Electron Transport Chain

(Generation of ATP)

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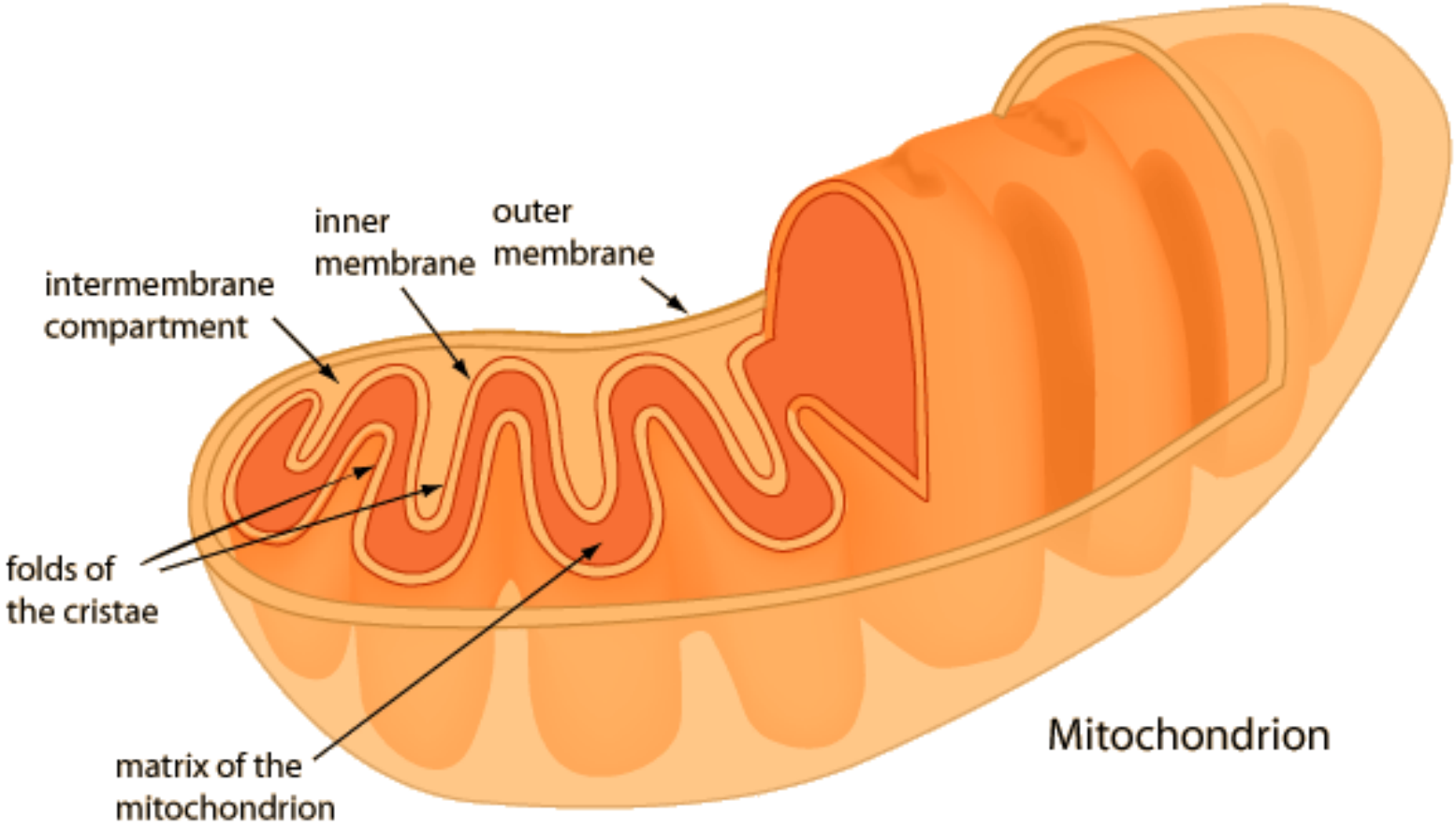
Mitochondria: The Power House



Most of the ATP is produced by enzyme - catalyzed reactions in the matrix, driven by electron transport processes associated with the innner membrane.

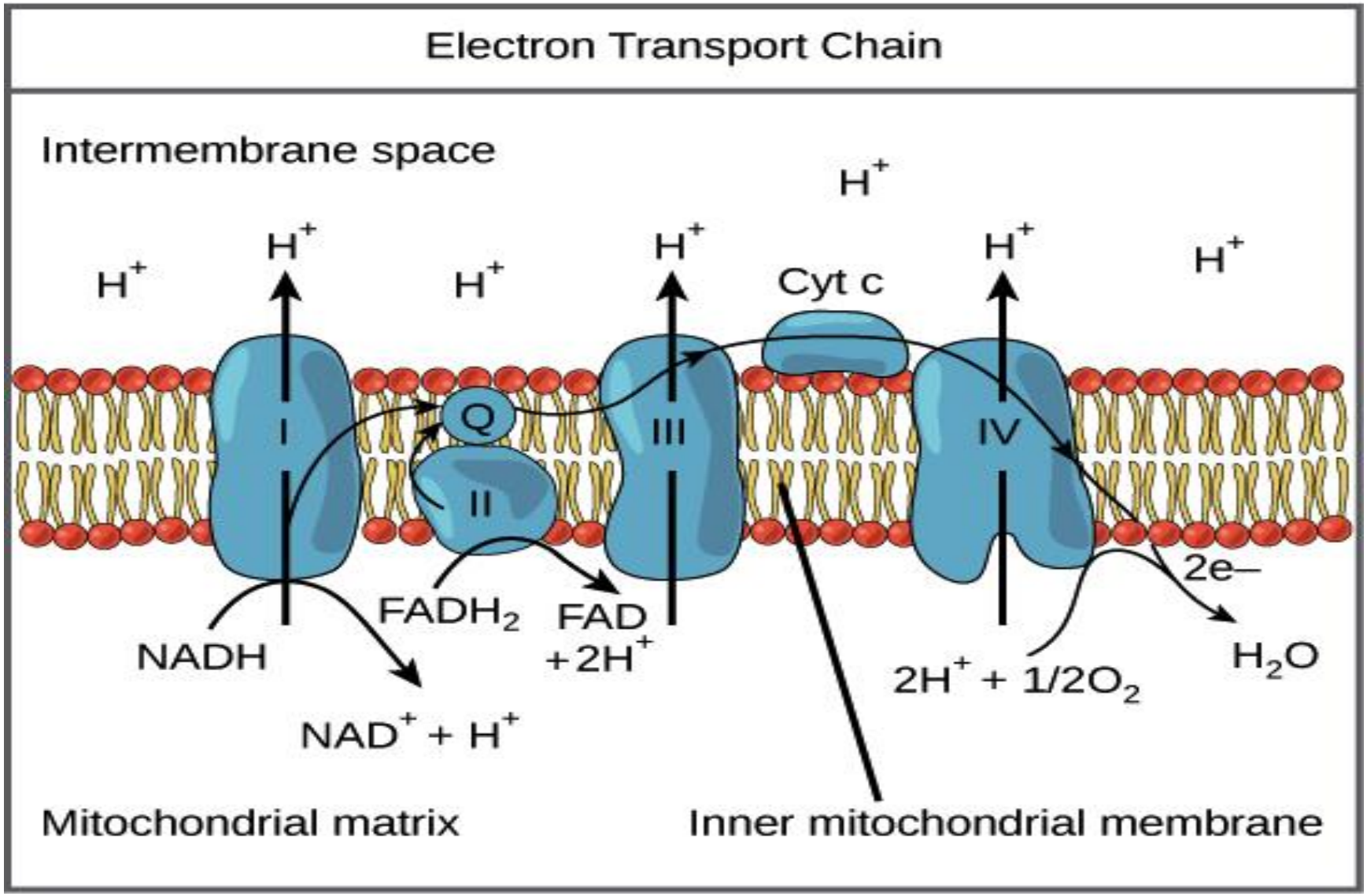
To combat Bacterial Diseases

Bacterial diseases	
Cholera	*Vibrio cholerae*
Diarrhea	*E. coli*
Dysentery	*Shigella* strain
Gonorrhea	*Niessena gonorrhoeae*
Leprosy	*Mycobacterium leprae*
Meningitis	*Neisseria meningitidis*
Pneumonia	*Streptococcus pneumoniae*
Rheumatic fever	*Streptococcus* group A
Tetanus	*Clostridium tetani*
Tuberculosis	*Mycobacterium tuberculosis*
Typhoid	*Salmonella typhi*
Urogenital tract infection	*Streptococcus* group B

To Combat Viral diseases

Viral diseases	
Acute infartile gastroenteritis	Rotavirus
Acute respiratory diseases	Influenza A and B viruses
AIDS	Human immunodeficiency virus
Chicken pox	Varicella-zoster virus
Encephalitis	Japanese encephalitis virus
Genital ulcers	Herpes simplex virus type-2
Hemorrhagic fever	Dengue virus
Liver damage	Hepatitis A virus
Liver damage	Hepatitis B virus
Upper and lower respiratory tract lesions	Yellow fever virus

