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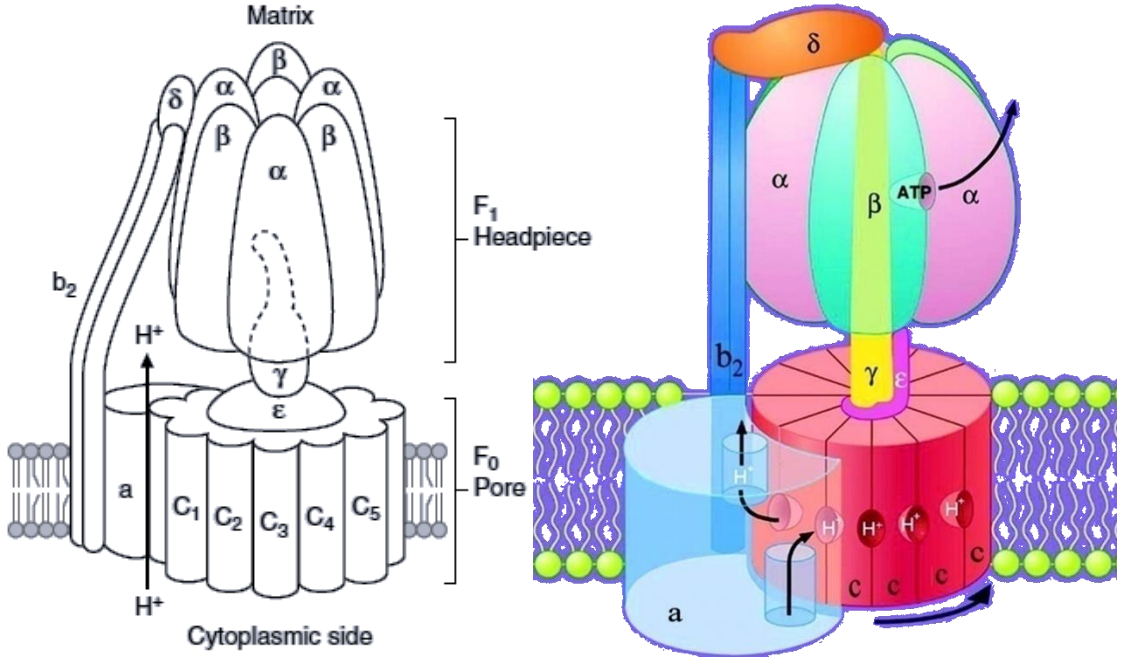
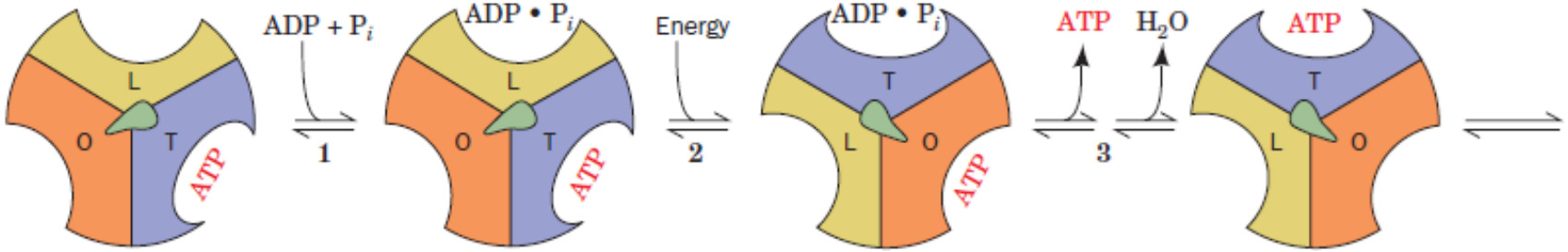
Oxidative Phosphorylation

