0.25	0.02	1.65	0
E. coli cell	7.90	1.04	0.82	7.9	0

*For erythrocytes the concentrations are those of the cytosol (human erythrocytes lack a nucleus and mitochondria). In the other types of cells the data are for the entire cell contents, although the cytosol and the mitochondria have very different concentrations of ADP. PCr is phosphocreatine, discussed on p. 505.

†This value reflects total concentration; the true value for free ADP may be much lower (see Box 13–1).

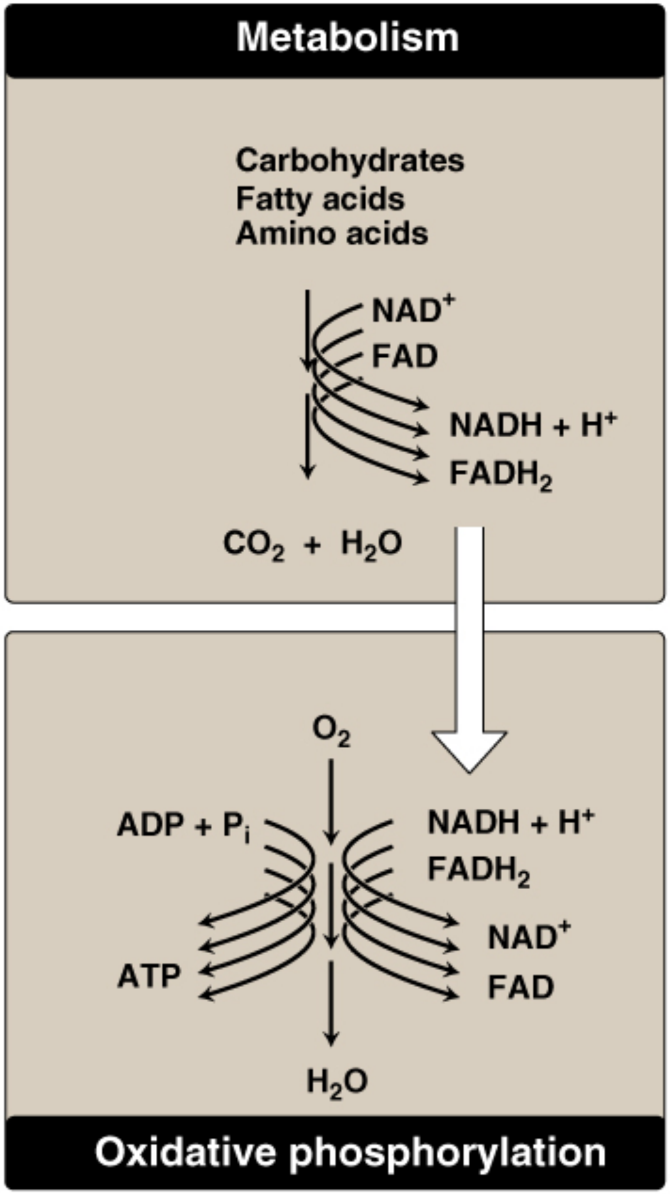


Figure 6.6

The metabolic breakdown of energy-yielding molecules.

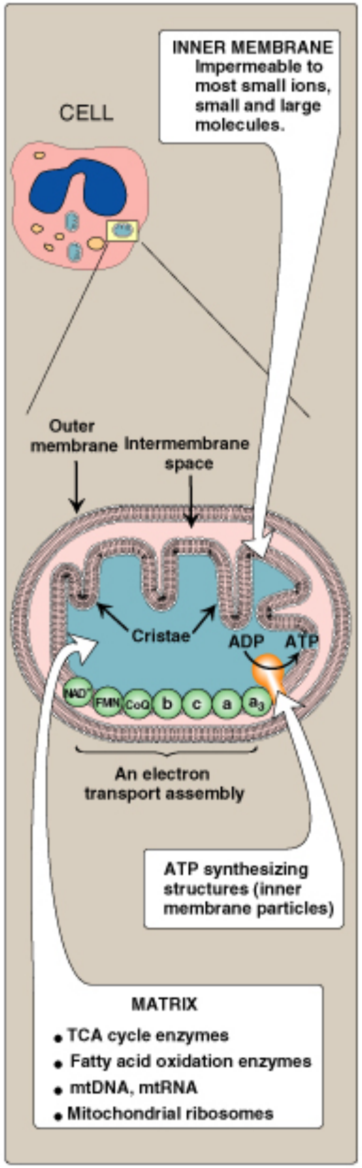
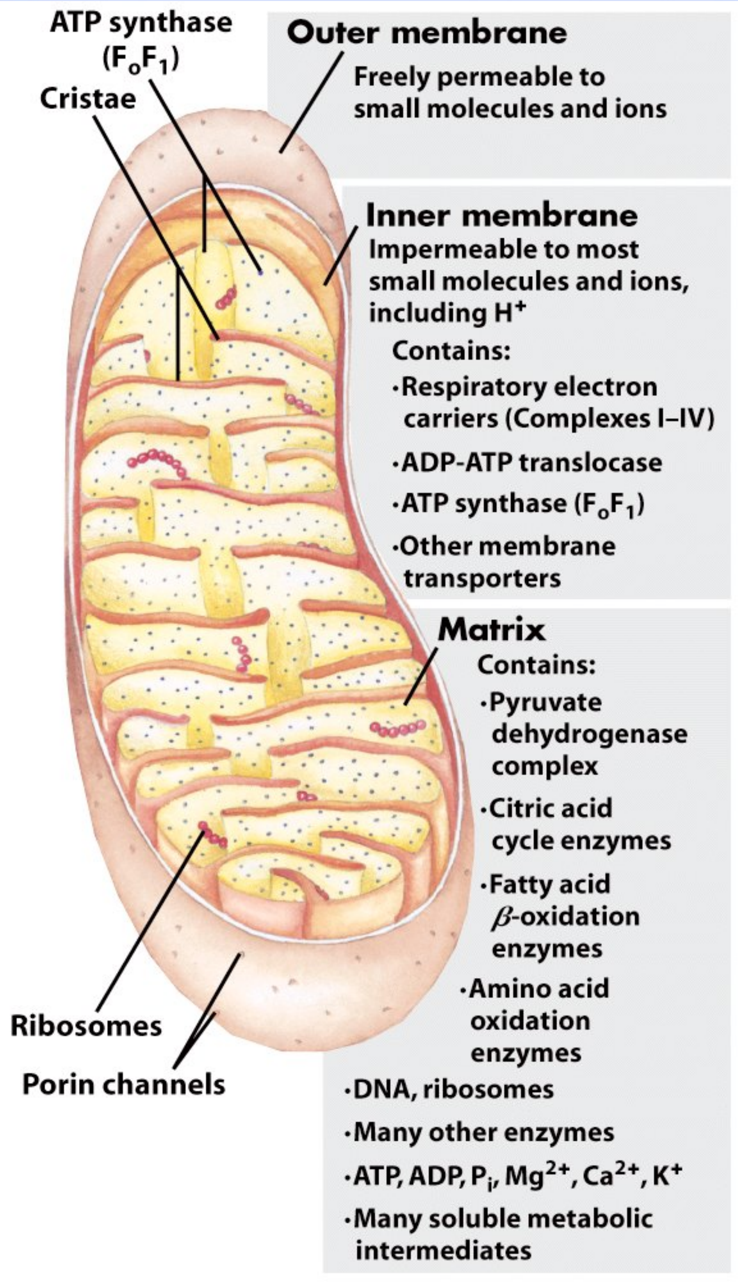
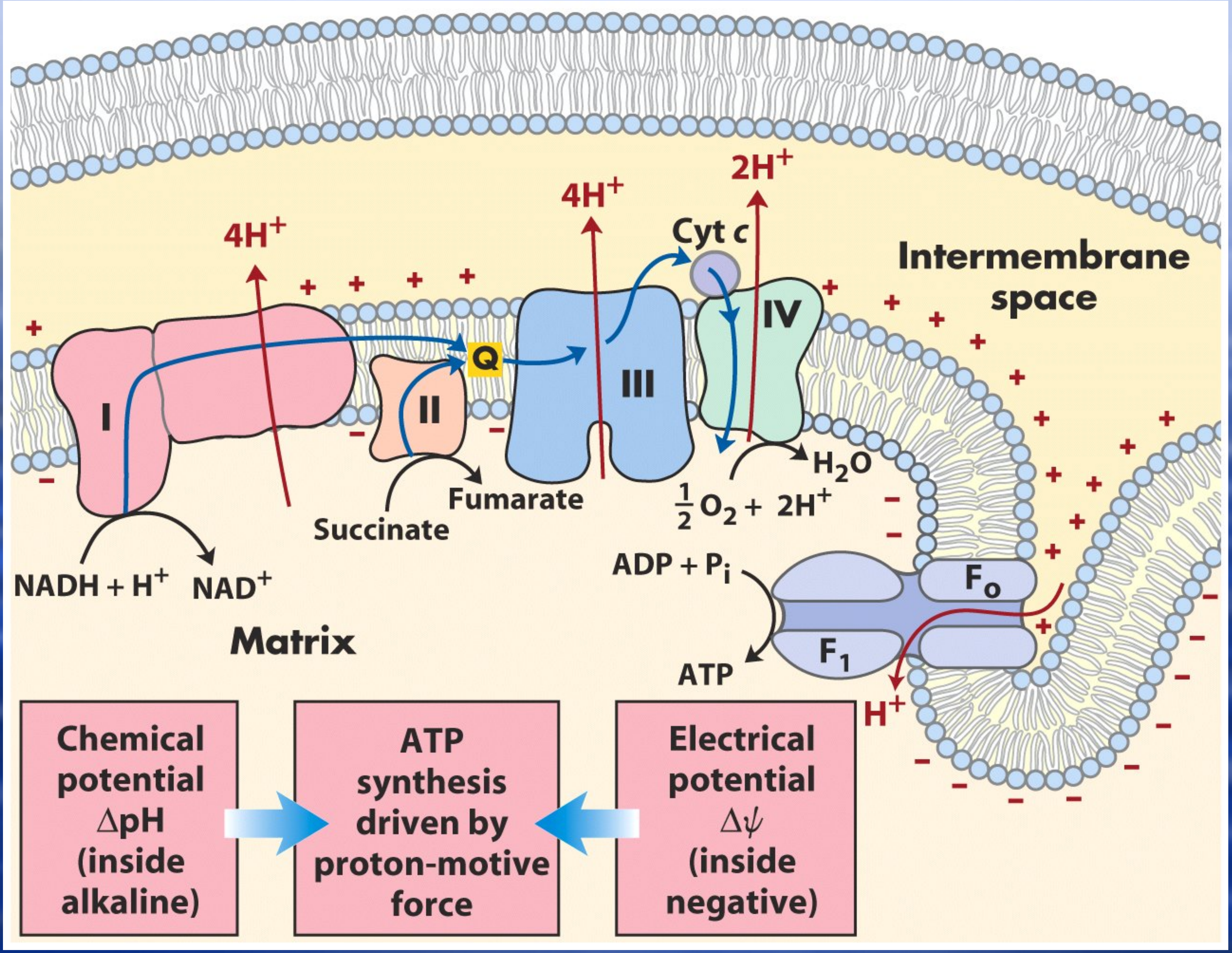


Figure 6.7
Structure of a mitochondrion showing schematic representation of the electron transport chain and ATP synthesizing structures on the inner membrane. mtDNA = mitochondrial DNA; mtRNA = mitochondrial RNA.



ATP synthase (F_oF_1)
Cristae
Outer membrane
Freely permeable to small molecules and ions
Inner membrane
Impermeable to most small molecules and ions, including H^+
Contains:
•Respiratory electron carriers (Complexes I–IV)
•ADP-ATP translocase
•ATP synthase (F_oF_1)
•Other membrane transporters
Matrix
Contains:
•Pyruvate dehydrogenase complex
•Citric acid cycle enzymes
•Fatty acid β-oxidation enzymes
•Amino acid oxidation enzymes
•DNA, ribosomes
•Many other enzymes
•ATP, ADP, P_i, Mg^{2+}, Ca^{2+}, K^+
•Many soluble metabolic intermediates
Ribosomes
Porin channels


4H+
4H+
2H+
Cyt c
Intermembrane space
Q
I
II
III
IV
Succinate
Fumarate
H2O
1/2 O2 + 2H+
NADH + H+
NAD+
ADP + Pi
ATP
Fo
F1
H+
Matrix
Chemical potential ΔpH (inside alkaline)
ATP synthesis driven by proton-motive force
Electrical potential Δψ (inside negative)