Reduction of NADH and H+



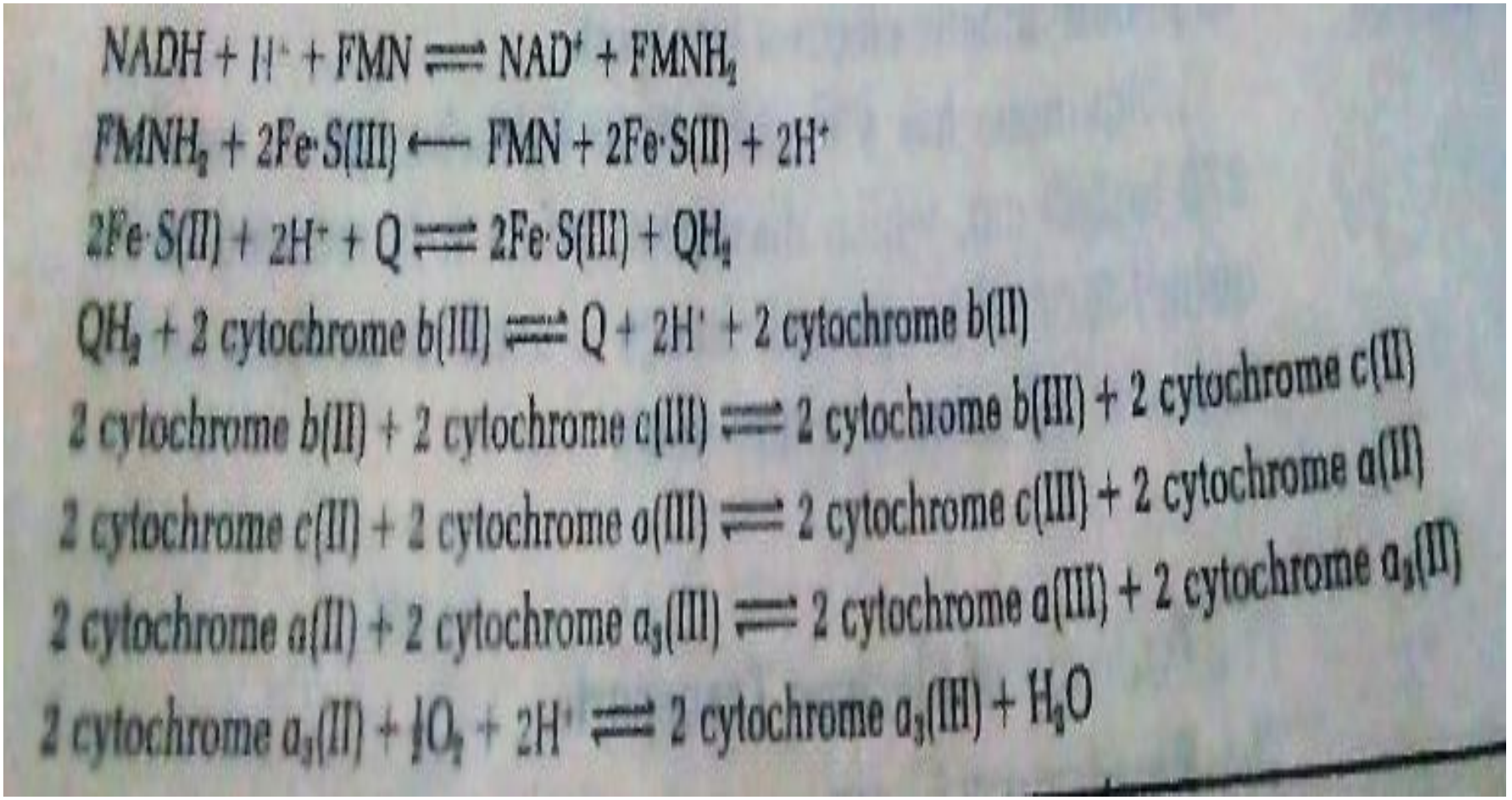
Chemioosmosis

Complexes I, III, and IV of the electron transport chain are proton pumps. As electrons move energetically downhill, the complexes capture the released energy and use it to pump H^+ ions from the matrix to the intermembrane space forming an electrochemical gradient across the inner mitochondrial membrane called the proton-motive force.Conceptually, ATP synthase is a lot like a turbine in a hydroelectric power plant. Instead of being turned by water, it's turned by the flow of H^+ ions moving down their electrochemical gradient and catalyzes the addition of a phosphate to ADP, generating ATP for our future work.

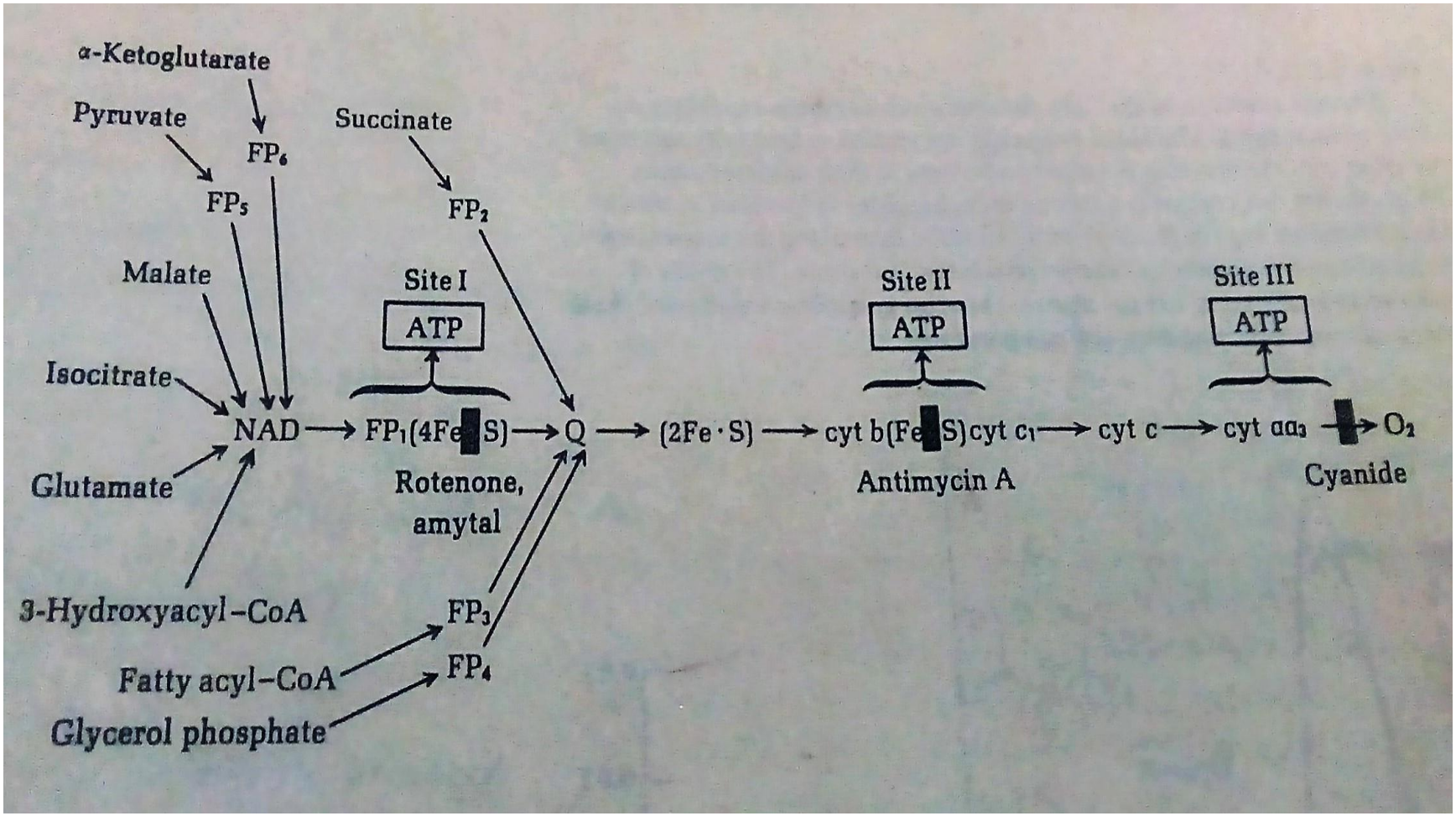
Oxidative Phosphorylation and ETC

The electron transport chain is a mitochondrial pathway in which electrons move across a redox span of 1.1 V from NAD+/NADH to O2/H2O. Three complexes are involved in this chain, namely, complex I, complex III, and complex IV. Some compounds like succinate, which have more positive redox potential than NAD+/NADH can transfer electrons via a different complex—complex II. Coenzyme Q, or simply Q, can travel within membrane while Cyt C is a soluble protein. Flavoproteins are components of complexes I and II and Fe-S is present in complexes I, II, and III. The Fe atom present in Fe-S complexes helps in electron transfer by shifting from Fe2+ to Fe3+ states. With the help of oxidation–reduction reactions a proton gradient is created which causes phosphorylation of ADP.