ATP Synthase

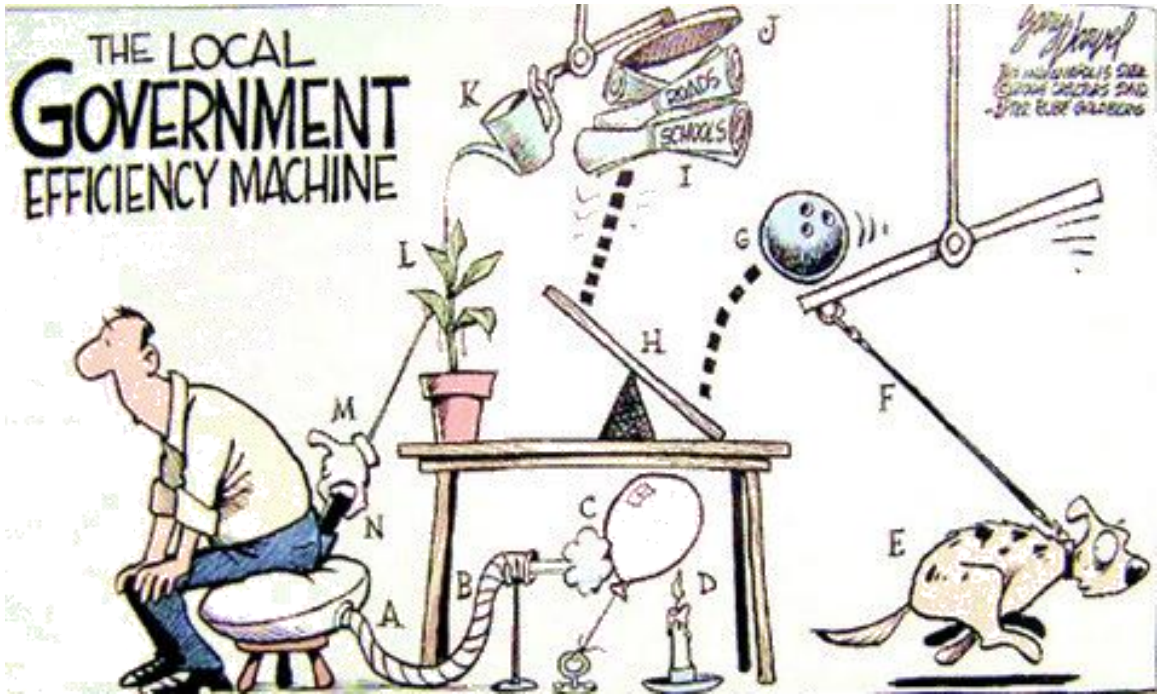
- F1:
  - "γ" subunit: rotates
  - "β" subunit: binds
  - "α" subunit: structural
  - 3 conformations: tight (T), loose (L), open (O)
- Fo:
  - "a" subunit: point of entry & exit
  - "c" subunit rotates
  - 4H+/ATP
- Can run backwards





Energy yield from the ETC

- NADH, -53 kcal, ATP?
- FADH2, -41 kcal, ATP?
- $\Delta G^{o\prime}$ is so negative, never reversible
- ATP machine efficiency, (anions, Ca^{+2}, heat, phosphate, substrates)
- Electron transport chain is our major source of heat



Regulation – the need for ATP

- What OxPhos needs? (NADH, O2, ADP, and Pi)
- In skeletal muscles, 20% drop in ATP concentration
- In the heart, Ca^{+2} activates TCA enzymes for extra push (NADH, ATP), no drop
- ET is tightly coupled to phosphorylation (simultaneously)
- ADP is the most important factor in determining the rate
- The regulation of the rate of oxidative phosphorylation by the ADP level is called respiratory control

Regulation – inhibition (coupling)


الصفحة الرئيسية > محليات

أشهر جرائم القتل العائلية في المملكة

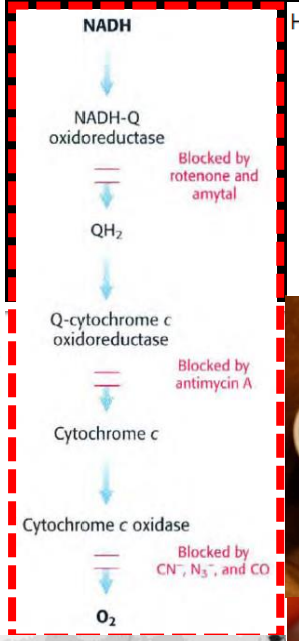
جراسا نيوز -

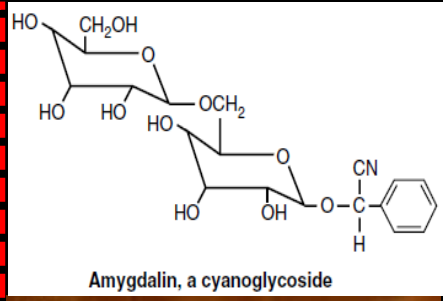
جراسا -نعرض فيما يلي قائمة بأشهر جرائم القتل العائلية التي حدثت في الاردن خلال السنوات الماضية ، والتي كان لكل منها وقع الصدمة حين وقوعها لما تمثله من فعل غريب على المجتمع وأعرافه ، فضلا عن مخالفتها الشرائع السماوية والقوانين النافذة والطبيعة الإنسانية بعامة.

قضية السيانيد

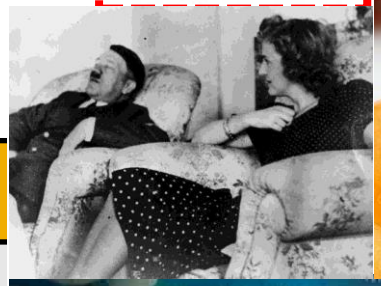
أول جريمة من نوعها يرتكبها أب ضد ولديه ، اذ قام الاب بوضع مادة السيانيد في كأس الحليب وطلب من طفليه ان يشربا منه ، حيث فارقا الحياة بعد 10 دقائق من مغادرة الام المنزل لتعود وتجدهما جثتين هامدتين.

وقد ادين الاب بعقوبة الاعدام شنقا الا ان والده اسقط الحق الشخصي كونه وليا عن الطفلين وحكم عليه بالاشغال المؤبدة.