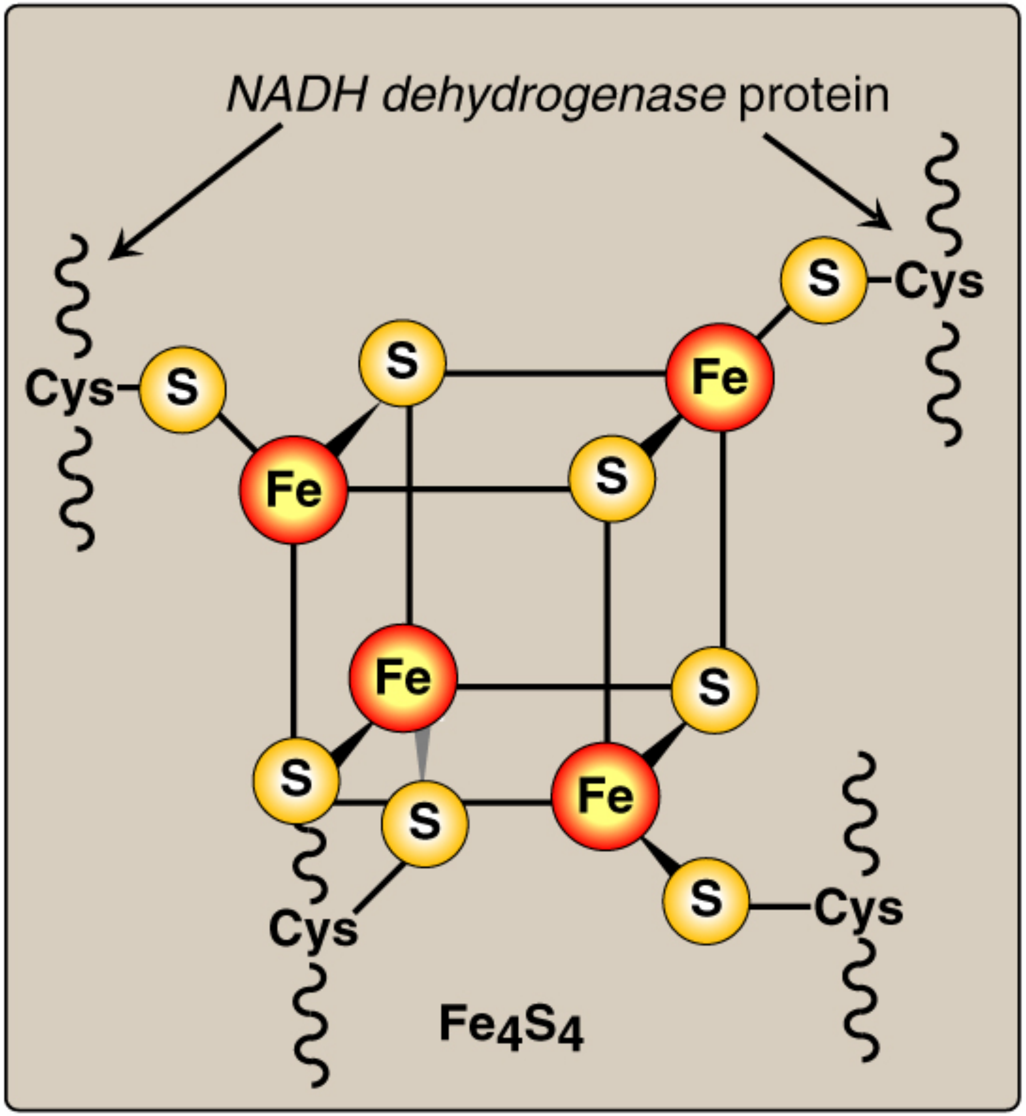
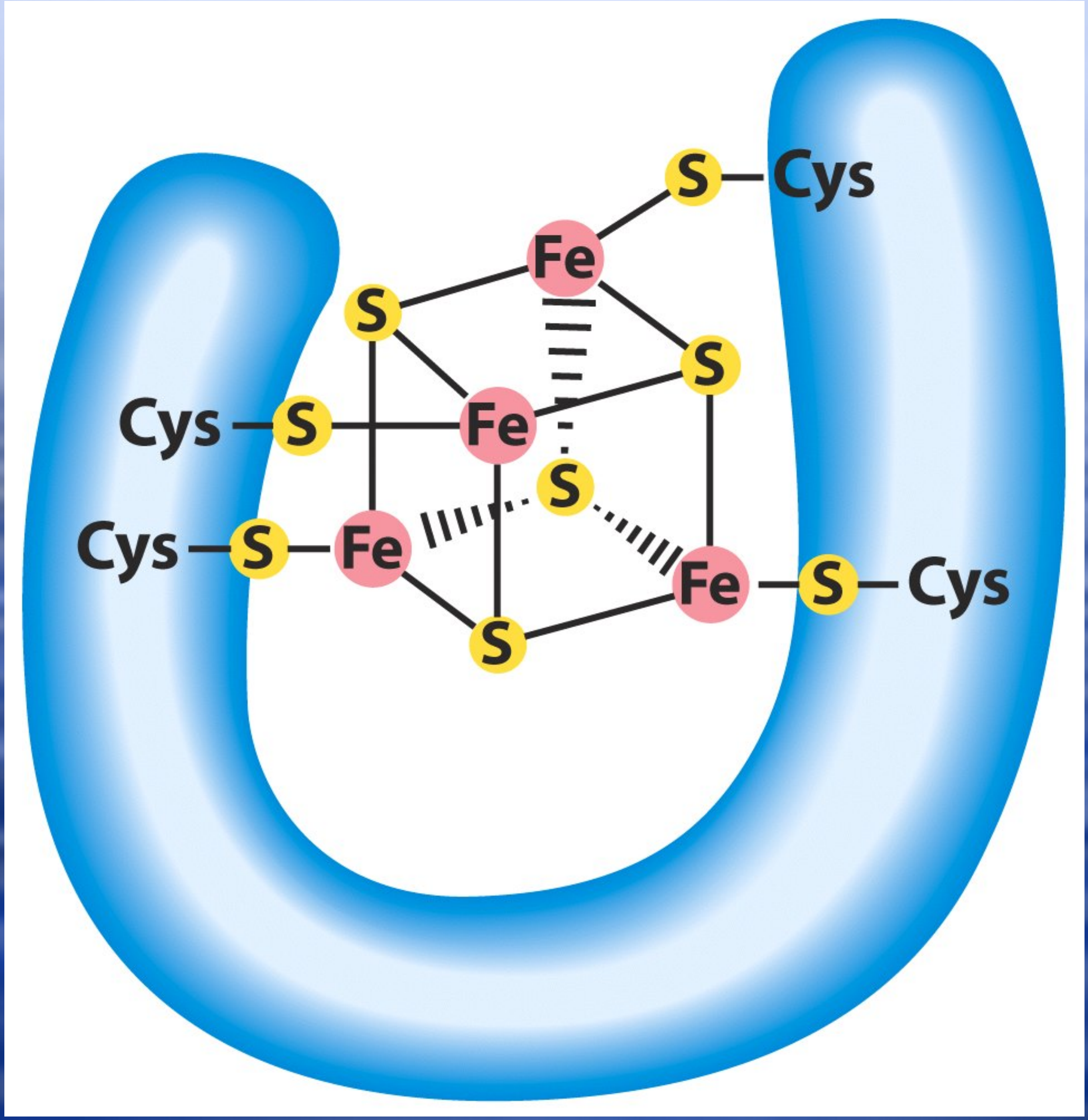
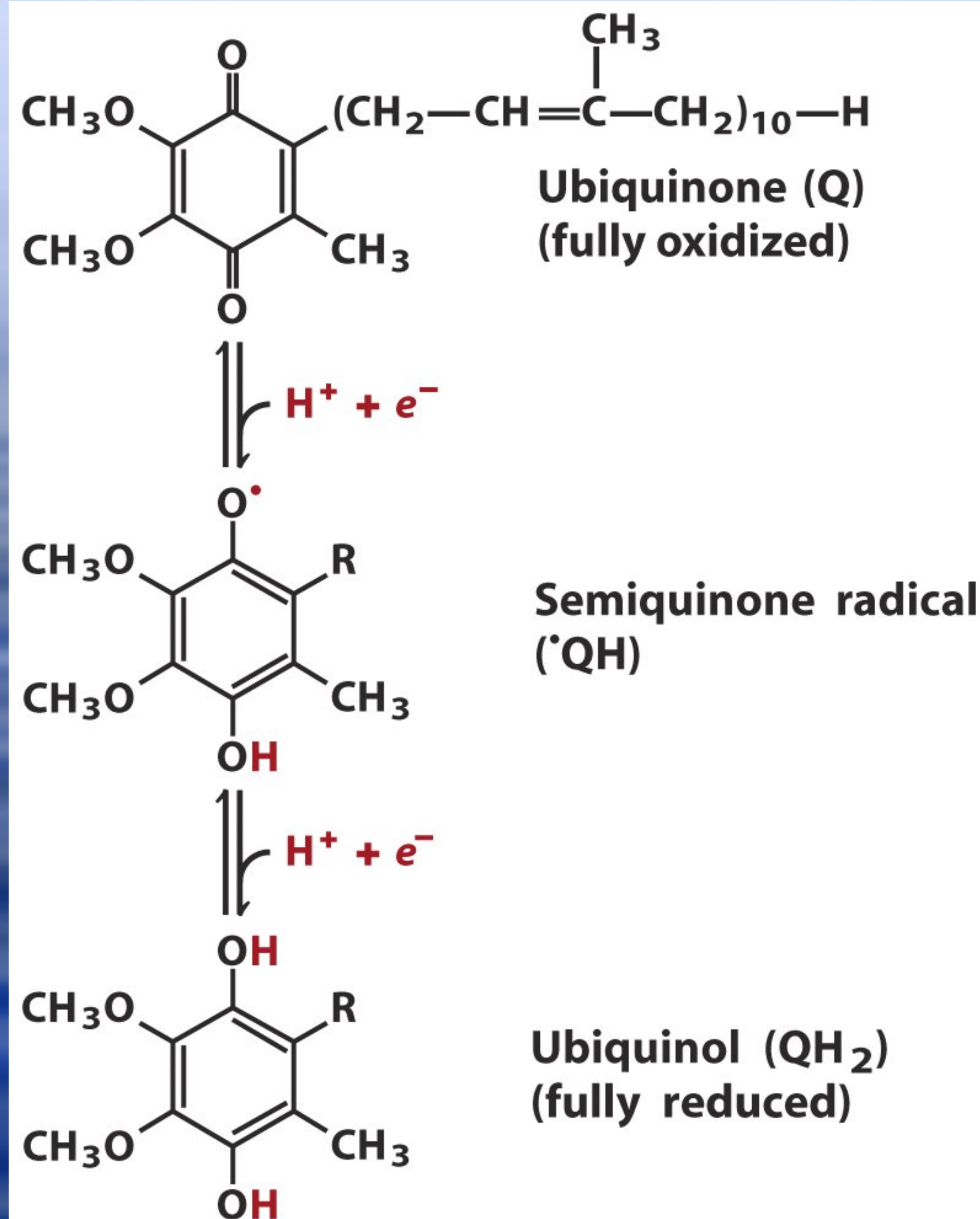
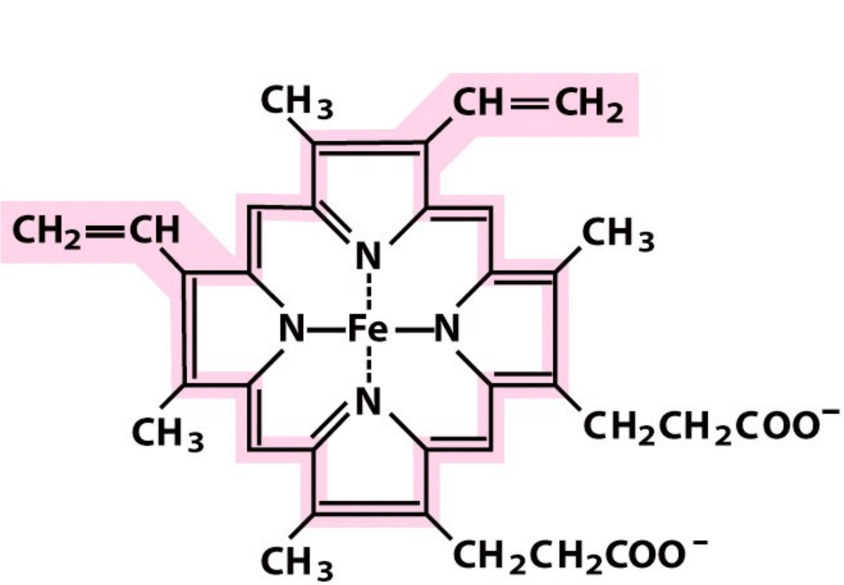


Figure 6.9
Iron-sulfur center of *NADH dehydrogenase*.