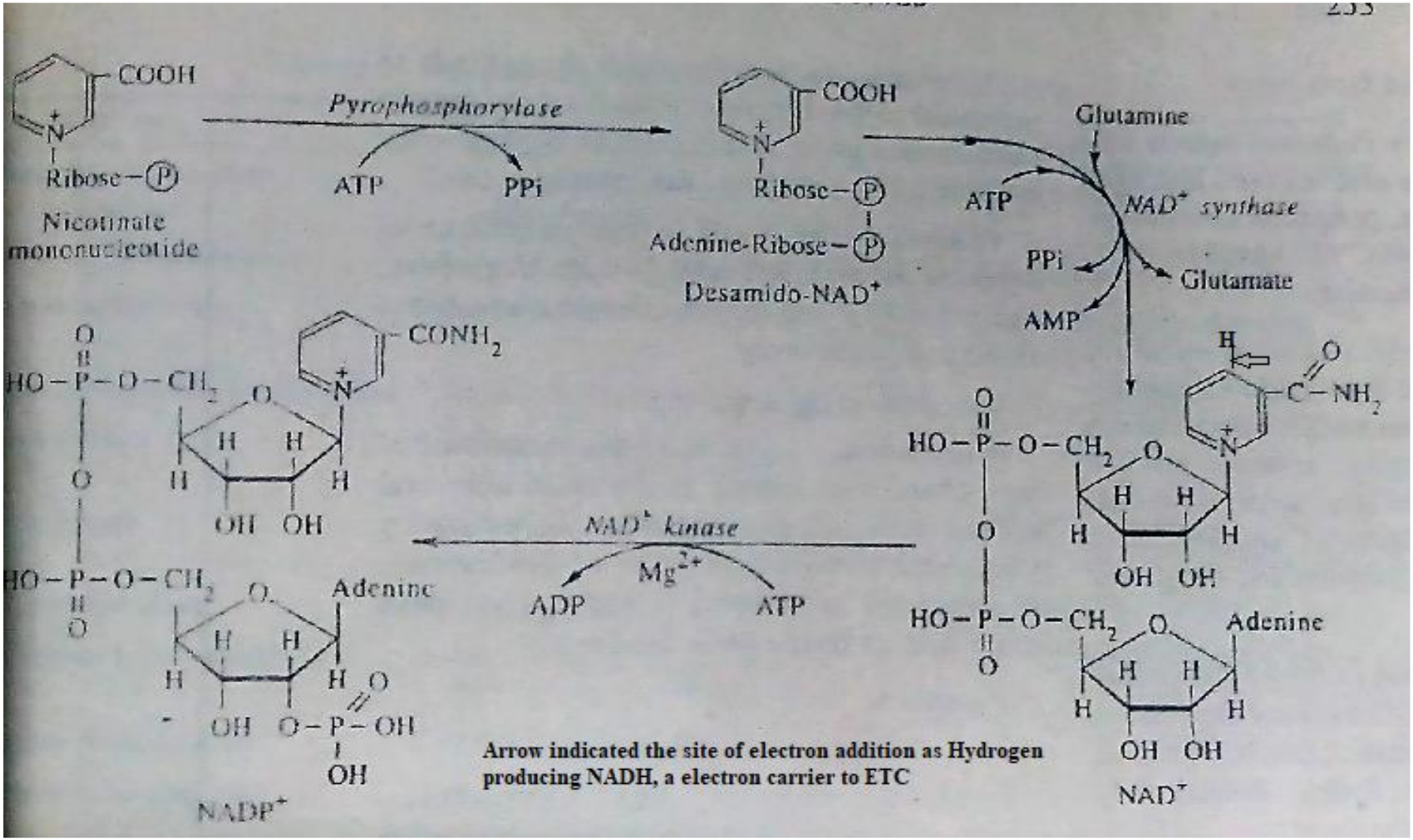
Steps in the ETC Reactions: NADH was obtained from glycolysis and TCA cycle



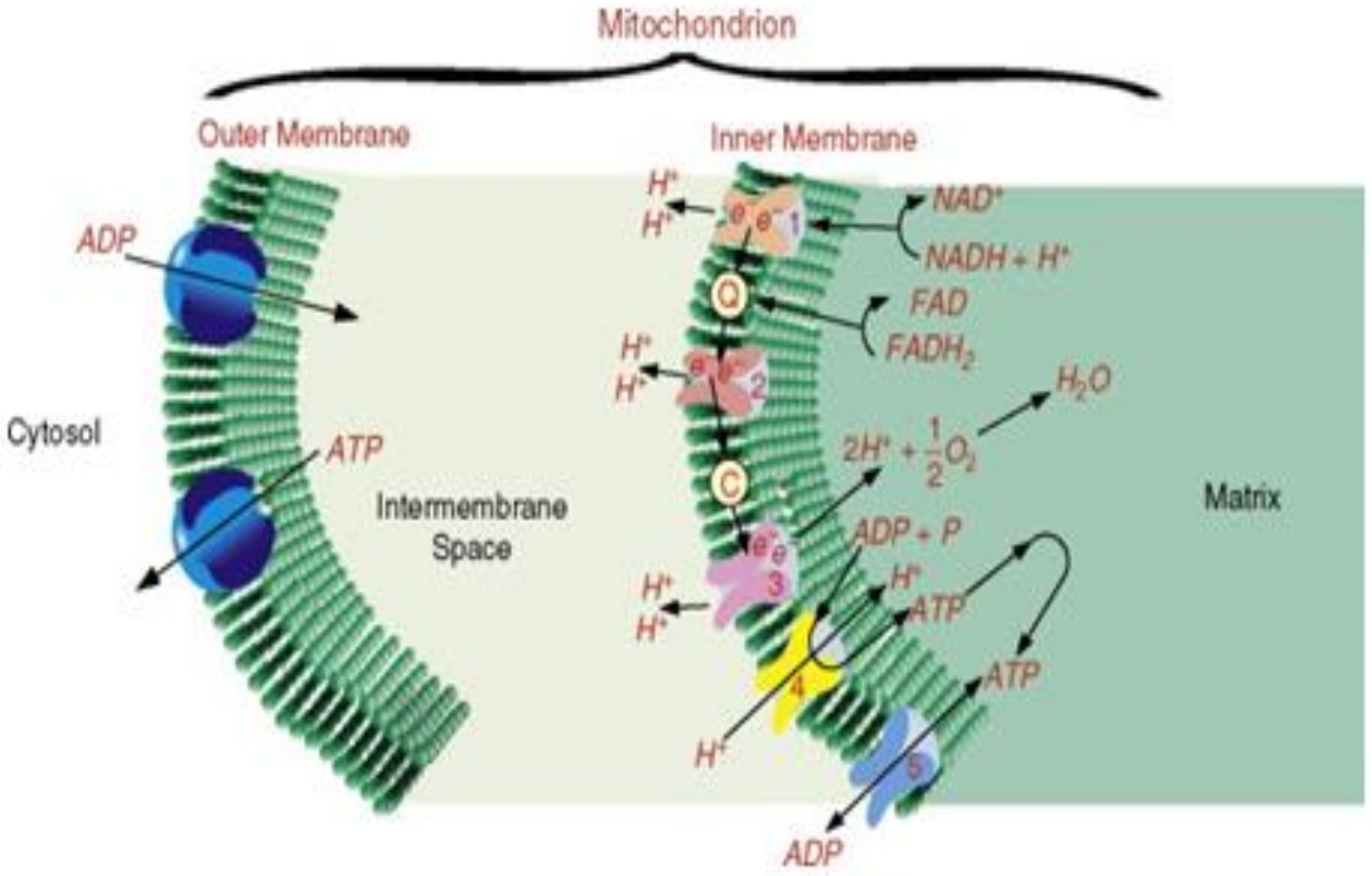
Electron Transport Chain at a Galance



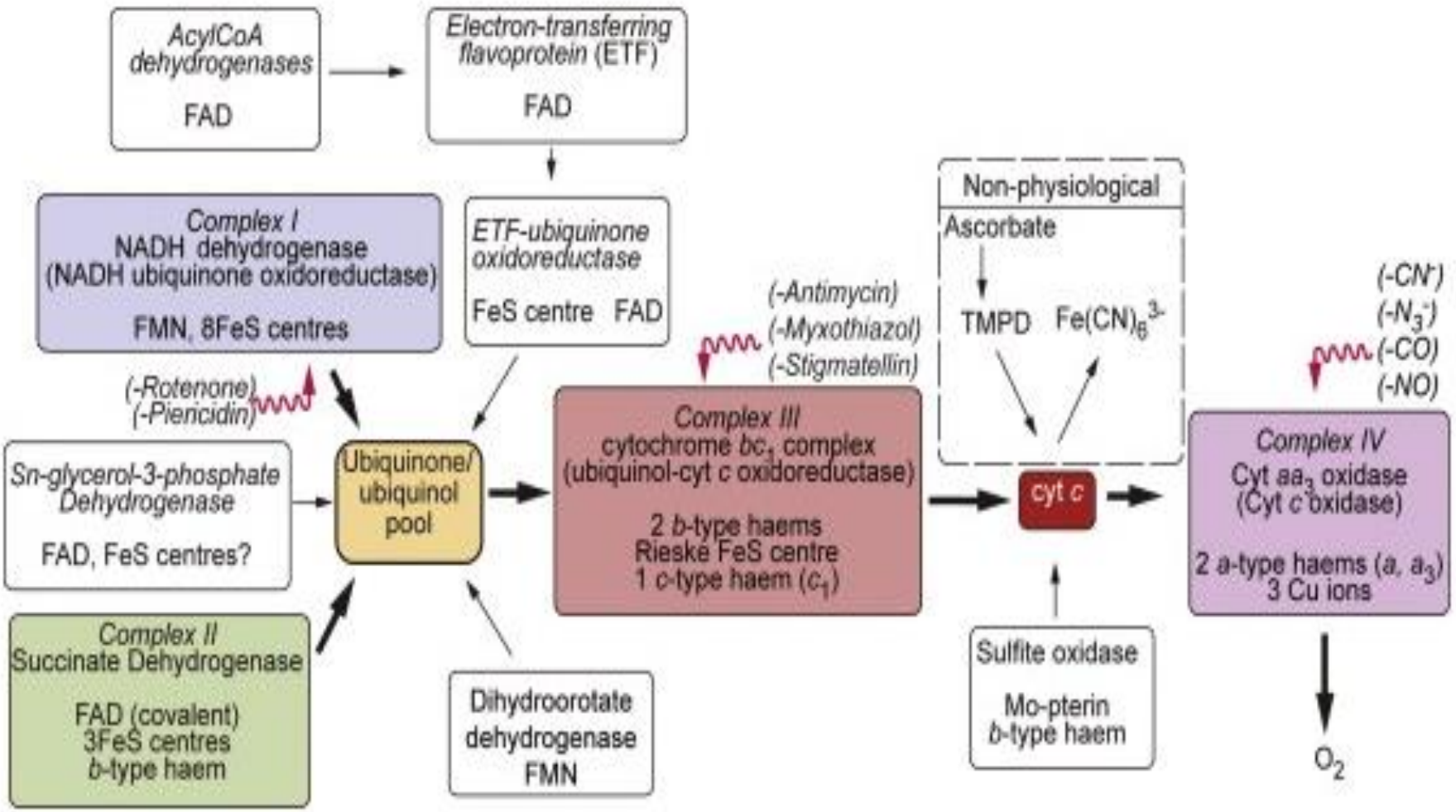
Structure of Niacin to NAD+ or NADP+ which carry electron