Amygdalin, a cyanoglycoside



- Can occur at any stage
- Specific inhibitors:

✓ Cyanoglycosides are present in edible plant pits: (e.g.amygdalin)

✓ Oligomycin prevents the influx of H+ through ATP synthase

Specific inhibitor	Target
Rotenone (insecticide) & Amytal (sedative)	Complex I
Antimycin A (antibiotic)	Complex III
Cyanide (CN-), Azide (N_3-), & (CO)	Complex IV
Oligomycin (antibiotic)	Complex IV
Atractyloside	Translocase

Specific Inhibitors of ETC – Doxorubicin

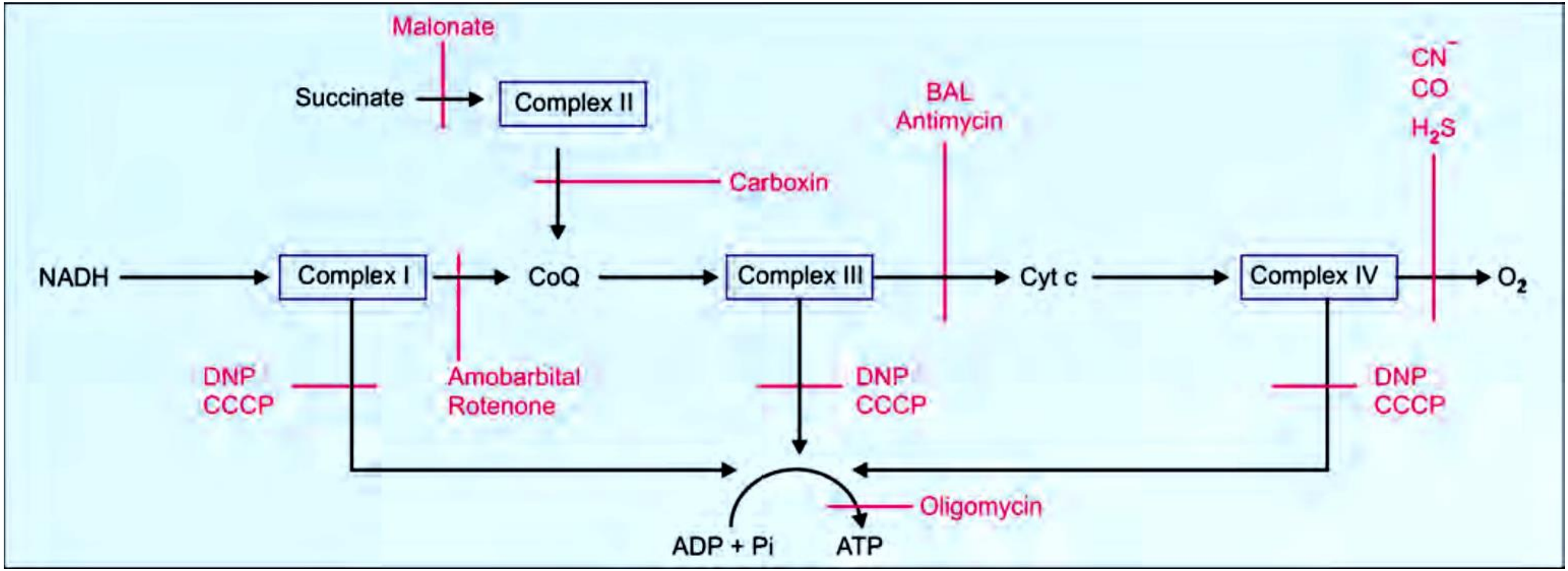
MECHANISM

- ✓ Binds to cardiolipin
- ✓ Inhibits succinate oxidation
- ✓ Inactivates cytochrome oxidase
- ✓ Interacts with CoQ
- ✓ Affects ion pumps
- ✓ Inhibits ATP synthase

EFFECT

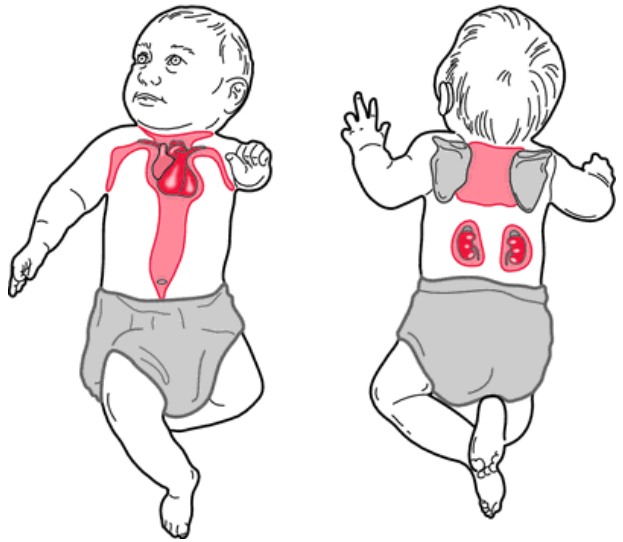
- ✓ Decreased ATP levels
- ✓ Swollen mitochondria
- ✓ Decreased mitochondrial ability to sequester calcium ions
- ✓ increased free radicals leading to mitochondrial membrane damage

