بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Cytology & Molecular Biology | Lecture 5

Mitochondrial diseases

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Mitochondrial diseases

General information

In general, it contains a good mix of mitochondria with good DNA.
- Some of them have defective DNA (a lot of mutations), as we mentioned previously,
- Mitochondria can fuse together, so a sort of **repair** to mitochondrial DNA occurs.

- The **mammalian oocyte** (the source of mitochondria for humans) contains around **10^5–10^8 mitochondria**, and each mitochondrion contains **2–10 copies of mitochondrial DNA**.
- As we said, the mitochondrial DNA came from the oocyte, so it's mainly **inherited by the mother**.
- The mitochondrial DNA **can be mutated**.

"With aging, the rate of mitochondrial DNA mutations increases, leading to an accumulation of these mutations."

- If the mitochondrial genomes carry a deleterious mutation, the embryo/fetus would generally not survive.
- Some mothers carry a mixed population of both mutant and normal mitochondrial genomes. Mitochondria can **fuse** and **share their contents**, mixing normal and mutant DNA within a single cell.
- Daughters and sons can inherit this mixture of normal and mutant mitochondrial DNAs and look healthy. If the **normal ones dominate**, they can still produce enough ATP, so the child **appears healthy**, even though they carry some mutant mitochondria.
- In cases of mitochondrial defects, muscle and nervous tissues are most at risk, because of their need for particularly large amounts of ATP

Mitochondria diseases can be classified according to their cause: genetic or biochemical.

The biochemical classification of mitochondrial diseases

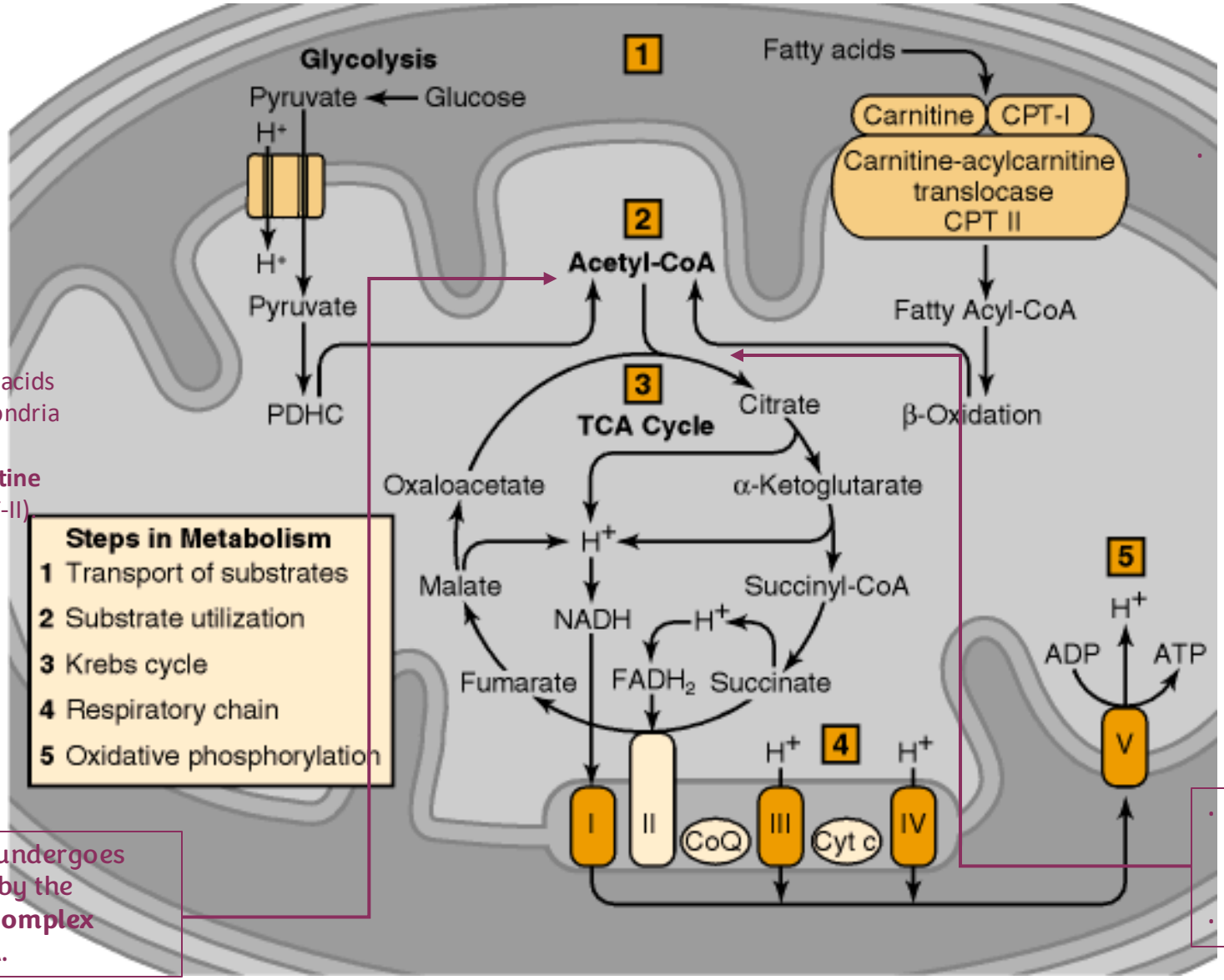
http://www.ncbi.nlm.nih.gov/books/NBK27914/

Remember the function of the mitochondria⟶ generation of energy via metabolism (break down sugars and fatty acids)

1.First, energy substrates like pyruvate and fatty acids are transported from the cytosol into the mitochondria through specific carriers. Long-chain fatty acids require the carnitine shuttle to cross the inner membrane.