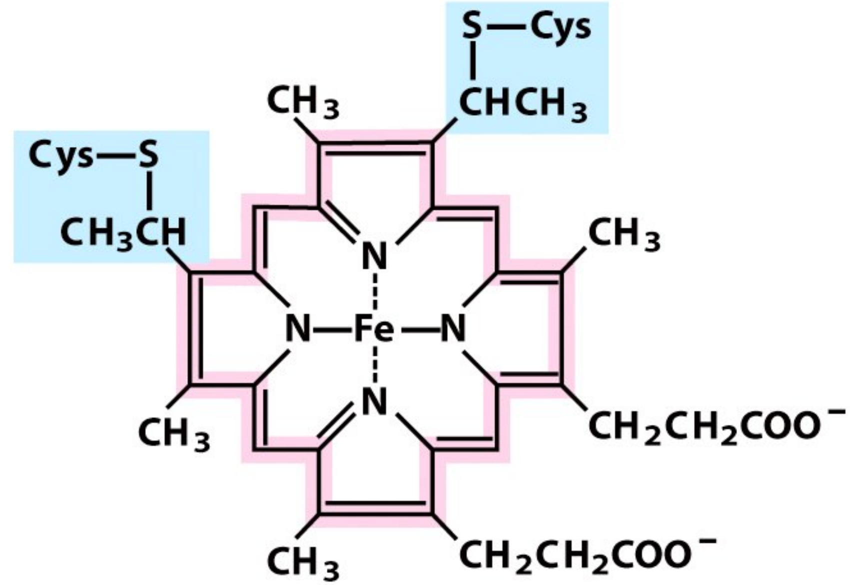

S
Cys
Fe
S
S
Cys
S
Fe
S
Cys
S
Fe
Fe
S
Cys
S



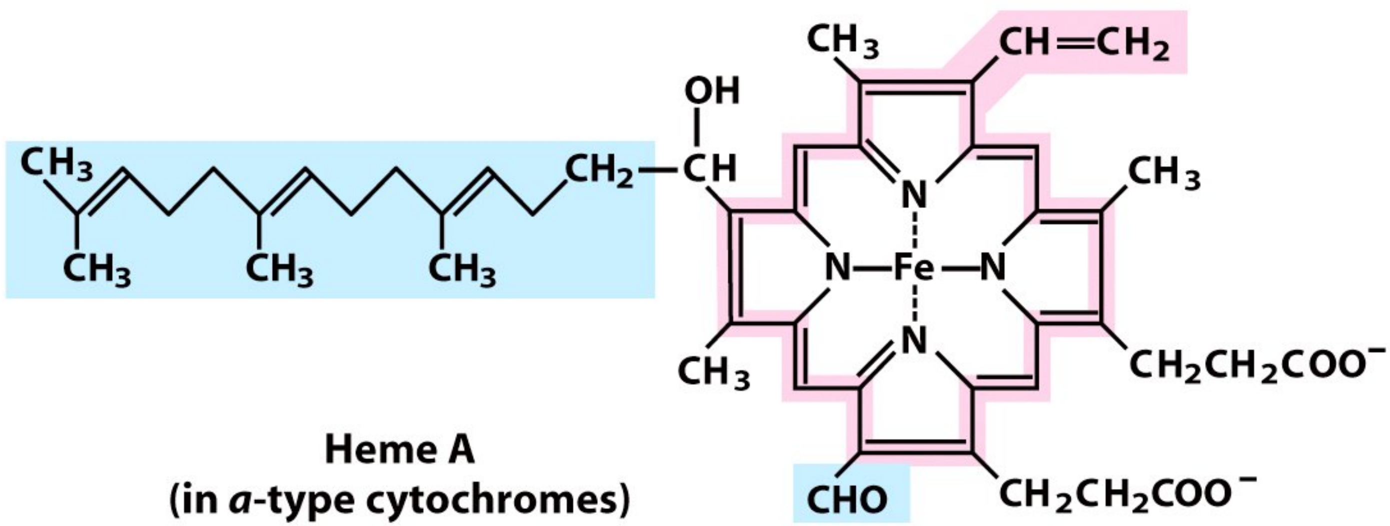
CH3
O
CH3O
(CH2—CH=C—CH2)10—H
Ubiquinone (Q)
(fully oxidized)
CH3O
CH3
O
H+ + e−
O•
CH3O
R
Semiquinone radical
(•QH)
CH3O
CH3
OH
H+ + e−
OH
CH3O
R
Ubiquinol (QH2)
(fully reduced)
CH3O
CH3
OH



Iron protoporphyrin IX
(in *b*-type cytochromes)



Heme C
(in *c*-type cytochromes)



Heme A
(in *a*-type cytochromes)

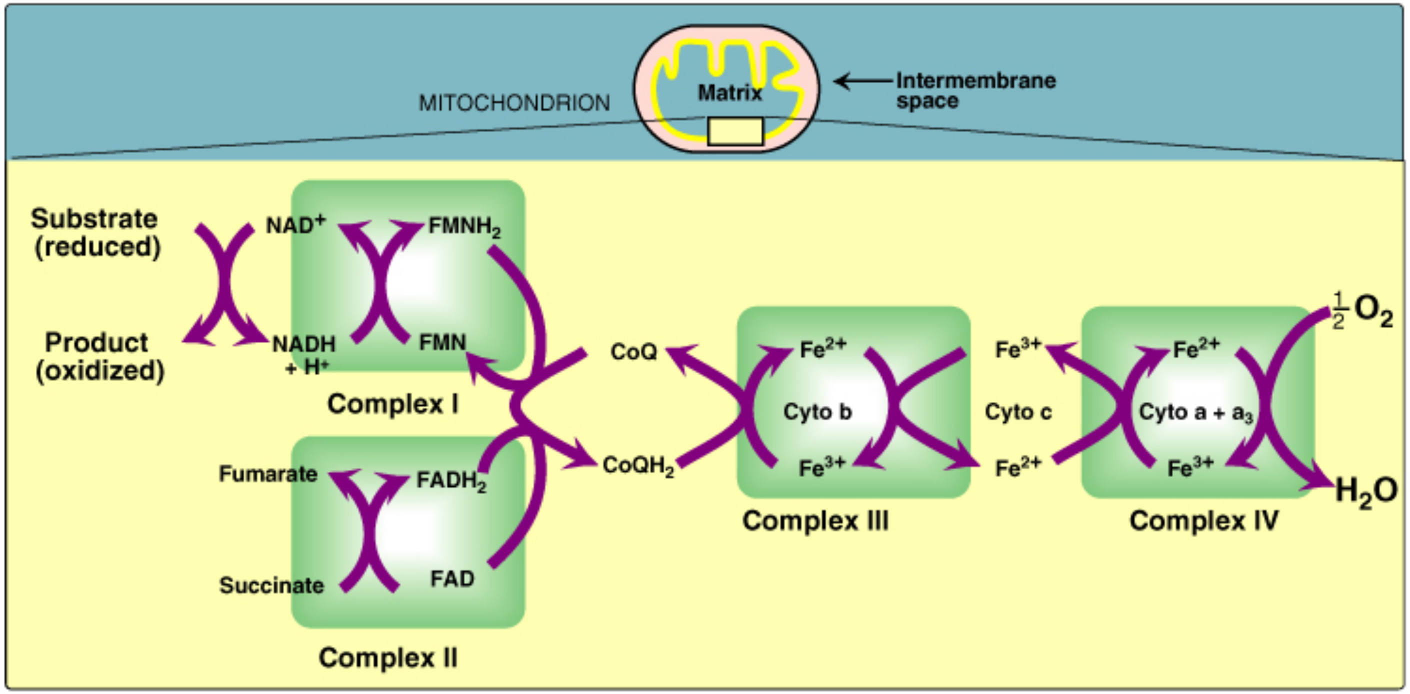
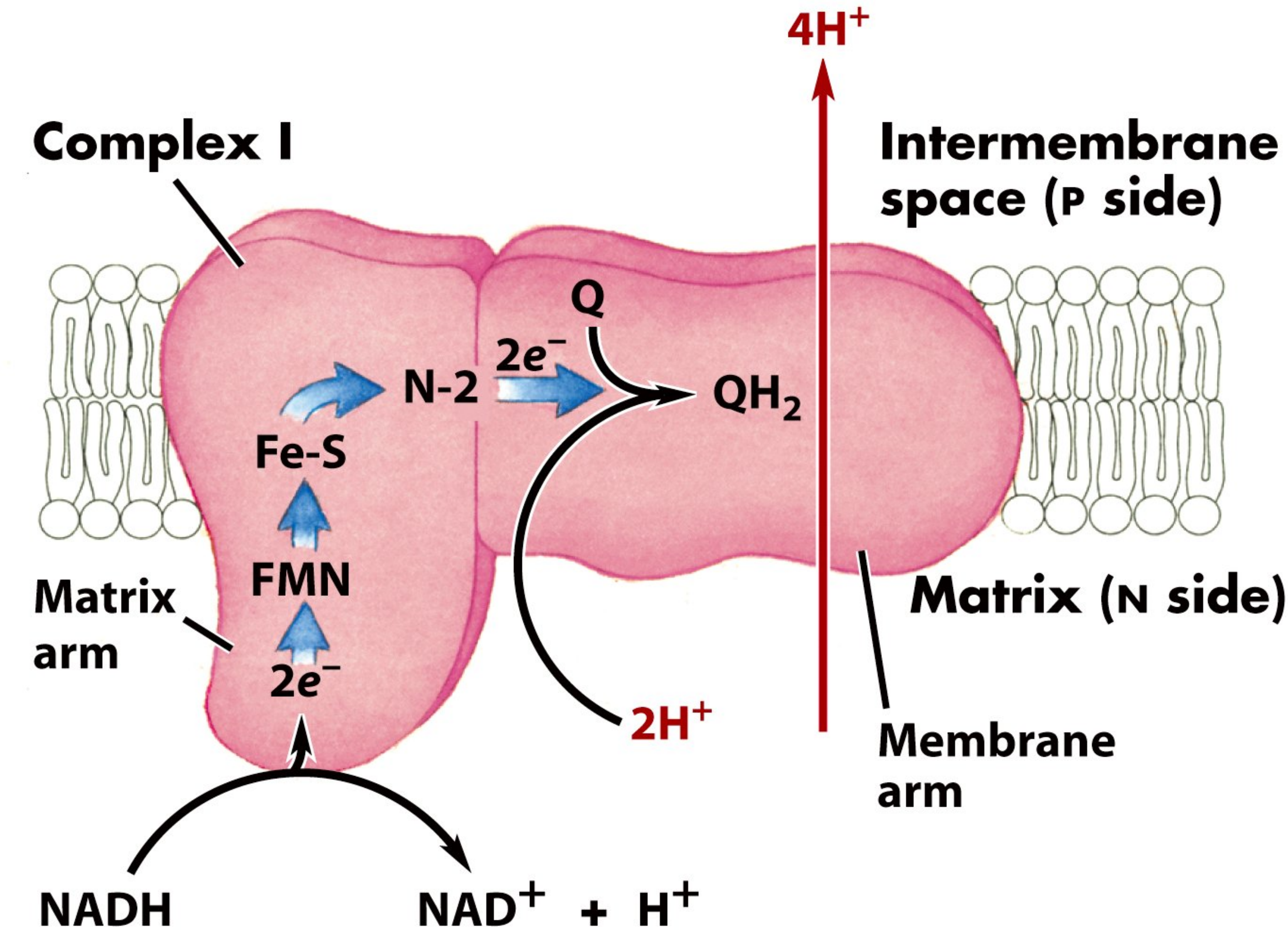
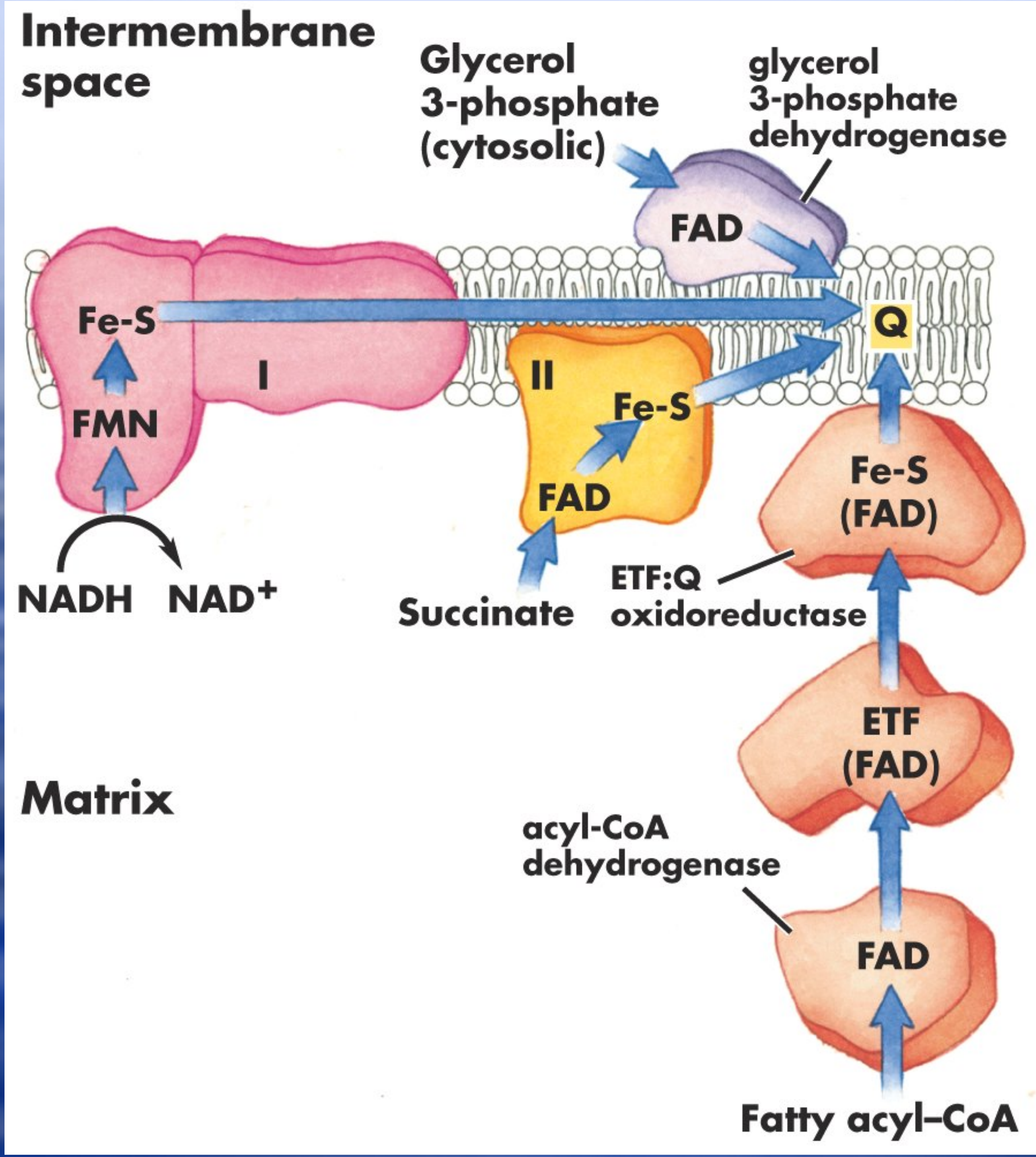
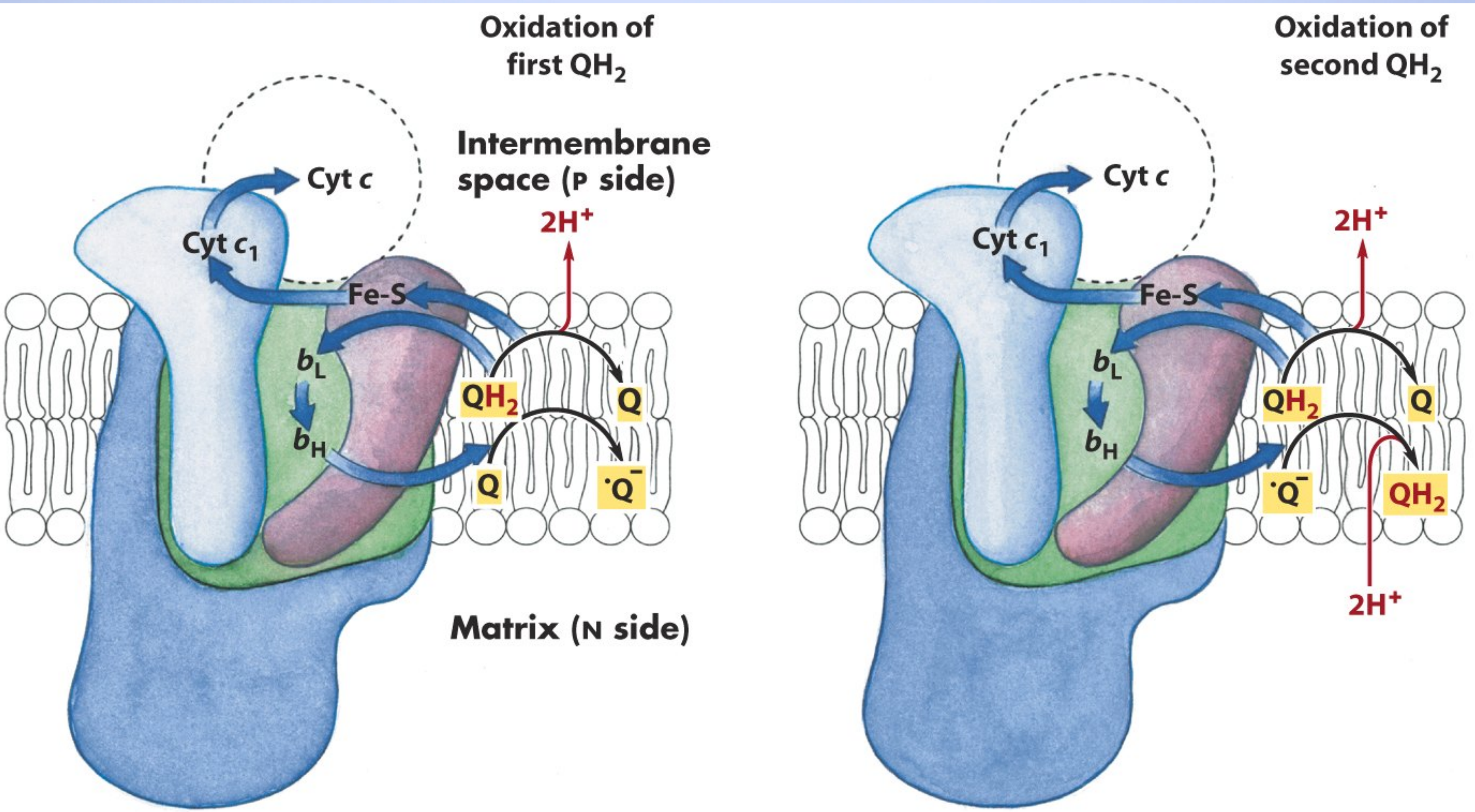