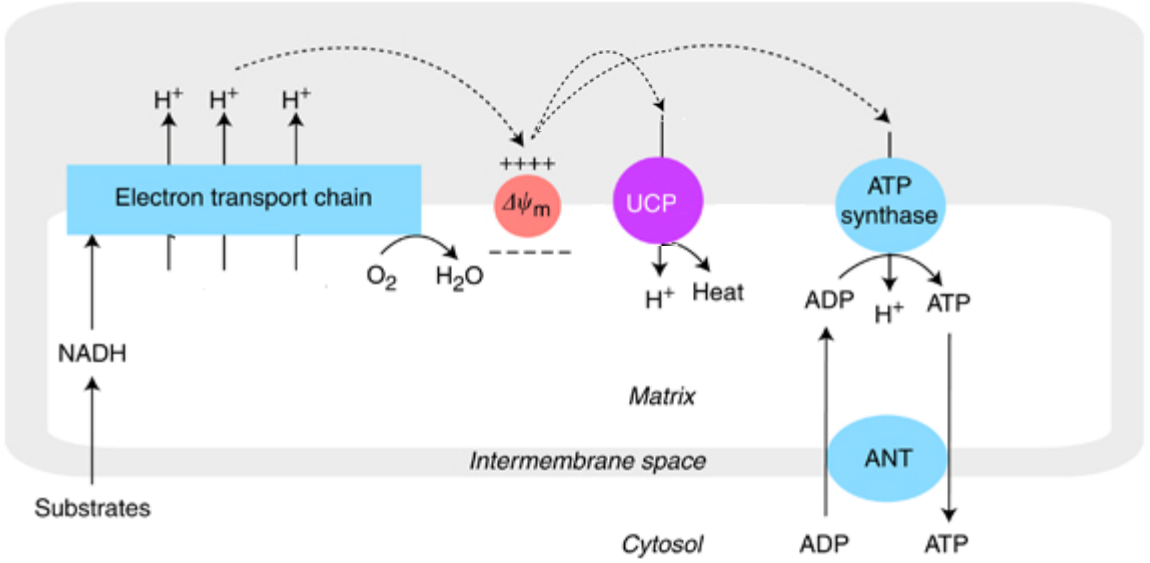
Regulation – Inhibition



Regulation – Uncoupling
Regulated - Uncoupling proteins (UCPs)

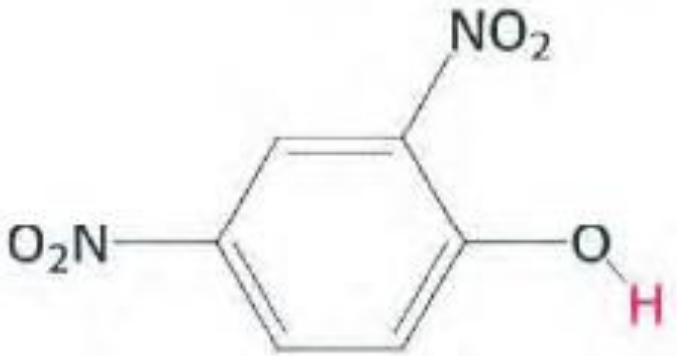
- Short-circuiting ATP synthase
- UCP1 (thermogenin):
  - ✓ Brown adipose tissue, non-shivering thermogenesis
  - ✓ Infants: neck, breast, around kidneys
  - ✓ Fatty acids directly activates UCP1
- UCP2 (most cells); UCP3 (skeletal muscle); {UCP4, UCP5} (brain)
- Obesity tendency in some populations