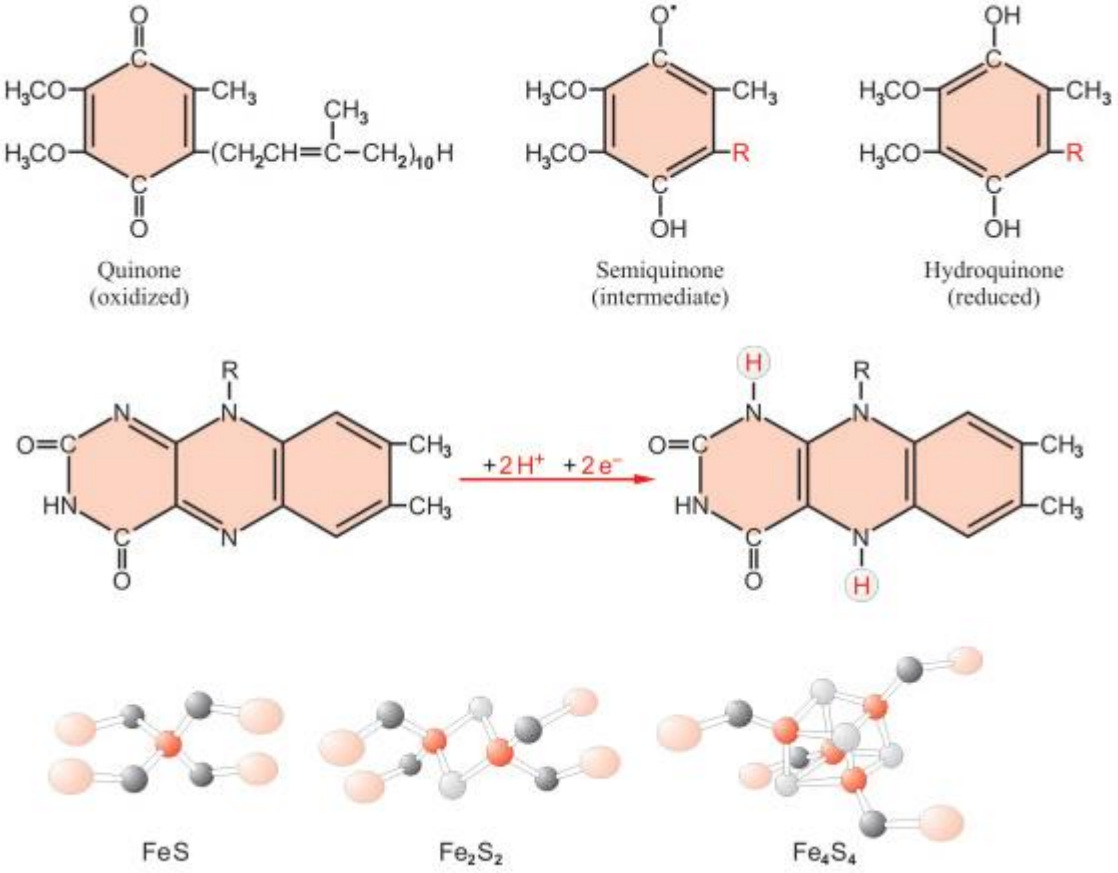
ADP enter into Mitochondria



Electron Carriers at the Mitochondria



Chemical structures of ETC



Respiratory Chain Components

The respiratory chain is a group of electron acceptors and reducing carriers imbedded in the inner membrane of mitochondria. Many of its components are clustered into multimolecular complexes that cross the entire thickness of the lipid bilayer. There are four complexes and two other single components of the chain (coenzyme Q and cytochrome c..

Reduced NAD is oxidized by the first complex in the respiratory chain, called NADH–ubiquinone reductase. This is a large complex (>900 kDa) consisting of about 45 polypeptide chains, one prosthetic group called flavin mononucleotide (FMN), and 16–24 iron atoms in 7–9 iron–sulfur centers..

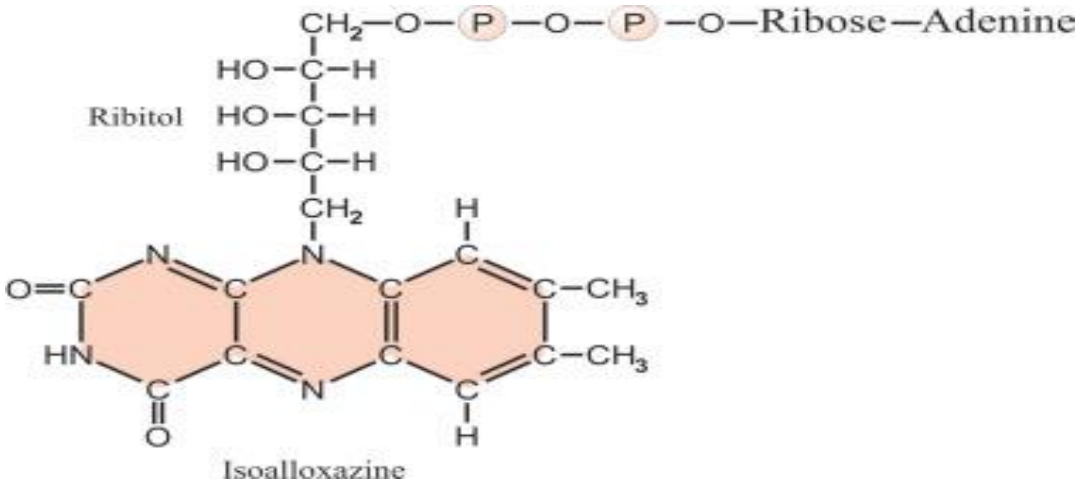
Electrons transferred from NADH to the NADH–ubiquinone reductase complex are initially accepted by FMN, which is reduced to FMNH2. Then, electrons pass successively through different Fe atoms in the Fe–S centers, and finally are transferred to ubiquinone or coenzyme Q. The FMN and Fe atoms are reoxidized and coenzyme Q is reduced (CoQH2).

Flavoproteins are firmly bound to the prosthetic group, flavin. NADH–ubiquinone reductase complex has FMN (formed by isoalloxazine), a penta alcohol derivative of ribose, ribitol, and orthophosphate.

Flavin adenine dinucleotide (FAD) is similar to FMN in that it is composed of isoalloxazine, ribitol, phosphate, plus another nucleotide, adenosine monophosphate (AMP). The AMP binds to the FMN phosphate through a pyrophosphate bond.

Flavin Dehydrogenase

Substrates in the mitochondrial matrix such as succinate, acyl coenzyme A, glycerol-3-phosphate, and others, are oxidized by flavin dehydrogenase using adenine dinucleotide (FAD) as a coenzyme. In the reaction, the FAD is reduced to FADH2. The isoalloxazine core and ribitol, part of FMN and FAD molecules, are components of riboflavin, a complex B vitamin. The isoalloxazine in FMN and FAD is the portion of the molecule, which accepts both of the transferred hydrogens.



Cytochromes and ETC

Cytochromes are heme proteins that are able to accept electrons. The heme iron captures an electron, passing from the oxidized state (Fe3+) to the reduced (Fe2+). Several types of respiratory chain cytochromes have been identified: two types of cytochrome-a (a and a3), two types of cytochrome-b (b566 and b562), and two types of cytochrome-c (c and c1). They differ in their reduction potential and light absorption spectrum. In the case of cytochromes-b, the subscript indicates the wavelength at which they have their maximum absorption. They can be ordered according to their increasing reduction potential: b566-b562-c1-c-a-a3.

Cytochrome-b

Cytochromes-b and cytochromes-c possess a prosthetic group identical to that found in hemoglobin and myoglobin (the heme and iron are complexed with protoporphyrin IX). Cytochromes-a contain heme A, with two different side chains. Molecules of cytochrome-a and cytochrome-a3 are equal, but have different reduction potentials because they are located in different environments within the complex. The cytochromes are associated with a copper ion, located near the heme A iron. Metals undergo redox reactions which aid in recycling between Fe3+/Fe2+ and Cu2+/Cu+ states.

Cytochrome-b and cytochrome-c1 form part of a complex called ubiquinone–cytochrome c reductase, which comprises 11 different polypeptide subunits, including the cytochromes. Also located in this complex is an iron–sulfur protein (Fe2–S2). From the ubiquinone–cytochrome c reductase complex, electrons pass to cytochrome-c.