Figure 6.8

Electron transport chain. [Note: Complex V is not shown.]


4H+
Complex I
Intermembrane space (P side)
Q
2e−
N-2
QH2
Fe-S
FMN
Matrix arm
2e−
Matrix (N side)
2H+
Membrane arm
NADH
NAD+ + H+


Intermembrane space
Glycerol 3-phosphate (cytosolic)
glycerol 3-phosphate dehydrogenase
FAD
Fe-S
Q
I
II
Fe-S
FMN
FAD
Fe-S (FAD)
NADH
NAD+
Succinate
ETF:Q oxidoreductase
ETF (FAD)
Matrix
acyl-CoA dehydrogenase
FAD
Fatty acyl–CoA

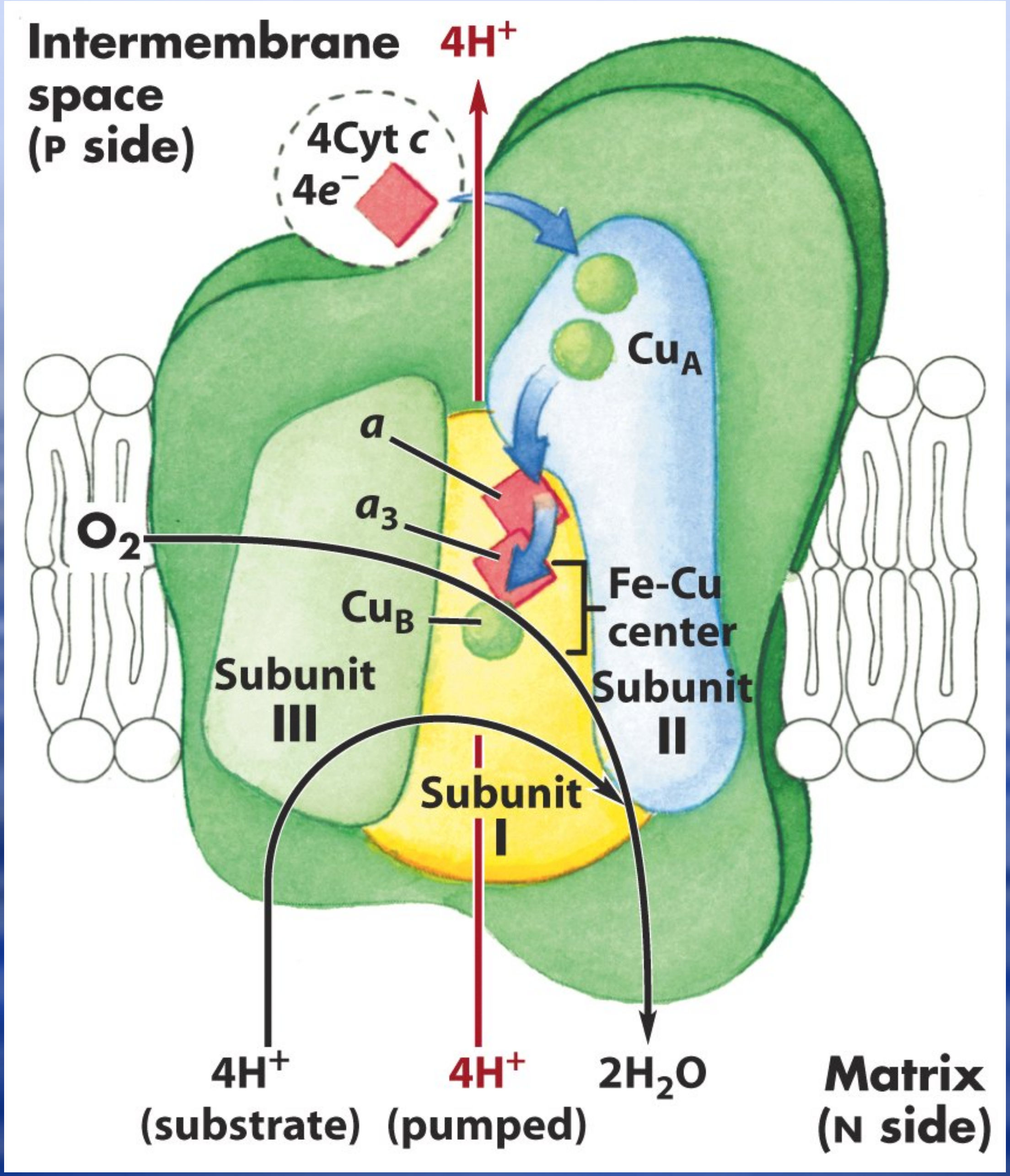


QH_2 + cyt c_1 (oxidized) $\longrightarrow$ $\cdot Q^-$ + $2H^+_P$ + cyt c_1 (reduced)

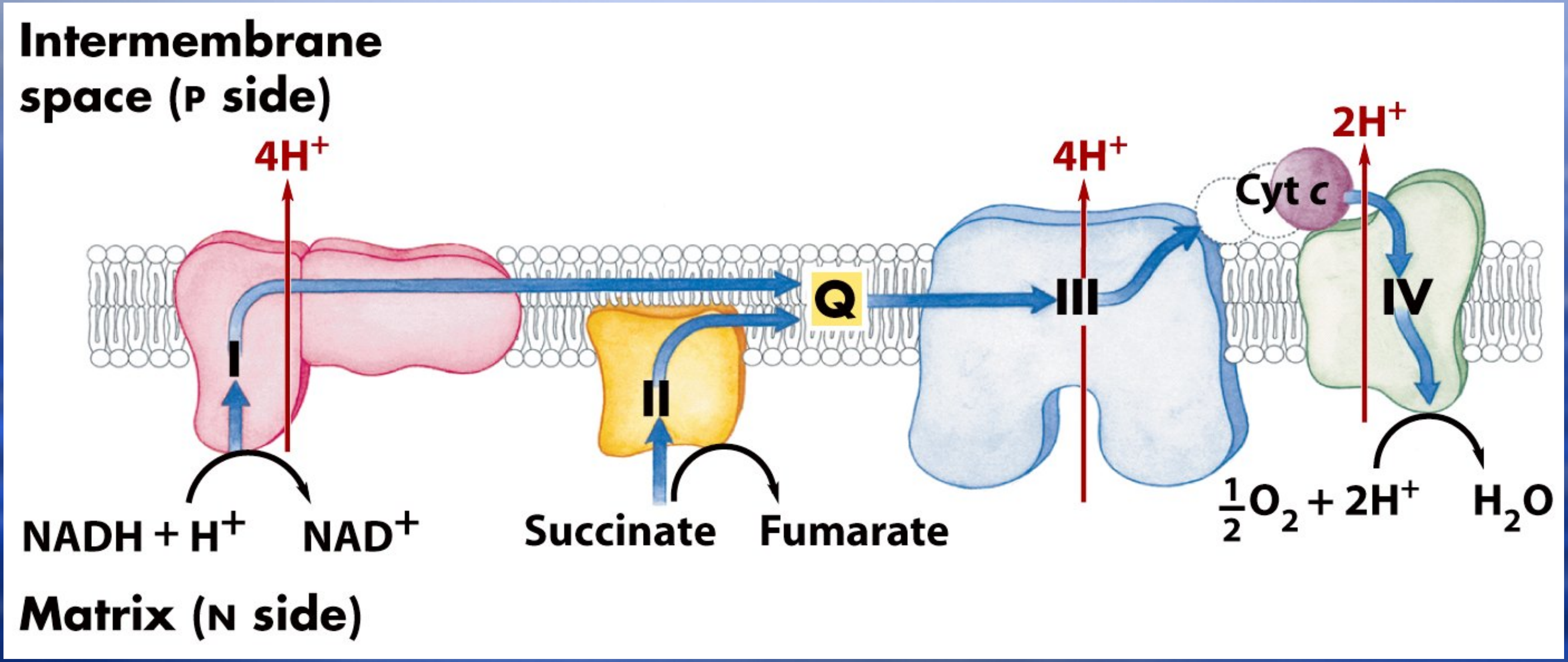
QH_2 + $\cdot Q^-$ + $2H^+_N$ + cyt c_1 (oxidized) $\longrightarrow$ QH_2 + $2H^+_P$ + Q + cyt c_1 (reduced)

Net equation:

$$QH_2 + 2\ \text{cyt}\ c_1\ (\text{oxidized}) + 2H^+_N \longrightarrow Q + 2\ \text{cyt}\ c_1\ (\text{reduced}) + 4H^+_P$$



Intermembrane space (P side)
4H+
4Cyt c
4e−
CuA
a
a3
O2
Fe-Cu center
CuB
Subunit III
Subunit II
Subunit I
4H+ (substrate)
4H+ (pumped)
2H2O
Matrix (N side)


Intermembrane space (P side)
4H+
4H+
2H+
Cyt c
Q
I
II
III
IV
NADH + H+
NAD+
Succinate
Fumarate
½O2 + 2H+
H2O
Matrix (N side)

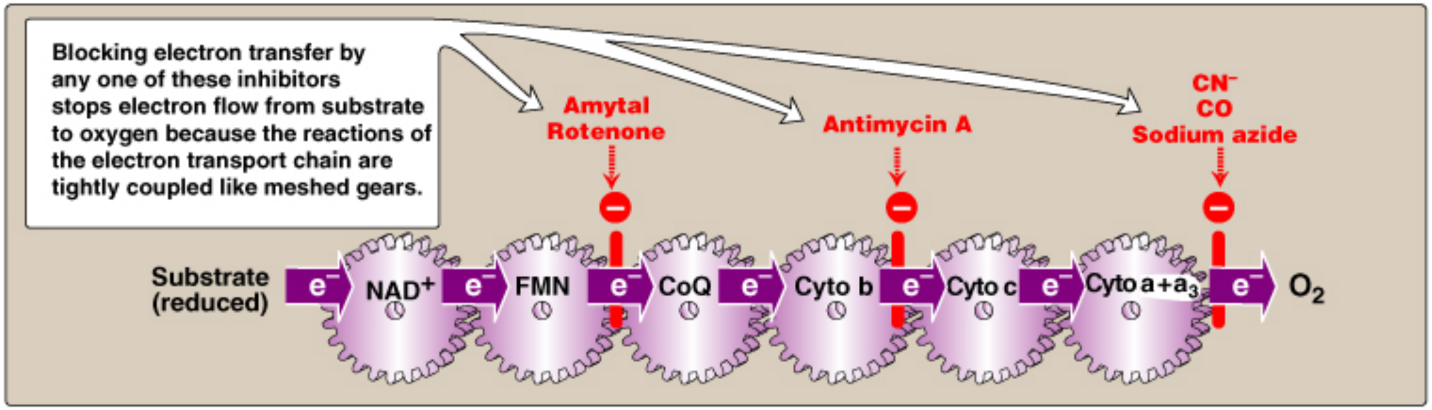


Figure 6.10

Site-specific inhibitors of electron transport shown using a mechanical model for the coupling of oxidation-reduction reactions. [Note: Figure illustrates normal direction of electron flow.]