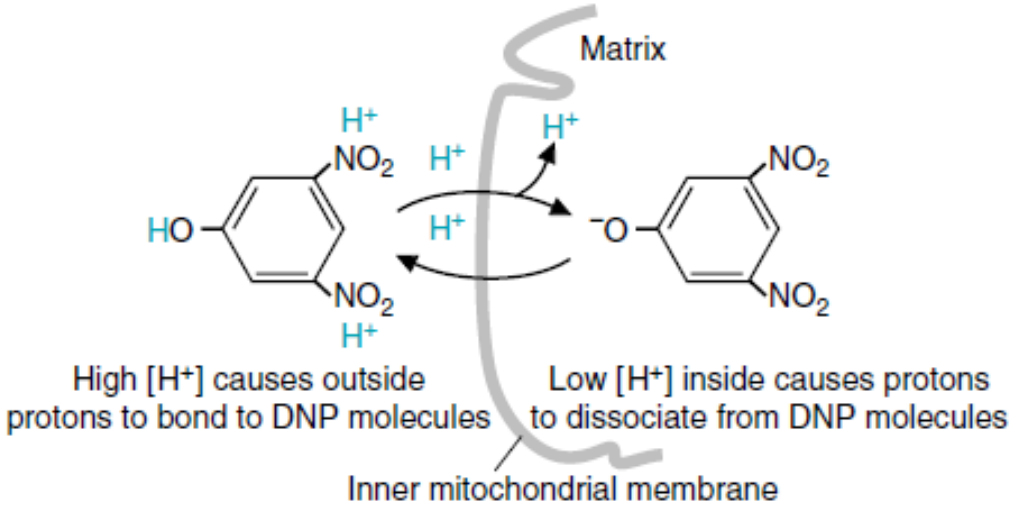


Regulation – Uncoupling
Unregulated – chemical uncouplers

- What is uncoupling?
- How does it occur? Dissipation of PMF
- What is the result?
- Is it physiological or not?
- 2,4-dinitrophenol (DNP) & other acidic aromatic compounds
- What changes happen? ↑ O2 consumption, ↑NADH oxidation
- Soviet soldiers were given DNP, FDA banned DNP (1938)



2,4-Dinitrophenol (DNP)



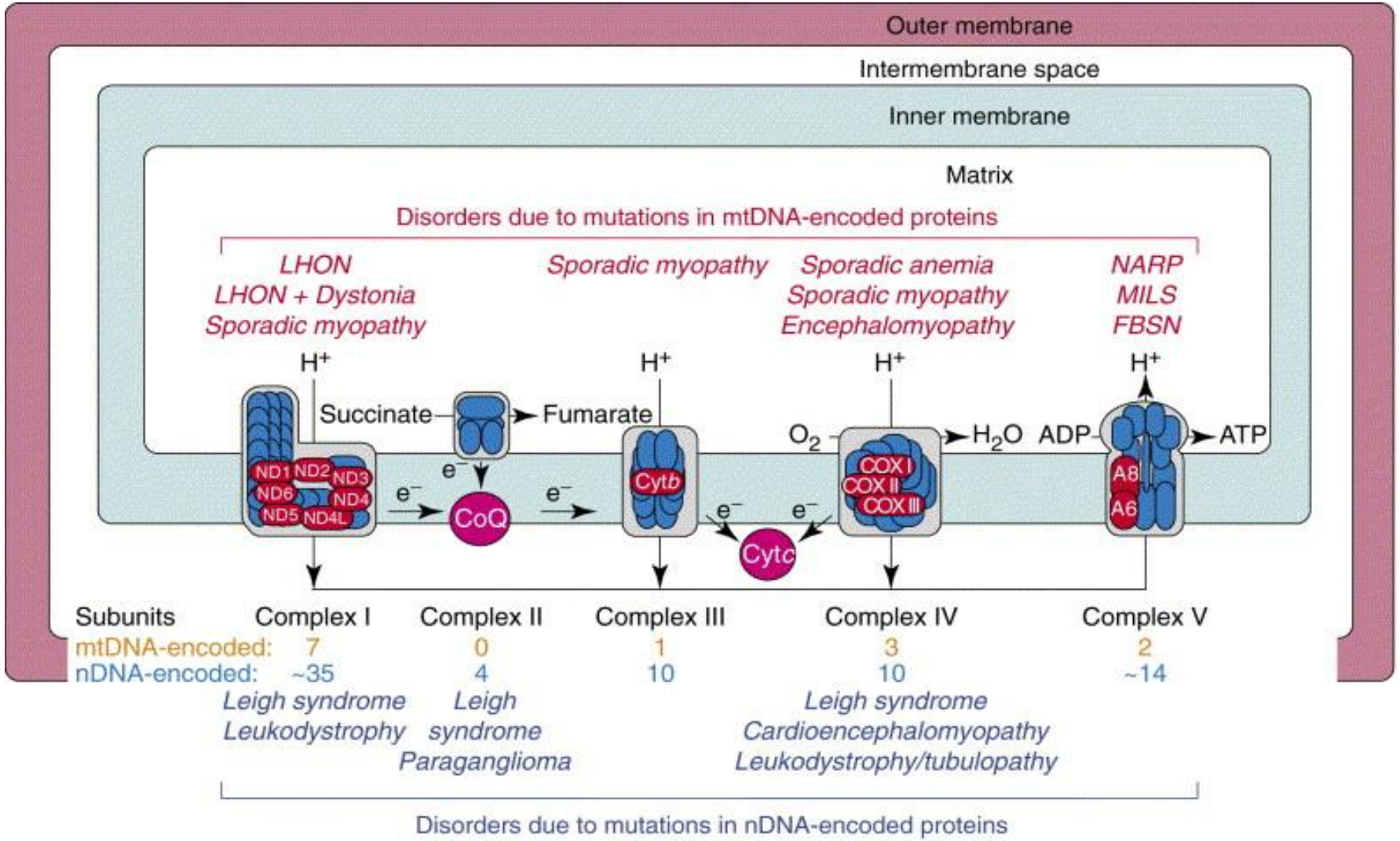
OxPhos Diseases (Genetic)