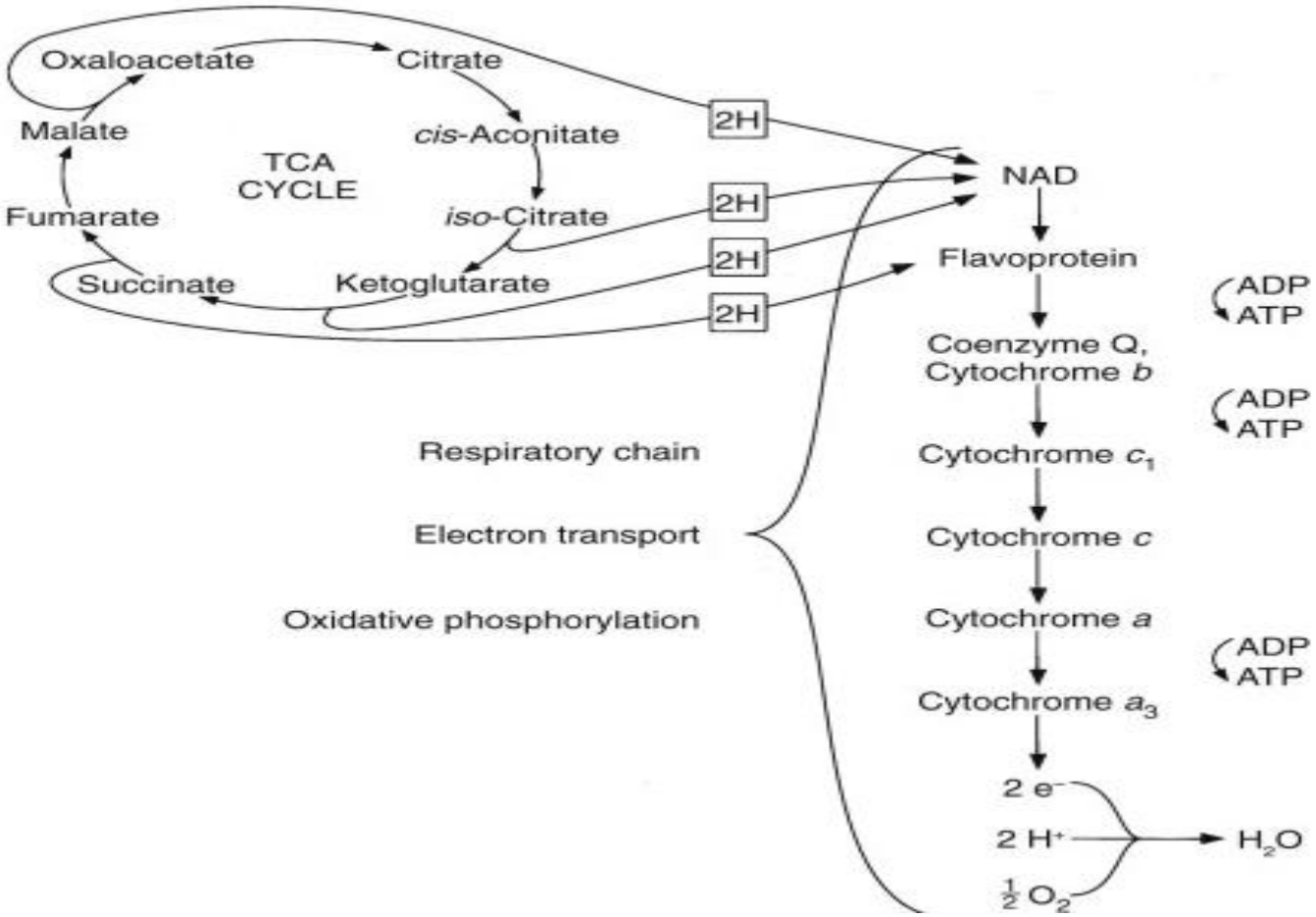
Cytochrome-c

- Cytochrome-c is a heme protein made up of 104 amino acids (13 kDa) and a prosthetic group identical to the heme of hemoglobin and myoglobin. The amino acid sequence of cytochrome-c has been preserved with little change along evolution. It is a peripheral protein located on the outer side of the inner mitochondrial membrane. It is associated with the membrane through electrostatic attractions to the polar heads of phospholipids.
- Cytochrome-c can be easily separated from the membrane by treatment with saline solutions. Its molecule has various side chains of lysine residues surrounding the area in which the heme is housed. The positive charges on the lysine are important for recognition and binding to the complexes located immediately before and after in the respiratory chain of electron acceptors. Cytochrome-c is a mobile carrier which receives electrons from ubiquinone–cytochrome-c reductase and transfers them to the cytochrome oxidase complex, responsible for the last stage of the system.

Cytochrome Oxidase

- Cytochrome oxidase is formed by 11–13 polypeptide subunits. This complex, just like the previous ones, spans the entire thickness of the membrane. It contains one cytochrome-a, one cytochrome-a3, and two copper ions that form two heme–Cu centers. Cytochrome oxidase is the only component of the electron transport system with the capacity to directly react with oxygen. An oxygen molecule (O2) captures four electrons to form two molecules of water. The overall reaction is
- $O2 + 4\ e^- + 4\ H^+ \rightarrow 2\ H2O$
- In this reaction, four electrons converge simultaneously. This poses a problem, since cytochrome-a3, the last acceptor of the chain, carries only one electron at a time and the converging electrons cannot exist free in the medium. To explain this phenomenon, it has been proposed that complete reduction of oxygen is performed in a cycle of several stages, called the Q cycle, which will be considered later

TCA Cycle and ATP + H_2O generation



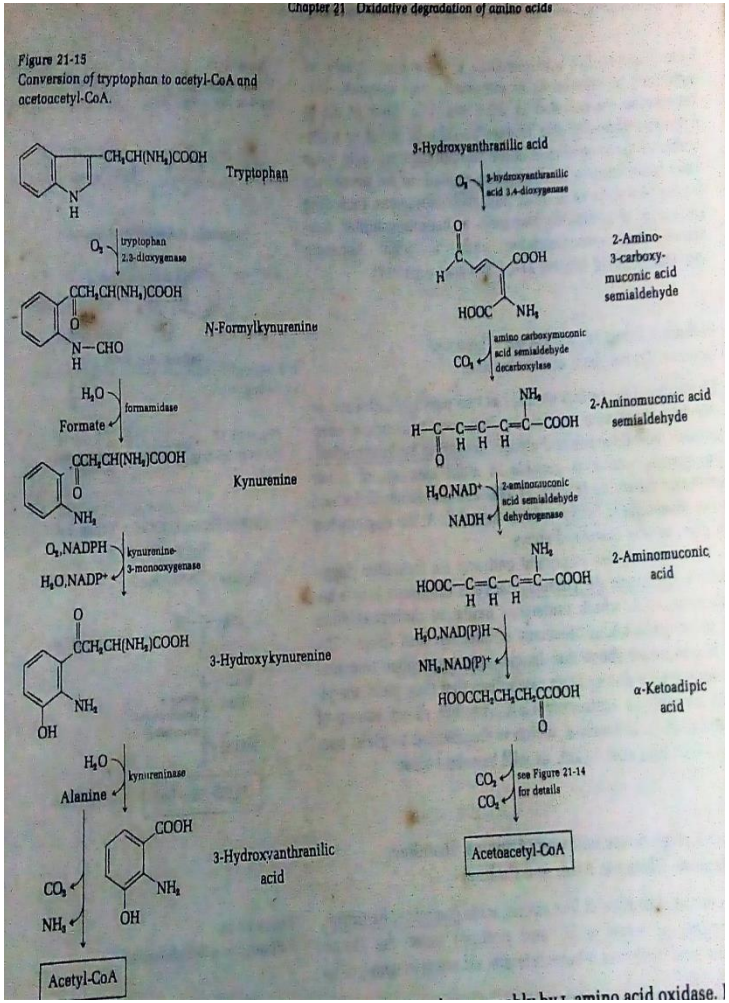
Breakdown of one molecule of glucose

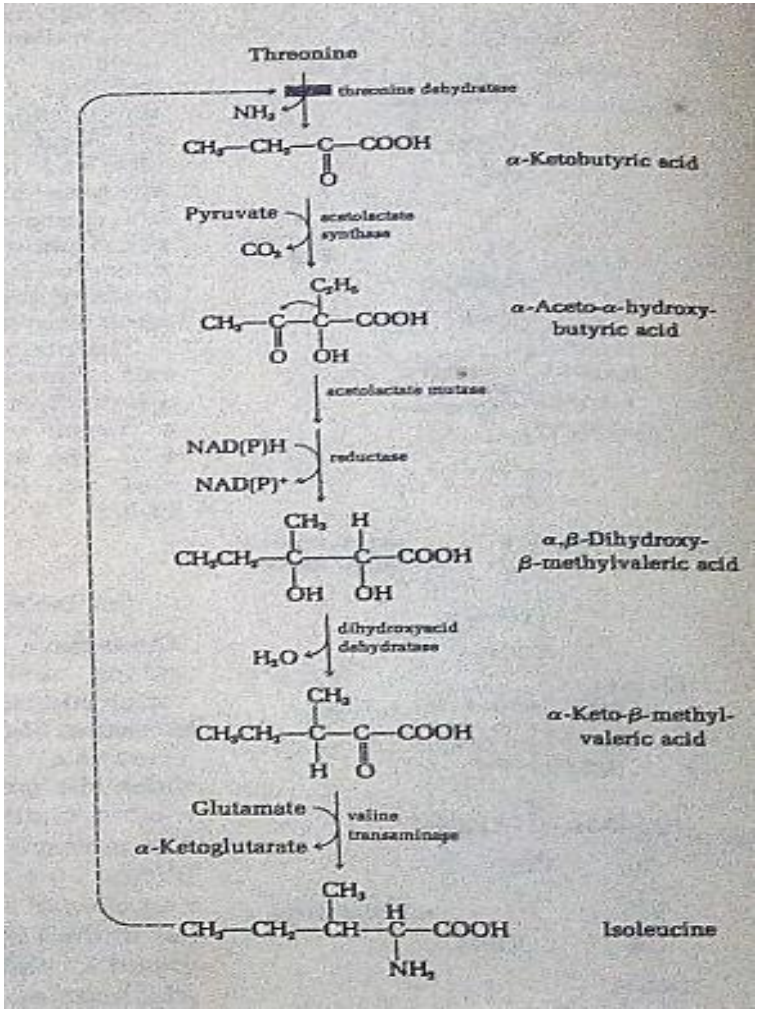
Stage	Direct products (net)	Ultimate ATP yield (net)
Glycolysis	2 ATP	2 ATP
	2 NADH	3-5 ATP
Pyruvate - oxidation	2 NADH	5 ATP
Citric acid-cycle	2 ATP/GTP	2 ATP
	6 NADH	15 ATP
	2 $FADH_2$	2-3 ATP
Total		30-32 ATP

1. Some cells of your body have a shuttle system that delivers electrons to the transport chain via FADH2. In this case, only 3 ATP are produced for the two NADH of glycolysis.