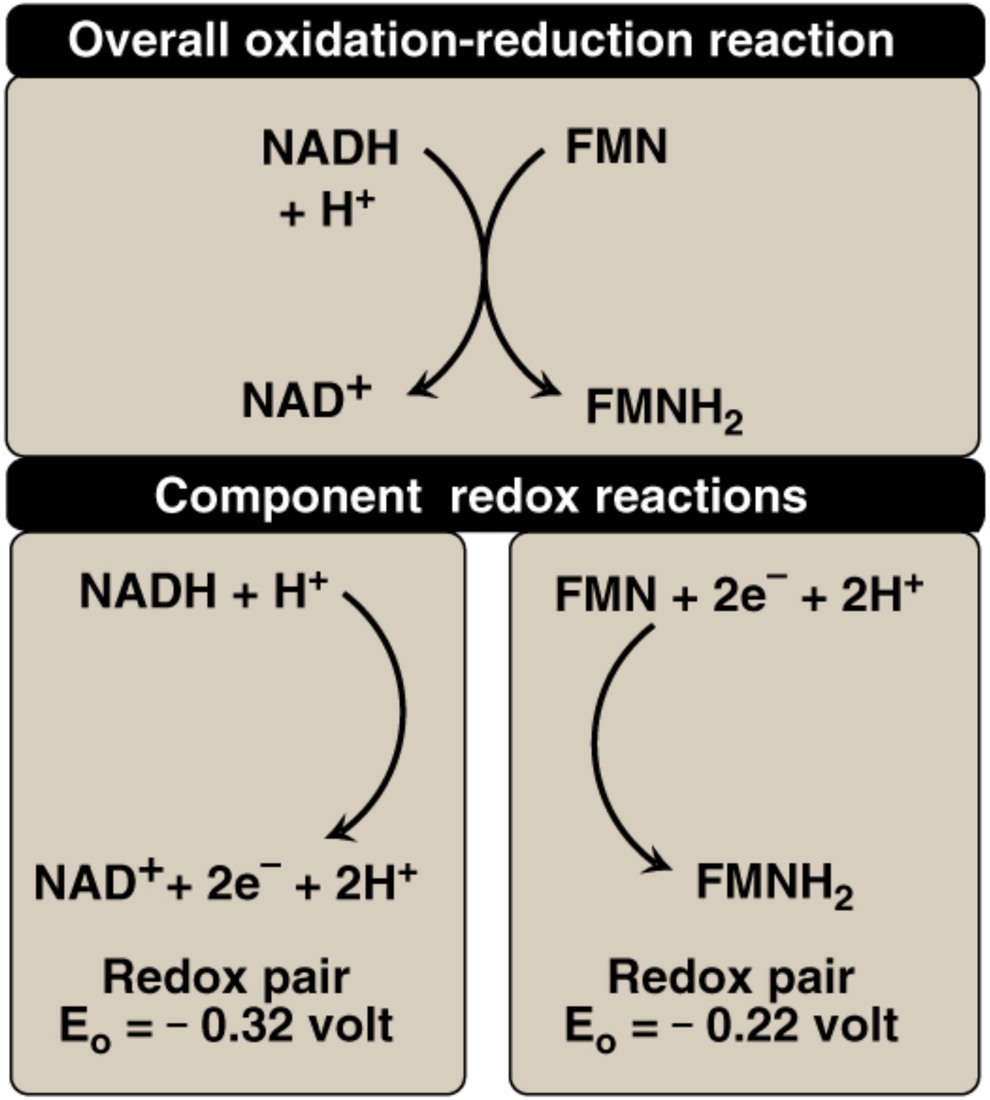


Figure 6.11
Oxidation of NADH by FMN, separated into two component redox pairs.

Compounds with a large negative E_o (located at top of the table) are strong reducing agents – that is, they have a strong tendency to lose electrons.

Redox pair	E_o
$NAD^+/NADH$	-0.32
$FMN/FMNH_2$	-0.22
Pyruvate/lactate	-0.19
Cytochrome c Fe^{3+}/Fe^{2+}	+0.07
$1/2\ O_2/H_2O$	+0.82

Compounds at the bottom of the table are strong oxidizing agents, that is, they want to accept electrons.

Figure 6.12
Standard reduction potentials of some reactions.

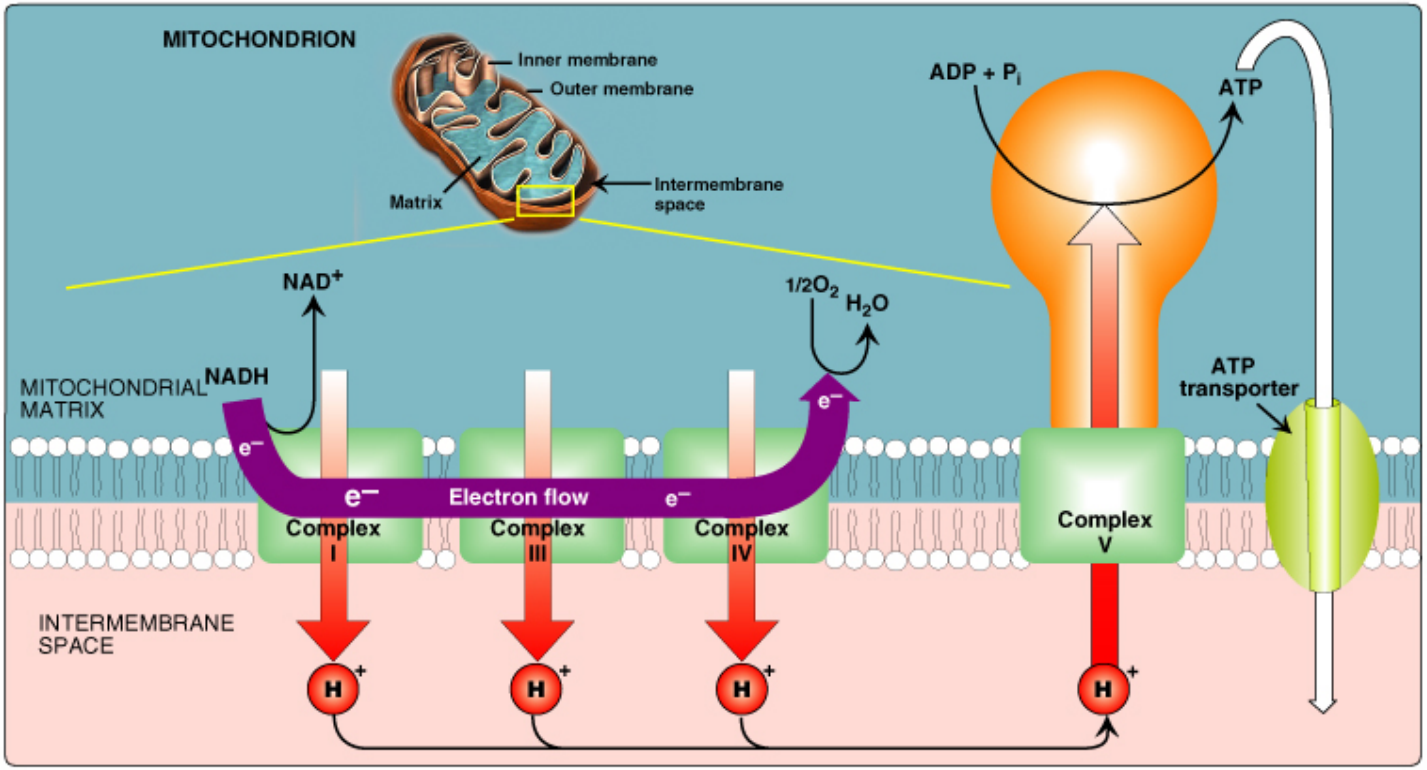
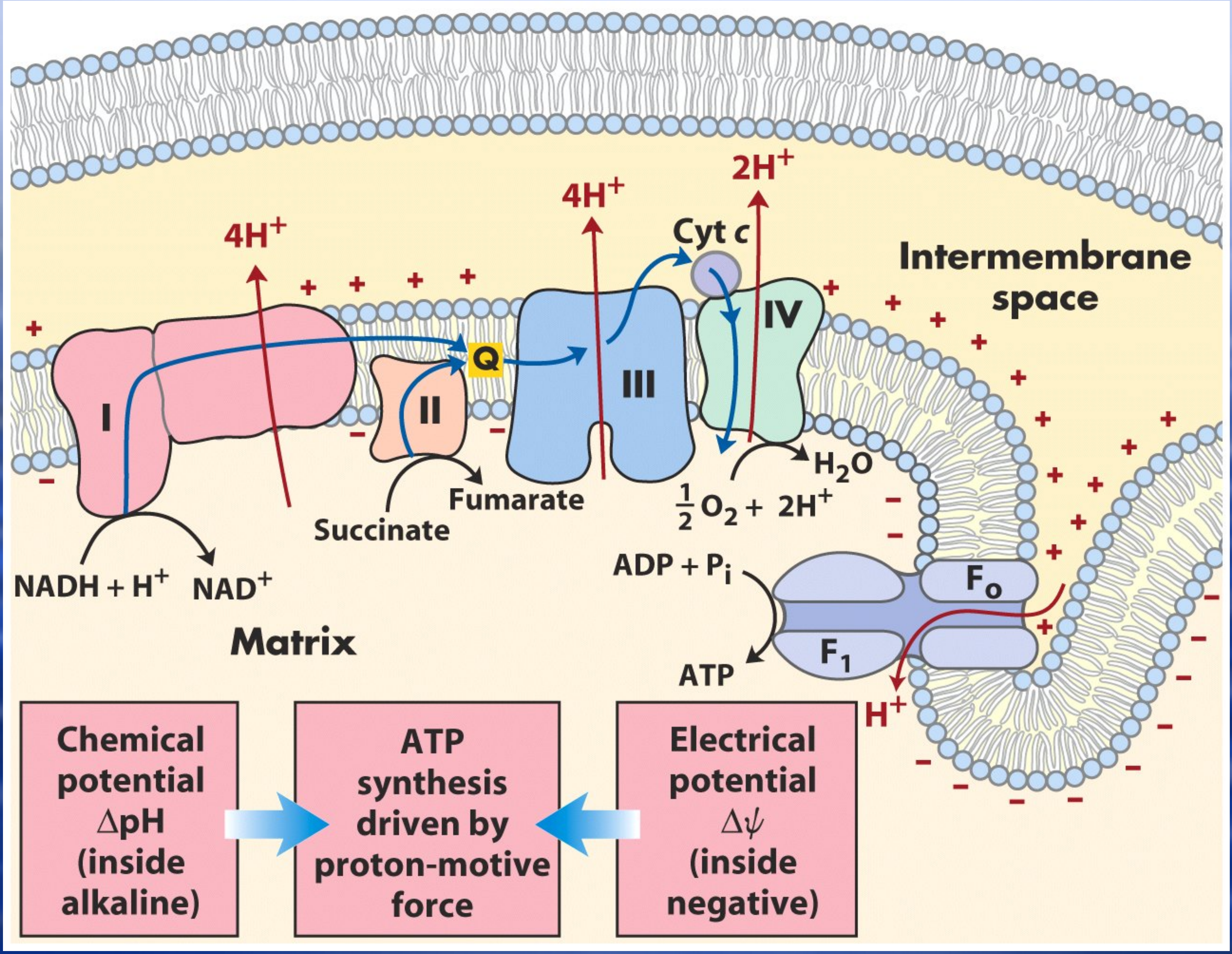
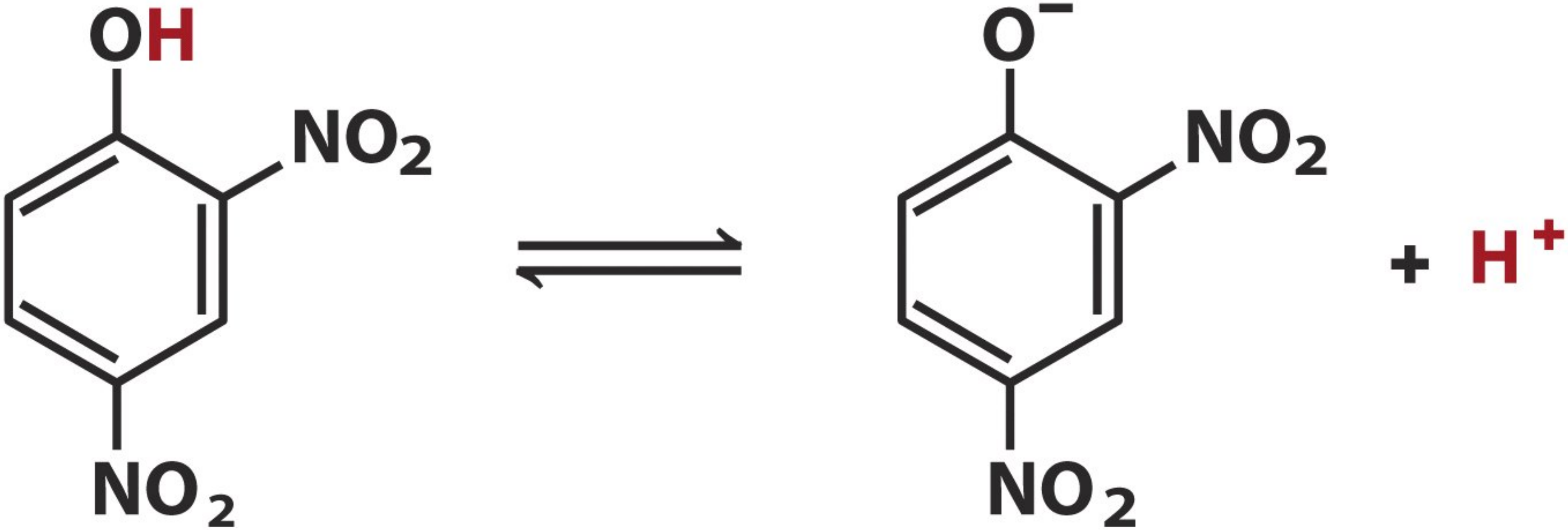


Figure 6.13
Electron transport chain shown coupled to the transport of protons. [Note: Complex II is not shown.]