- A. Mitochondrial DNA and OXPHOS Diseases
  - ✓ Small (16,569) base pair, double-stranded, circular DNA
  - ✓ Encodes 13 subunits: 7 (I) , 1 (III), 3 (IV), 2 (Fo)
  - ✓ Also encodes necessary components for translation of its own mRNA: a large and small rRNA and tRNAs
  - ✓ Maternal inheritance, replicative segregation & heteroplasmy
  - ✓ Accumulation of somatic mutations with age
  - ✓ Highest ATP demands: CNS, heart, skeletal muscle, and kidney, liver

OxPhos Diseases (Genetic)

- B. Nuclear Genetic Disorders of Oxidative Phosphorylation
  - ✓ 1,000 proteins
  - ✓ Usually autosomal recessive
  - ✓ Expressed in all tissues
  - ✓ Phenotypic expression with high ATP demand

OxPhos Diseases (Genetic)



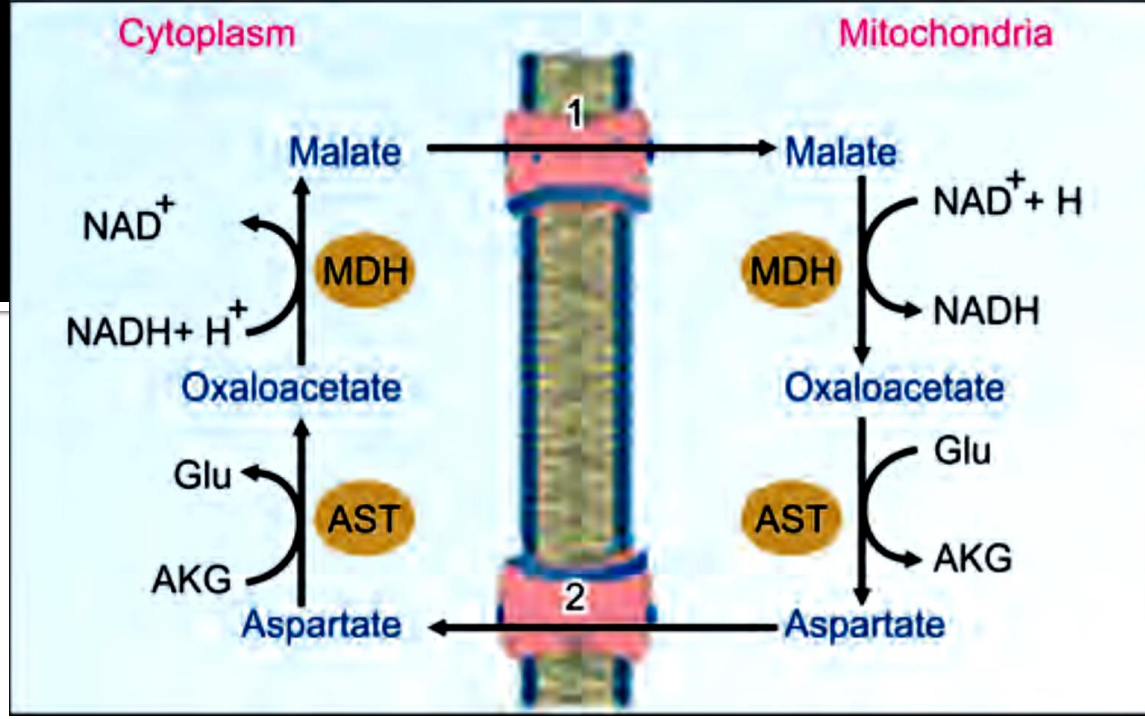
Some NADH producing enzymes

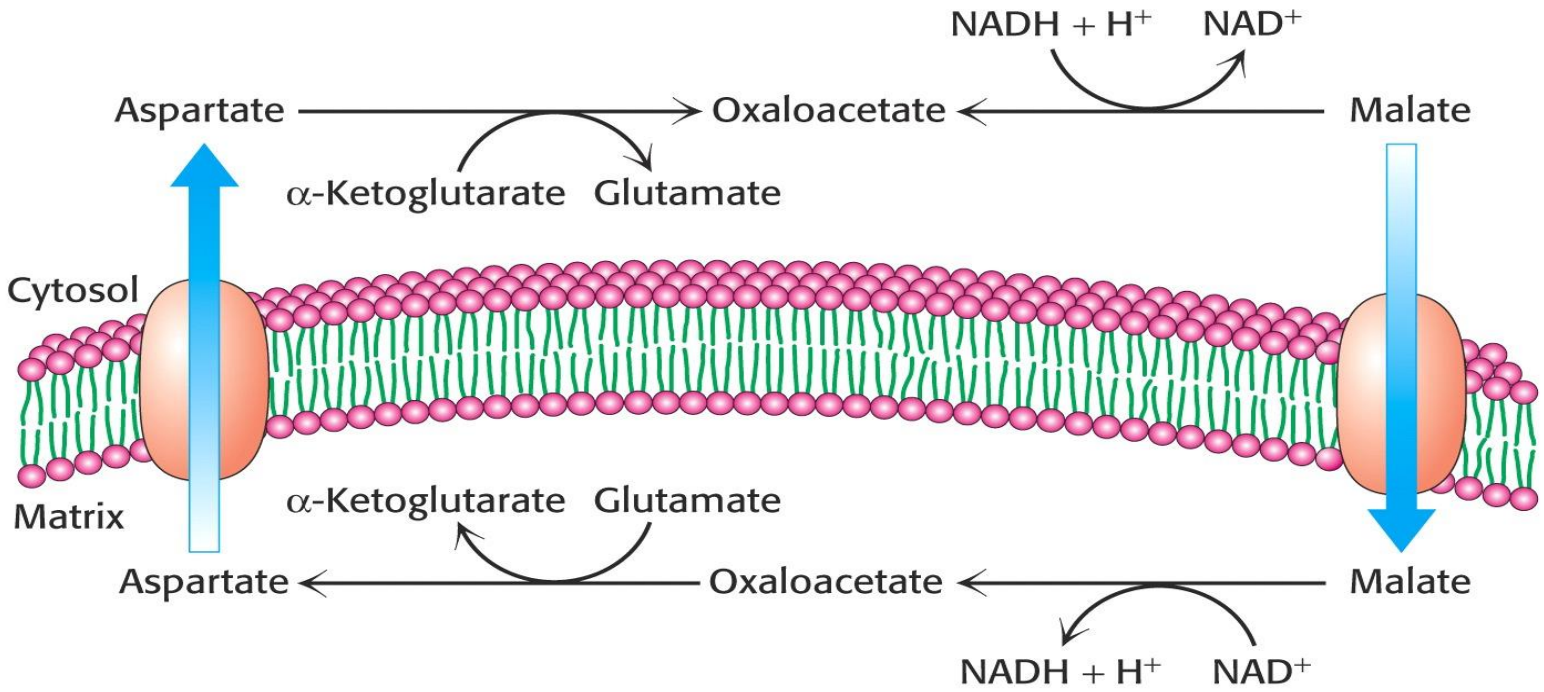
Box 37.3: NAD^+ dependent enzymes

1. Lactate dehydrogenase (lactate → pyruvate) (see Fig. 9.14)