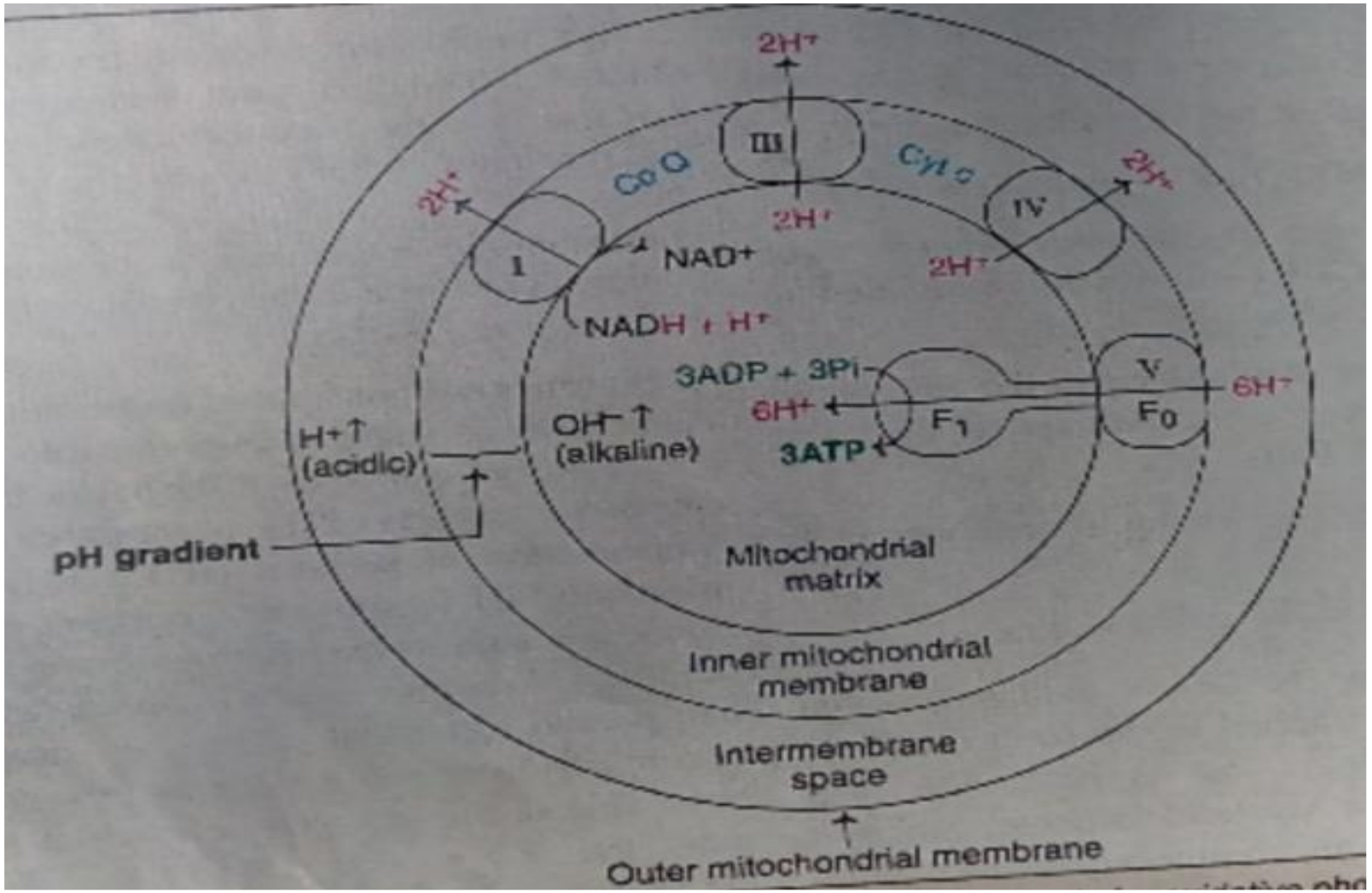
2. Other cells of your body have a shuttle system that delivers the electrons via NADH, resulting in the production of 5 ATP.

Acetyl-COA from Amino Acids
(Protein Metabolism)





Chemiosmotic Hypothesis of Oxidative Phosphorylation



F1-Fo ATP Synthase is oligomeric protein that forms ATP from ADP

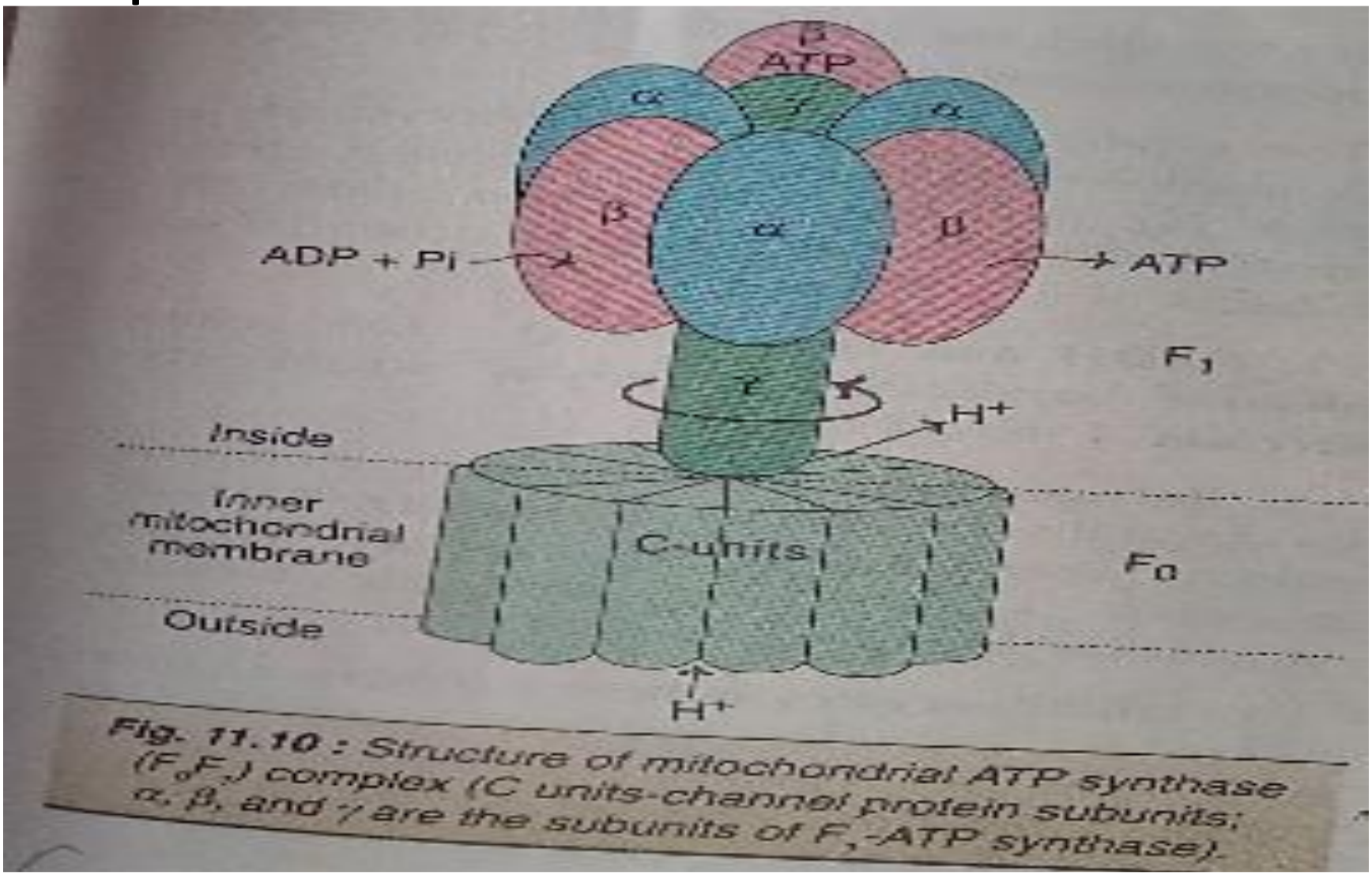
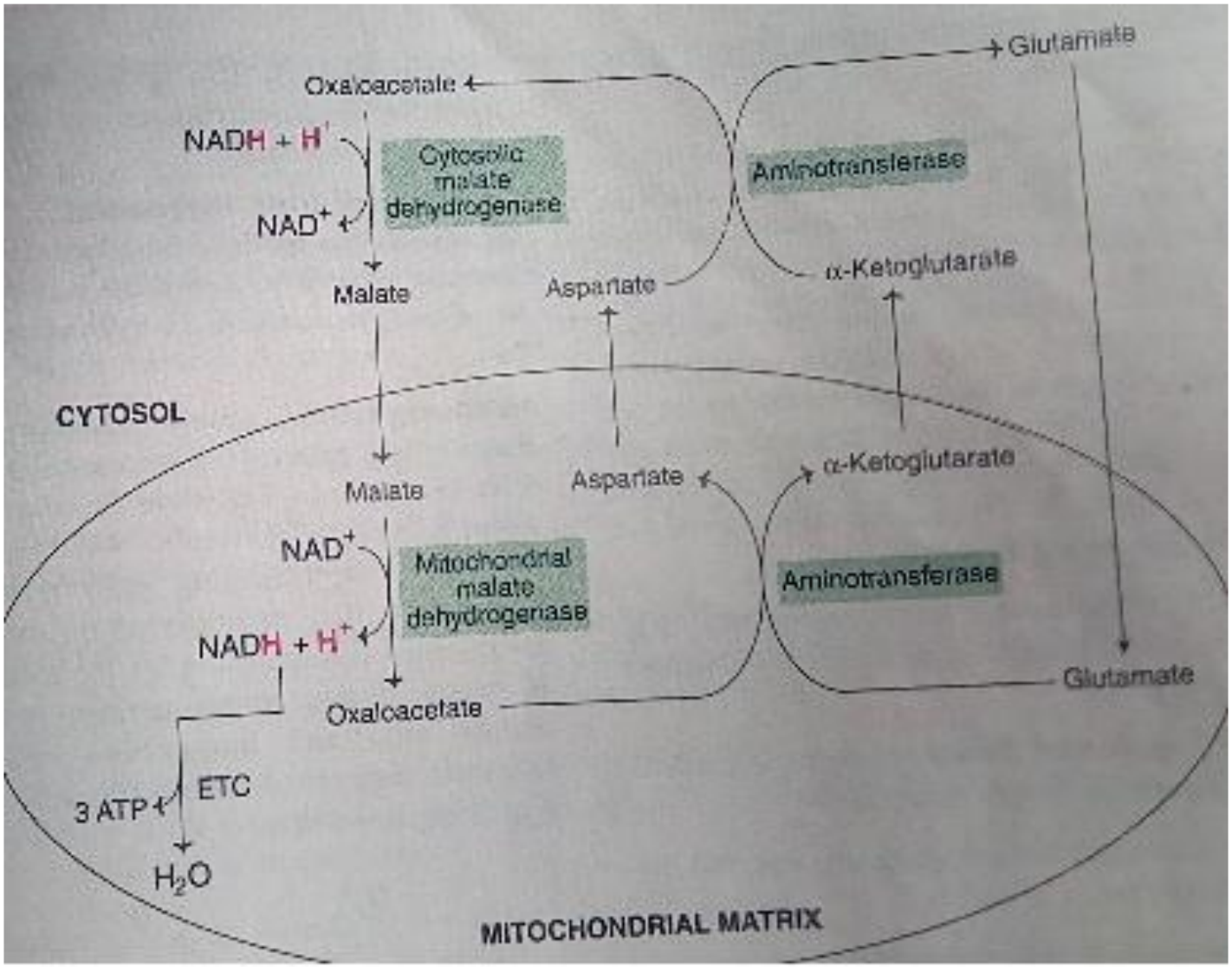