4H+
4H+
2H+
Cyt c
Intermembrane space
Q
I
II
III
IV
Succinate
Fumarate
NADH + H+
NAD+
H2O
1/2 O2 + 2H+
ADP + Pi
ATP
Fo
F1
H+
Matrix
Chemical potential ΔpH (inside alkaline)
ATP synthesis driven by proton-motive force
Electrical potential Δψ (inside negative)



2,4-Dinitrophenol
(DNP)

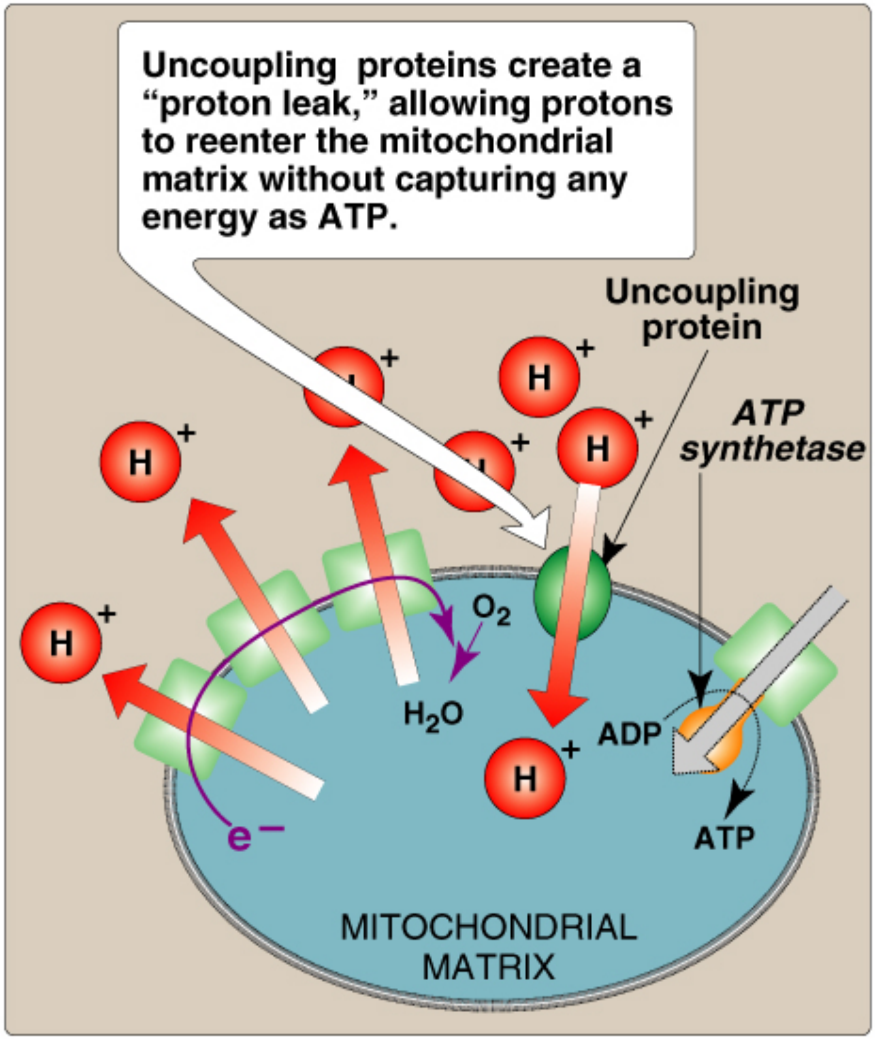
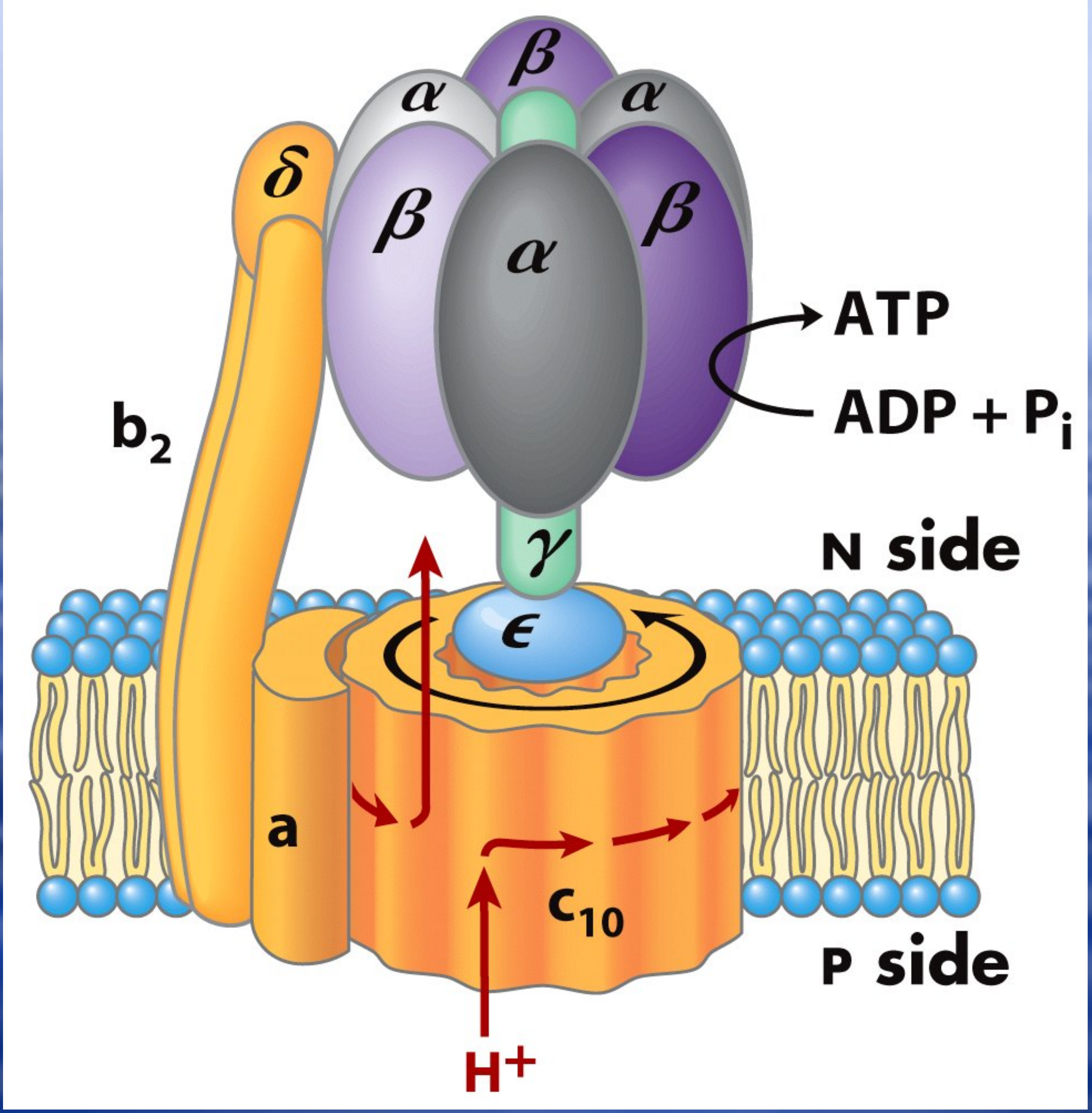
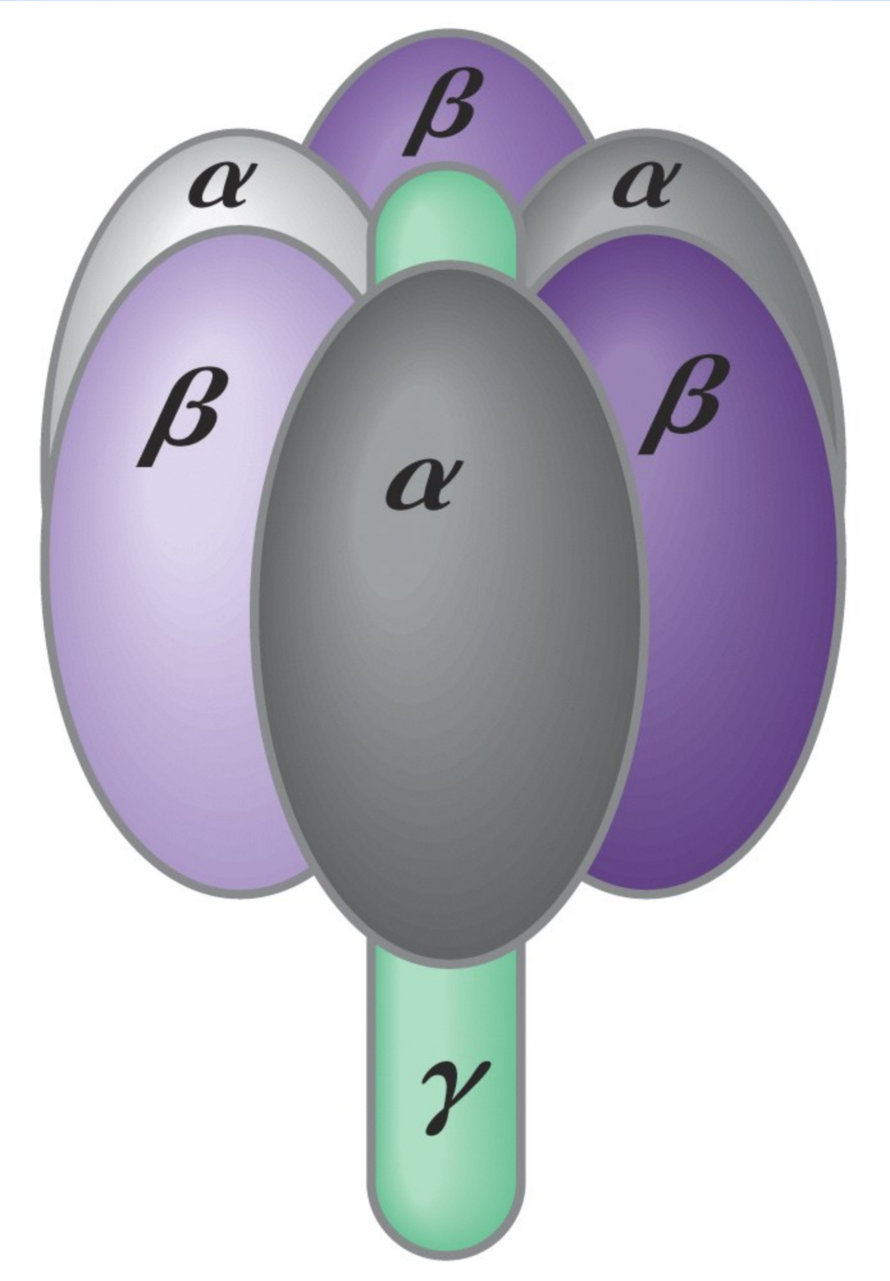
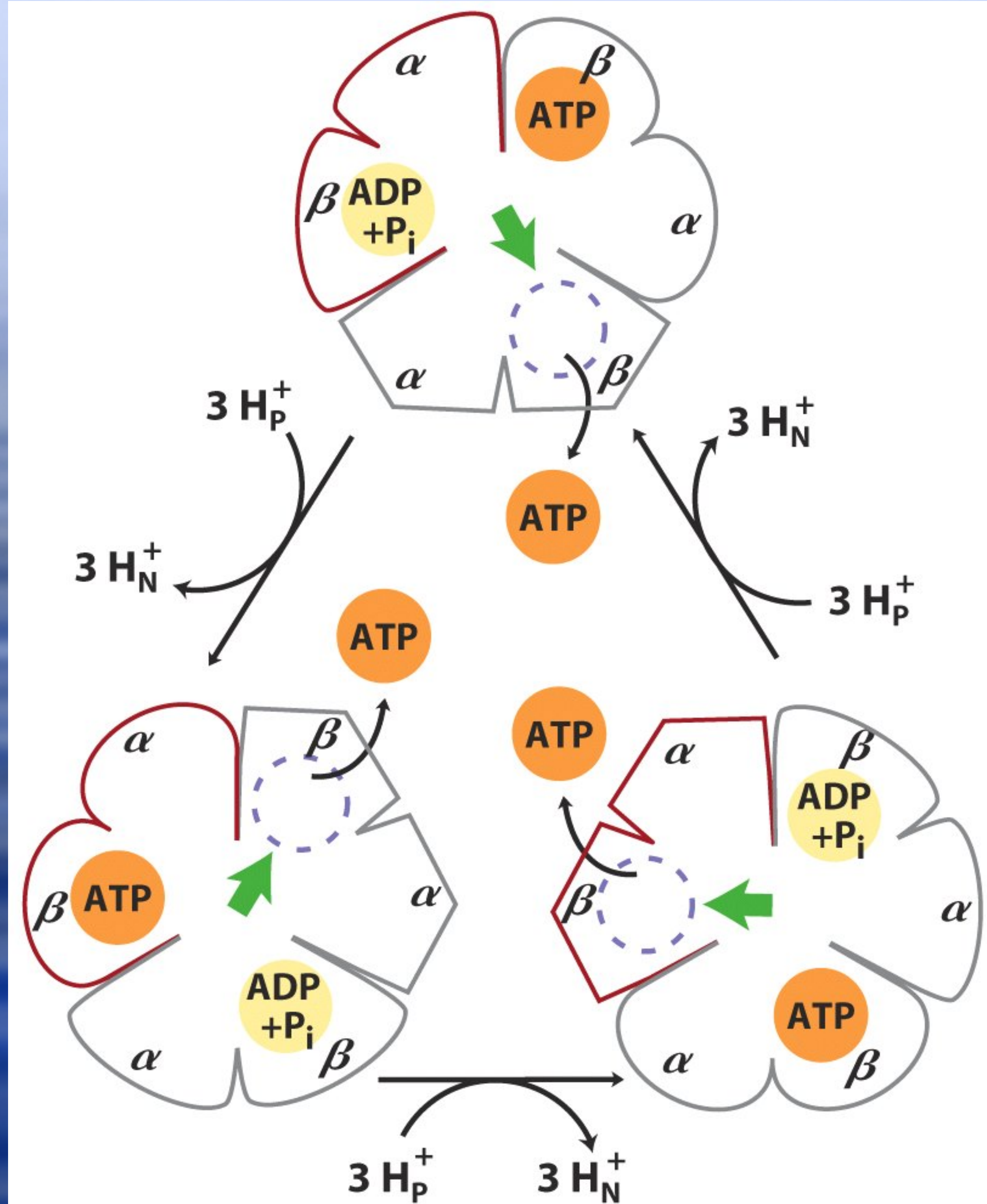