2. Glyceraldehyde-3-phosphate dehydrogenase (glyceraldehyde-3-phosphate → 1,3-bisphosphoglycerate) (see Fig.9.10)
3. Pyruvate dehydrogenase (pyruvate → acetyl CoA) (see Fig.9.22)
4. Alpha ketoglutarate dehydrogenase (alpha ketoglutarate → succinyl CoA) (see Fig.19.2)
5. Beta hydroxyacyl CoA dehydrogenase (beta hydroxyacyl CoA → beta ketoacyl CoA (see Step 3, Fig.12.9)
6. Glutamate dehydrogenase (Glutamate → alpha ketoglutarate (see Fig.15.9)

Mitochondrial shuttling systems - "Cytosolic NADH"

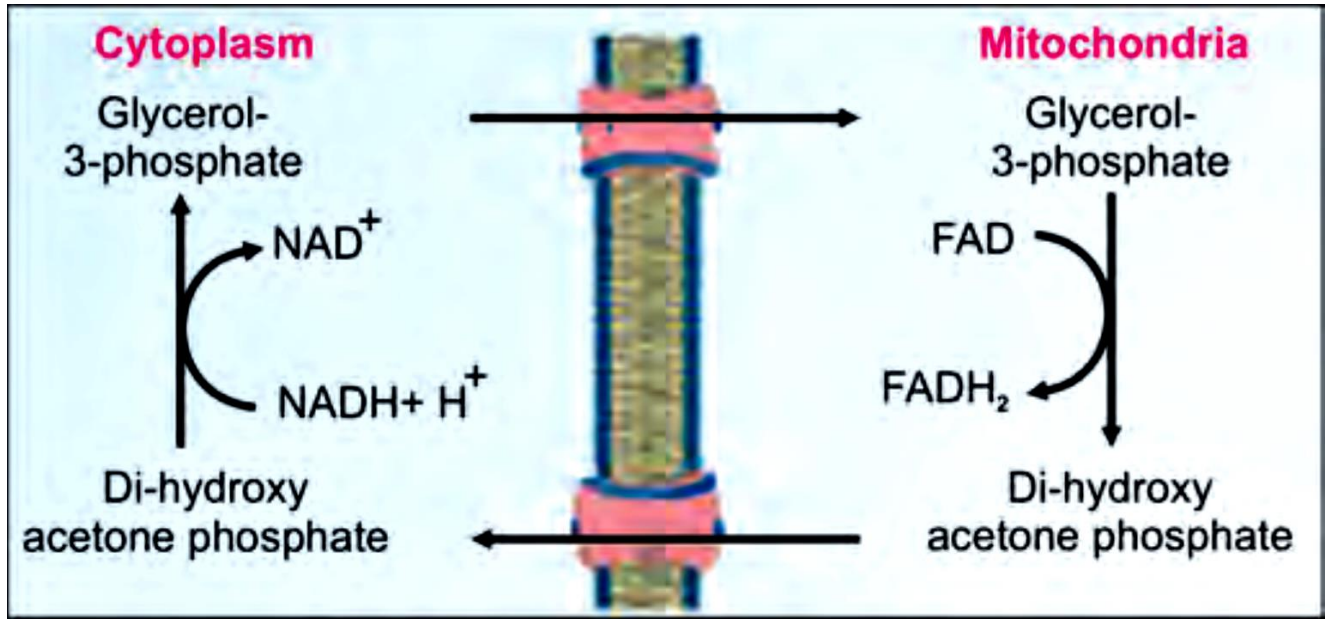
- Malate-Aspartate shuttle
- Operates mainly in liver, kidney and heart
- 2 membrane carriers & 4 enzymes
- Readily reversible (vs. Glycerol 3-phosphate shuttle)
- NADH can be transferred only if the NADH/NAD+ ratio is higher in the cytosol than in the mitochondrial matrix
- Exchange of key intermediates between mitochondria & cytosol