Fig. 11.10 : Structure of mitochondrial ATP synthase (F_oF_1) complex (C units-channel protein subunits; α, β, and γ are the subunits of F_1-ATP synthase).

Oxidative Phosphorylation



ETC INHIBITORS

Inhibitors of mitochondrial respiratory chain complexes

rotenone,

antimycin A,

myxothiazole,

metformin,

cyanide,

dinitrophenol,

valinomycin,

nigericin.

TTFA

Inhibitors of mitochondrial ATPase:

oligomycin C,

apoptolidin A,

resveratrol,

Bz-423,

diindolyl-methane,

aurovertin,

PK11195,

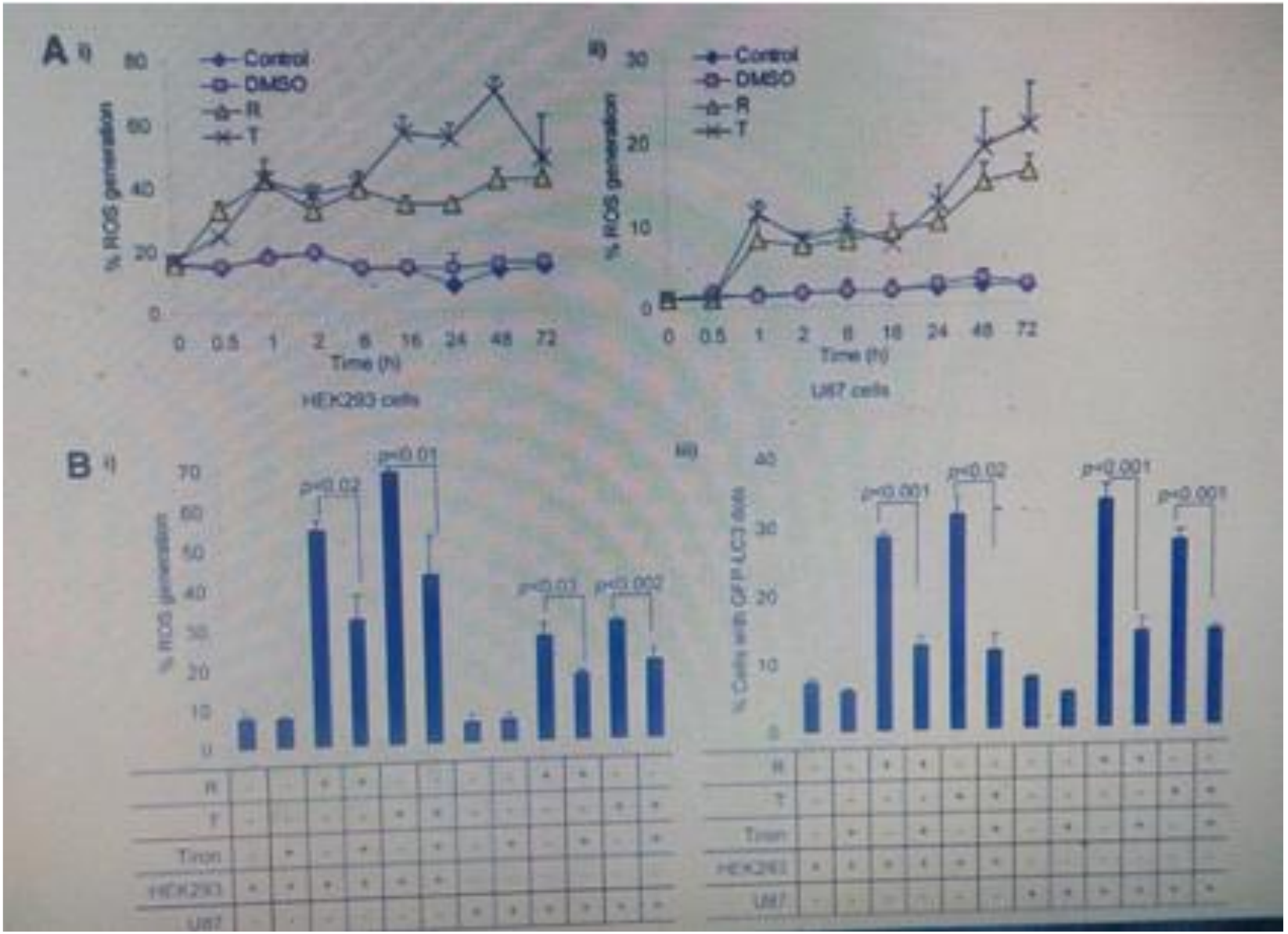
R207910

Mitochondrial Targets : Cancer Drugs

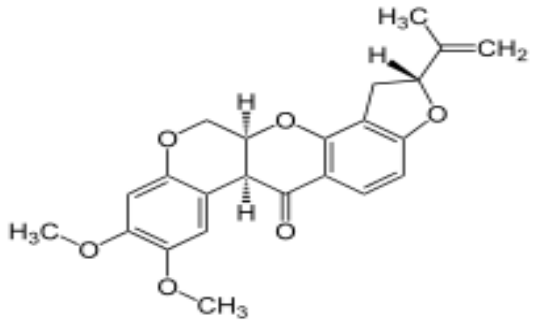
Jasmonate, 3-bromopyruvate, 2deoxyglucose, methyl mannoheptulose, gossypol, ABT-737, antimycin A, A-385358, ABT-263, HA14-1, AT-101, obatoclax, arsenic trioxide, lonidamide, , GSAO, PK11195, clodronate, betulinic acid, CD437, Ro5-4684, and a-TOS

Tamoxifen, resveratrol, piceatannol, rhodamine-123, dichloroacetate, CAP-232/TLN-232, MJE3, vitamin K3, fialuridine, 2-methoxyestradiol, b-lapachone, menadione, STA-478 and mangafodipir

Increase of ROS by Rotenone (Complex-I)



Rotenone : structure and Function

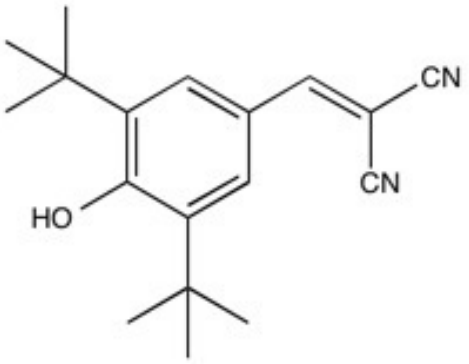


Rotenone

Rotenone works by interfering with the electron transport chain in mitochondria. It inhibits the transfer of electrons from iron-sulfur centers in complex I to ubiquinone (CoQ). Rotenone was implemented in 2010 to kill an invasive goldfish population present in Mann Lake, but no Trout.

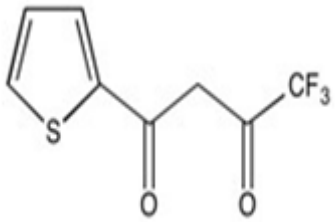
- Rotenone is an odorless, colorless, crystalline isoflavone used as a broad-spectrum insecticide, piscicide, and pesticide. It occurs naturally in the seeds and stems of several plants, such as the jicama vine plant, and the roots of several members of Fabaceae. It was the first described member of the family of chemical compounds known as rotenoids.

Tyrphostin 9 and TTFA Inhibitor



Tyrphostin 9

Tyrphostin 9 (10537-47-0) inhibits PDGF receptor tyrosine kinase (IC50 = 1.2 µM) and is a potent (10 nM) inhibitor of oxidative phosphorylation.