Figure 6.14

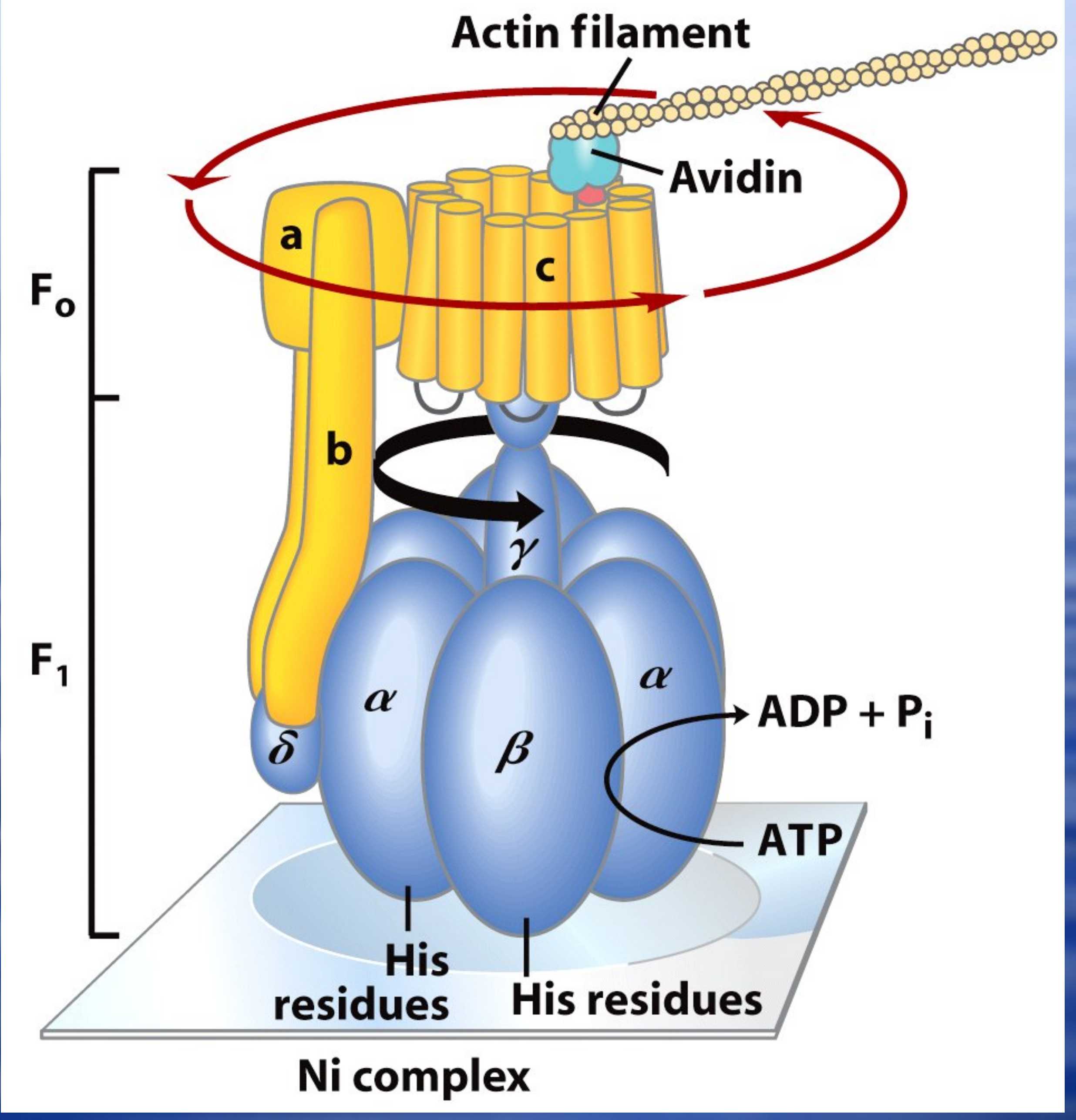
Transport of H^+ across mitochondrial membrane by 2,4-dinitrophenol.


β
α
α
δ
β
α
β
ATP
ADP + Pi
b2
γ
N side
ε
a
c10
P side
H+


β
α
α
β
β
α
γ



α
β
ATP
β
ADP
+Pi
α
α
β
3 H+P
3 H+N
ATP
3 H+N
3 H+P
ATP
ATP
α
β
β
ATP
α
ADP
+Pi
α
β
α
β
ADP
+Pi
β
α
ATP
α
β
3 H+P
3 H+N



Actin filament
Avidin
F_o
a
c
b
γ
F_1
α
α
β
δ
ADP + P_i
ATP
His residues
His residues
Ni complex

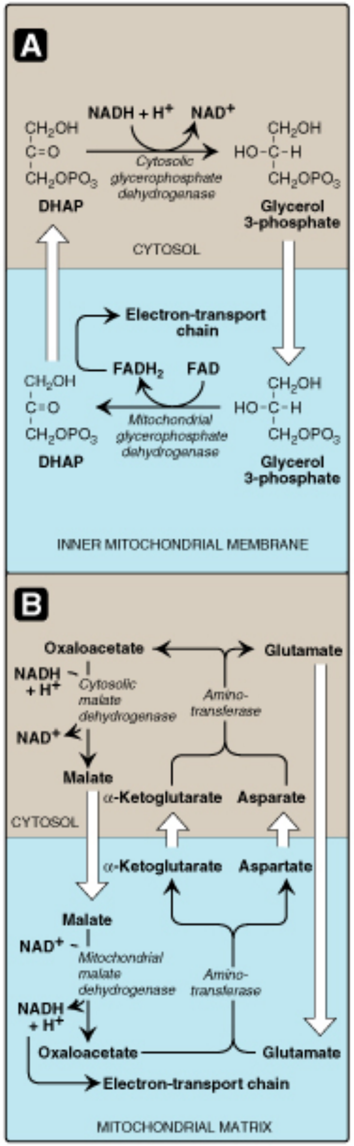
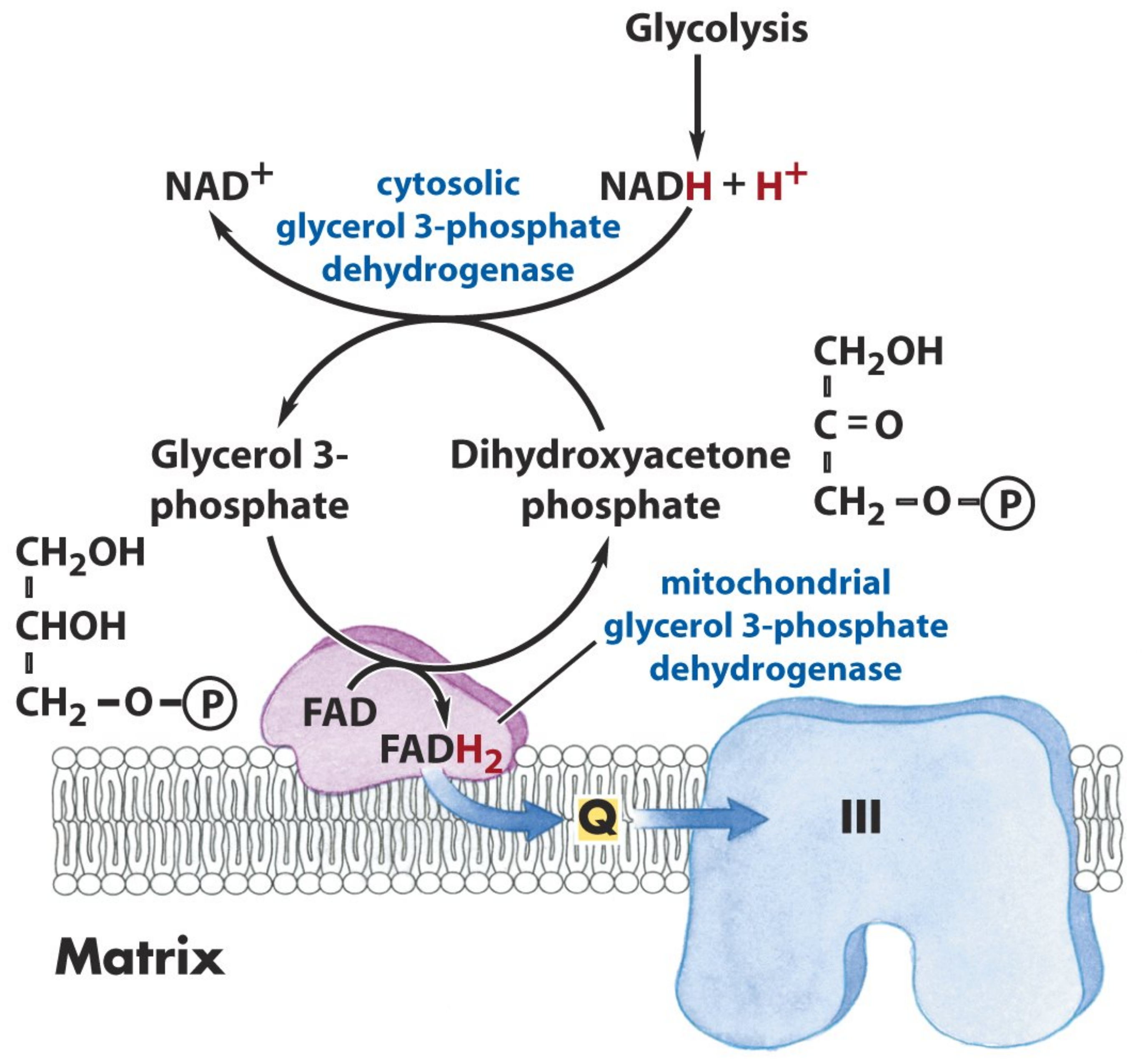
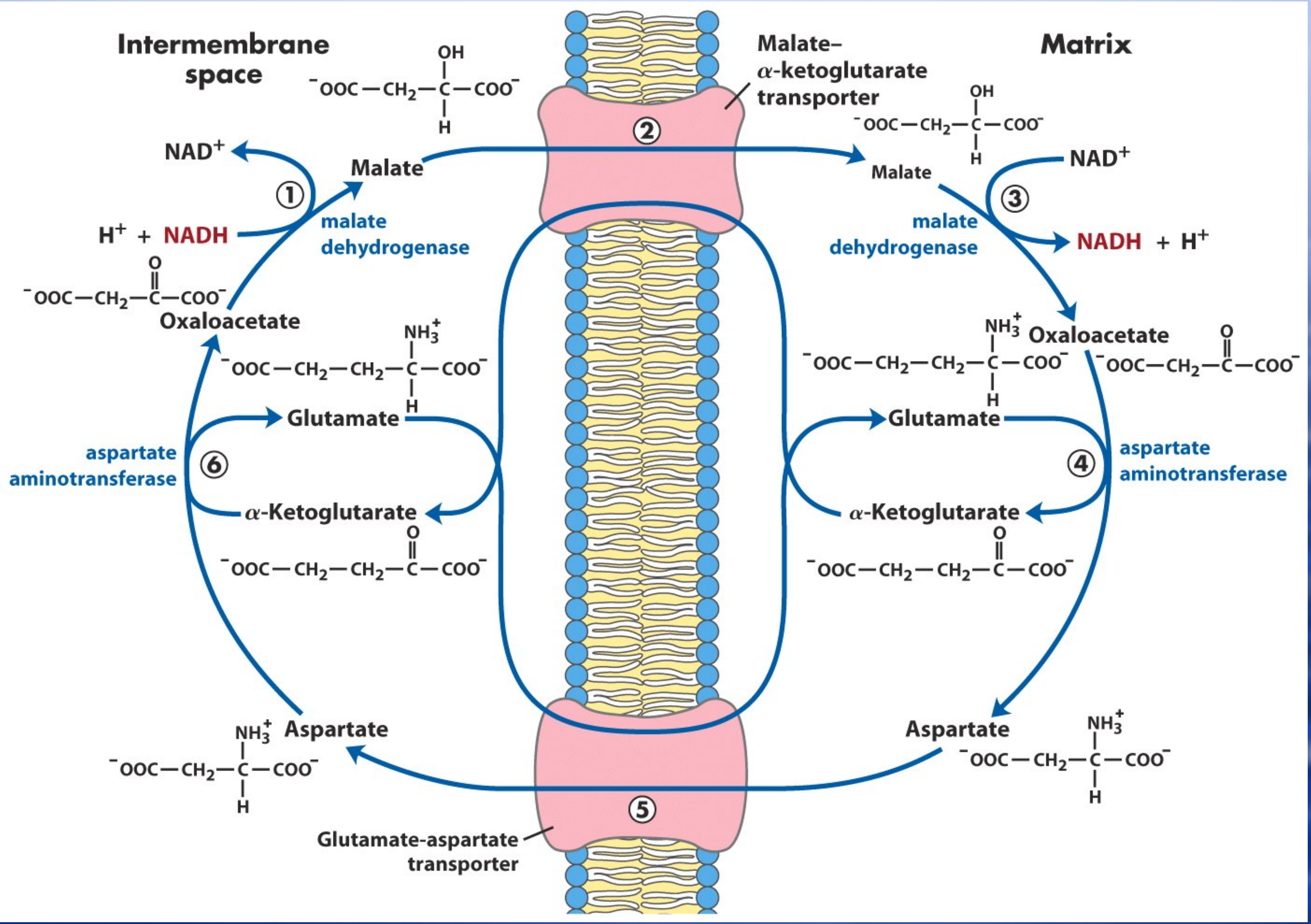


Figure 6.15

Shuttle pathways for the transport of electrons across the inner mitochondrial membrane.
A. Glycerophosphate shuttle.
B. Malateaspartate shuttle.