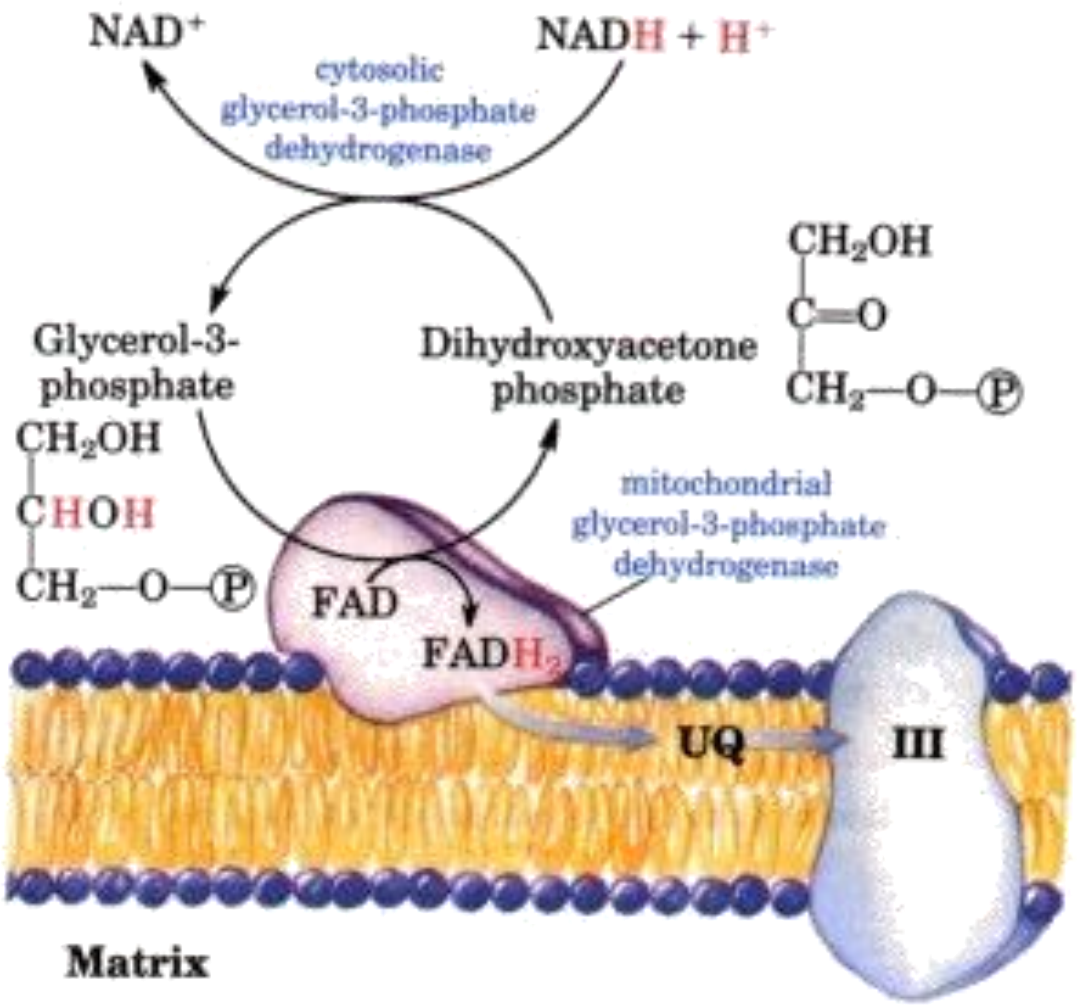




Mitochondrial shuttling systems "Cytosolic NADH"

- Glycerol 3-phosphate shuttle
- In skeletal muscle and brain
- Glycolytic pathway as an example
- How NADH passes?
- ATP yield?





Mitochondrial shuttling systems "ATP/ADP"

- ATP-ADP Translocase (also called adenine nucleotide translocase or ANT)
- The flows of ATP and ADP are coupled (ADP enters only if ATP exits, and vice versa)
- Highly abundant (14% of IMM proteins)

- Contains a single nucleotide-binding site (alternates)
- Similar affinity to ATP and ADP
- Endergonic (25% of ETC)
- Inhibition leads to subsequent inhibition of cellular respiration