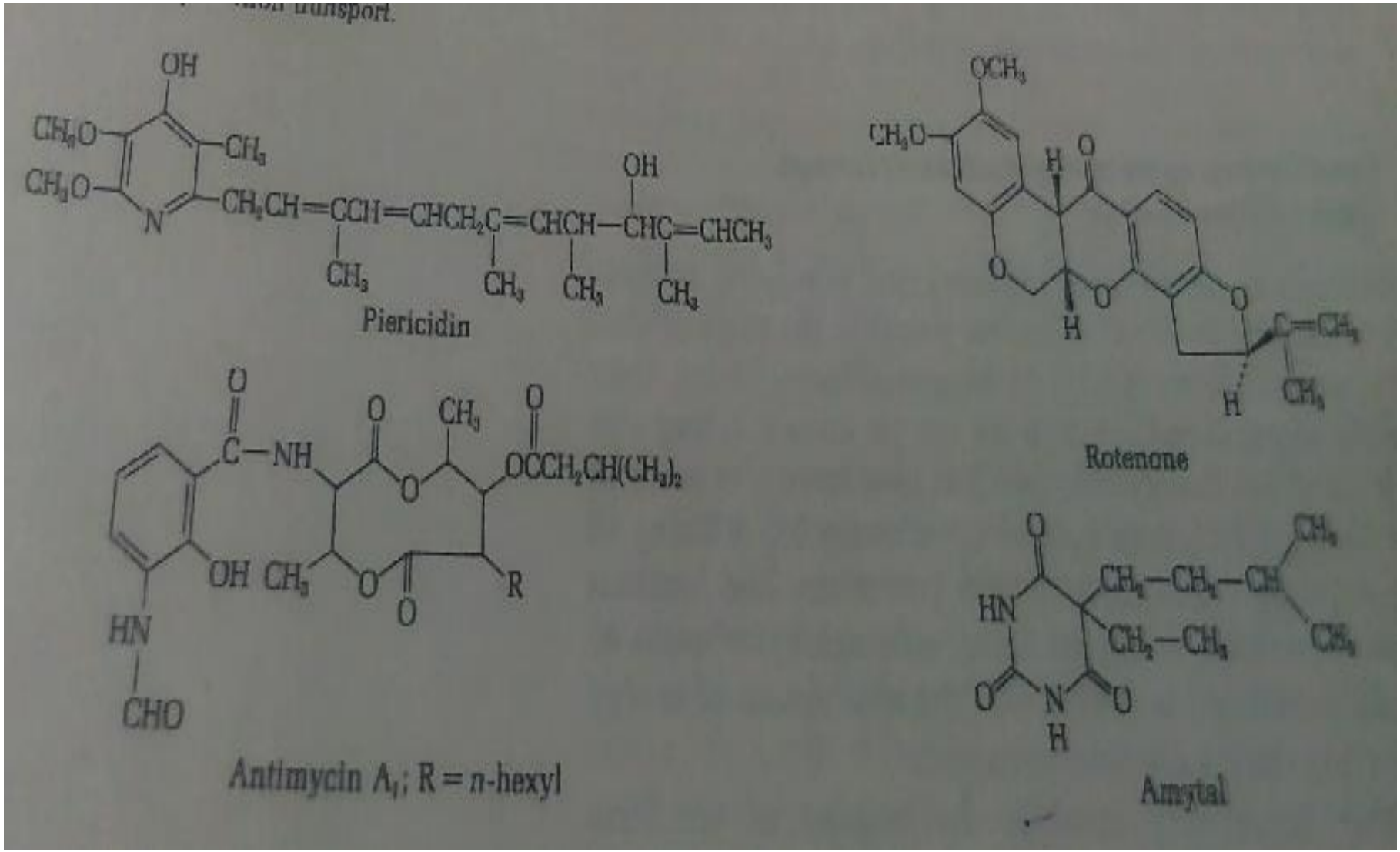
TTFA

TTFA (326-91-0) blocks the respiratory chain complex II causing inhibition of mitochondrial respiration. Respiratory chain complex II inhibition is caused via binding of TTFA to two ubiquinone binding sites, Qp and Qd.

Mitocans as cancer drugs

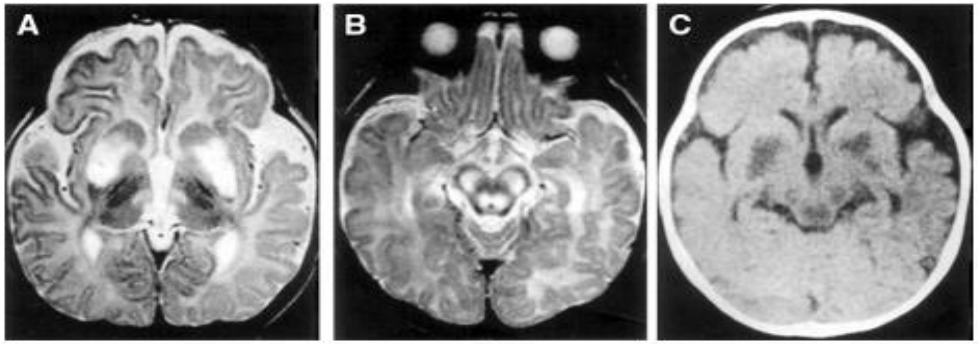
Class	Type	Examples
I	Hexokinase inhibitors	3-Bromopyruvate, 2-Deoxyglucose, Oxamate
II	Bcl-2/Bcl-xL mimetics	Gossypol, α-Tocopheryl succinate, Antimycin A
III	Thiol redox inhibitors	Isothiocyanates, Arsenites , Arsenic trioxide
IV	VDAC/ANT targeting drugs	Lonidamine, Retinoid analogs such as CD437
V	Electron transport chain targeting drugs	4-Hydroxy retinamide, Tamoxifen, Antimycin A
VI	Lipophilic cations targeting inner membrane	Rhodamine-123, MKT-077, $(KLAKKLAK)_2$ peptide, Mastoparan, Viral protein-R of HIV-1
VII	Drugs targeting other sites	Resveratrol (ATPase), Betulinic acid

Structures Of ETC Inhibitors



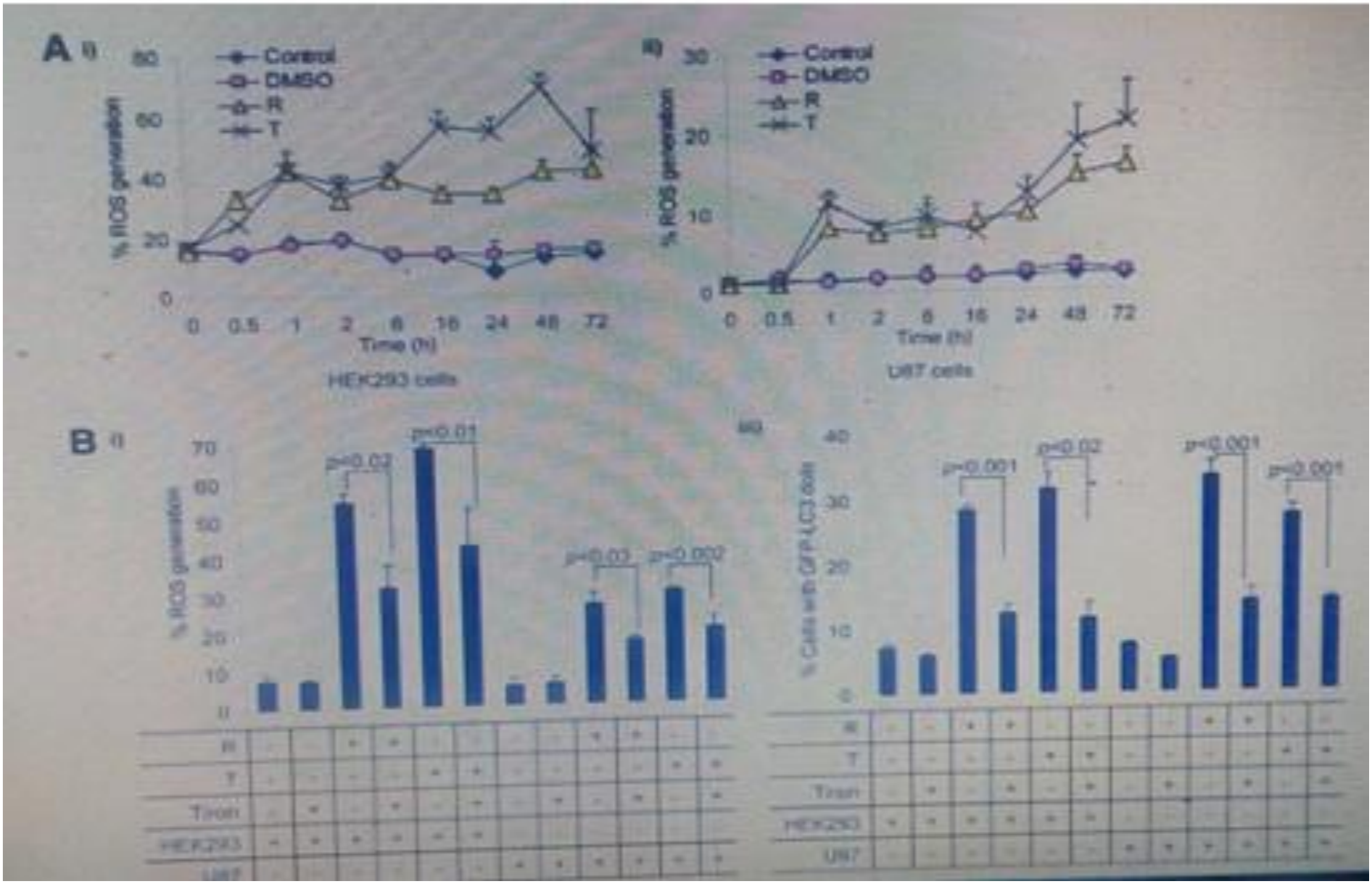
ETC Deficency and Disease

COX or Cytochrome oxidase (complex IV) defects or defects in SURF1 (COX assessory protein) lead to cytochrome c oxidase deficiency causing a progressive neurological disorder called Leigh syndrome (LS), named after the person who first described this form of subacute necrotizing encephalopathy (Leigh, 1951). While studies show that SURF1 is responsible for the majority of cases of LS due to cytochrome c oxidase deficiency, LS is genetically heterogeneous and can be caused by defects in other nuclear genes and mtDNA (DiMauro and Schon, 2008).



MRI findings in a 6-month-old baby girl affected by Leigh syndrome. (A,B) T2-weighted transversal sections showing signal abnormalities in the brainstem, with hyperintense lesions in the periaqueductal region and substantia nigra (A), lenticular nuclei and medial thalamic areas (B). A CT scan (C) shows hypodense lesions in the lenticular nuclei and periaqueductal region

Effect of Rotenine on ETC



Regulation of ETC in the mitochondria