Glycolysis
NAD+
cytosolic
glycerol 3-phosphate
dehydrogenase
NADH + H+
Glycerol 3-
phosphate
Dihydroxyacetone
phosphate
CH2OH
C=O
CH2 –O–P
CH2OH
CHOH
CH2 –O–P
mitochondrial
glycerol 3-phosphate
dehydrogenase
FAD
FADH2
Q
III
Matrix



Intermembrane space
Matrix
Malate–
α-ketoglutarate
transporter
NAD+
H+ + NADH
Malate
① malate dehydrogenase
Oxaloacetate
Glutamate
α-Ketoglutarate
⑥ aspartate aminotransferase
Aspartate
②
Malate
③ malate dehydrogenase
NADH + H+
Oxaloacetate
Glutamate
α-Ketoglutarate
④ aspartate aminotransferase
Aspartate
⑤
Glutamate-aspartate
transporter

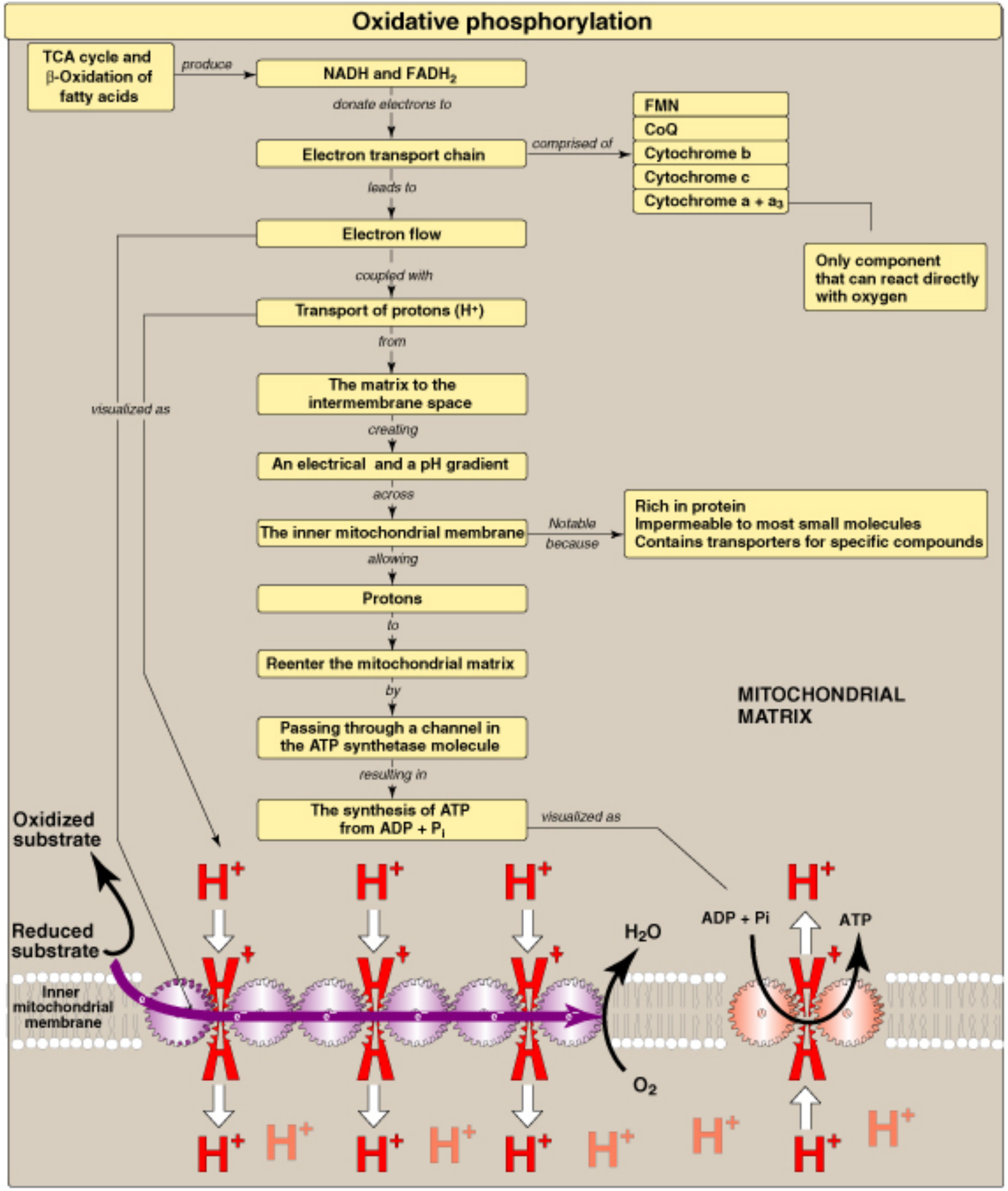
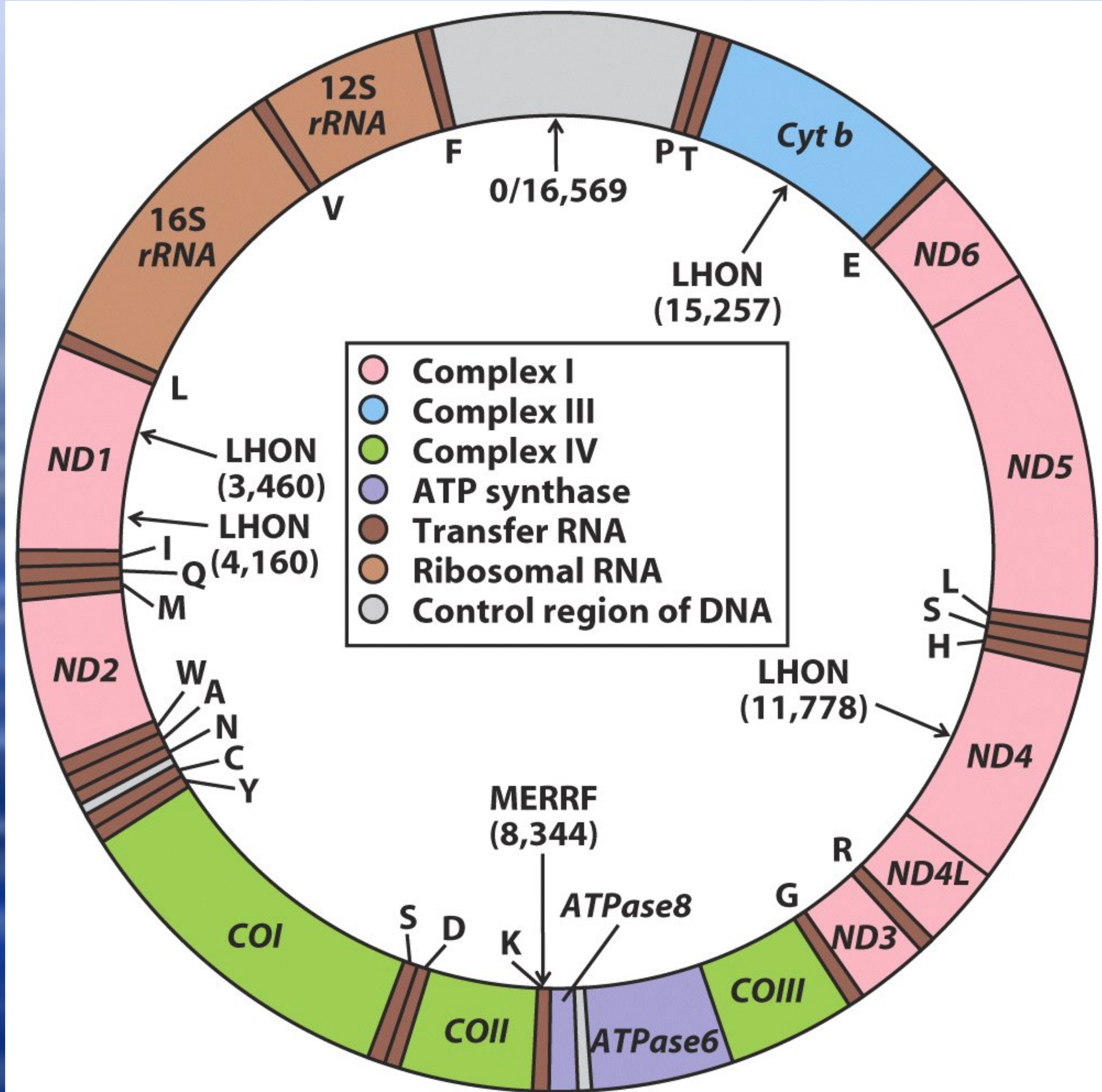


Figure 6.17
Summary of key concepts for oxidative phosphorylation. [Note: Electron flow and ATP synthesis are are envisioned as sets of interlocking gears to emphase the idea of coupling.]

TABLE 19–6 **Respiratory Proteins Encoded by Mitochondrial Genes in Humans**

Complex	*Number of subunits*	*Number of subunits encoded by mitochondrial DNA*
I NADH dehydrogenase	>43	7
II Succinate dehydrogenase	4	0
III Ubiquinone:cytochrome *c* oxidoreductase	11	1
IV Cytochrome oxidase	13	3
V ATP synthase	8	2



Complex I
Complex III
Complex IV
ATP synthase
Transfer RNA
Ribosomal RNA
Control region of DNA
0/16,569
F
12S rRNA
V
16S rRNA
L
ND1
LHON (3,460)
LHON (4,160)
I
Q
M
ND2
W
A
N
C
Y
COI
S
D
COII
K
MERRF (8,344)
ATPase8
ATPase6
COIII
G
ND3
R
ND4L
ND4
LHON (11,778)
H
S
L
ND5
ND6
E
Cyt b
LHON (15,257)
P
T

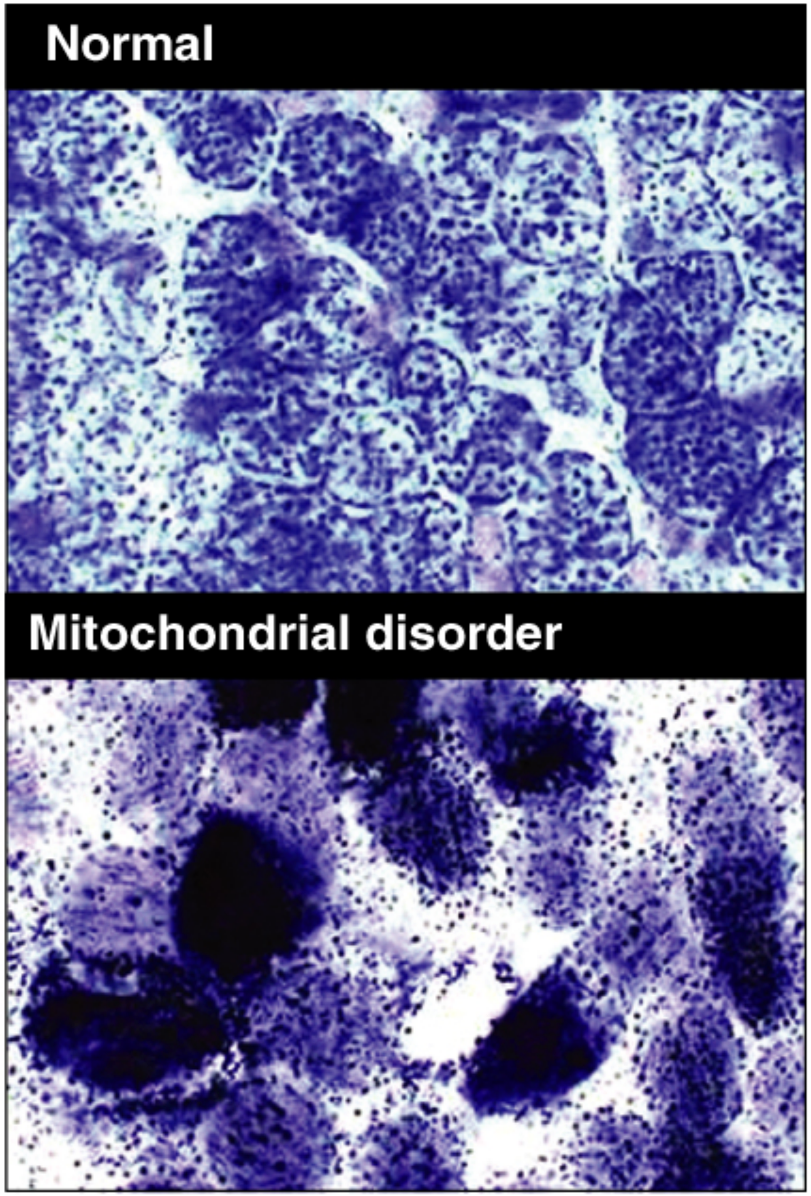


Figure 6.16

Muscle fibers from a patient with a mitochondrial myopathy show abnormal mitochondrial proliferation when stained for succinic dehydrogenase.