- Pyruvate (from glycolysis) and fatty acids (from cytoplasm) enter the mitochondria through specific transport systems.
- Long-chain fatty acids use the **carnitine shuttle** (CPT-I → translocase → CPT-II).

2. Once inside, pyruvate and fatty acids are converted into Acetyl-CoA – the key molecule that enters the TCA cycle. This step provides the fuel for further oxidation.



- Fatty acids undergo **β-oxidation**, removing two carbons at a time to form Acetyl-CoA.

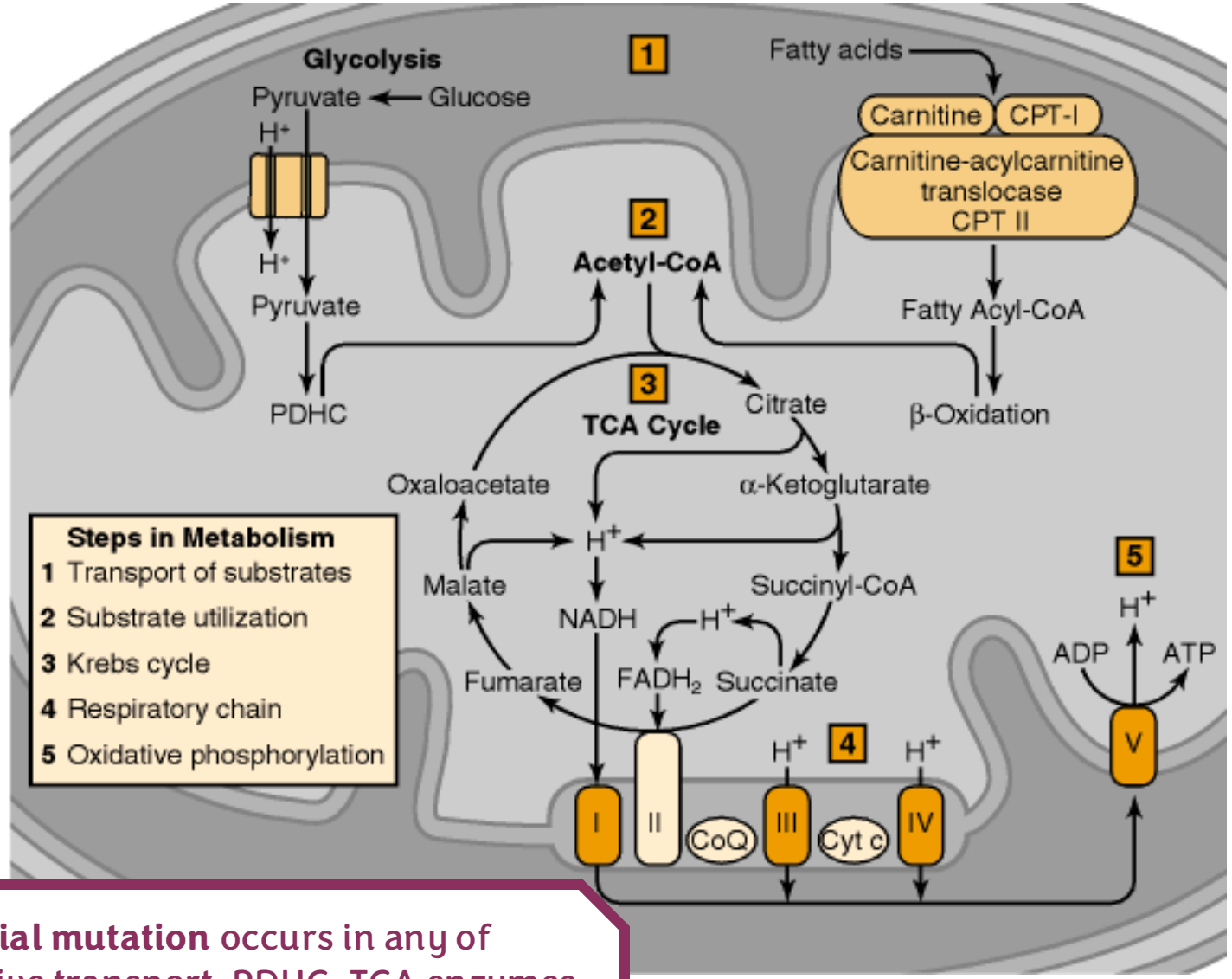
3. In the TCA cycle, Acetyl-CoA is oxidized completely, producing high-energy electron carriers – NADH and $FADH_2$ – which are essential for ATP generation."

- Inside the matrix, pyruvate undergoes **oxidative decarboxylation** by the **Pyruvate Dehydrogenase Complex (PDHC)** to form **Acetyl-CoA**.

- Acetyl-CoA combines with oxaloacetate to form **citrate** and goes through multiple reactions.
- Produces **NADH**, **$FADH_2$**, and **ATP**

4. The electrons from NADH and $FADH_2$ move through the respiratory chain complexes, creating a proton gradient across the inner mitochondrial membrane

- Electrons from NADH and $FADH_2$ pass through complexes I–IV.
- This flow of electrons drives **proton (H^+) pumping** into the intermembrane space.



5. Finally, protons flow back into the matrix through ATP synthase, coupling oxidation with phosphorylation — this step produces ATP, the energy currency of the cell

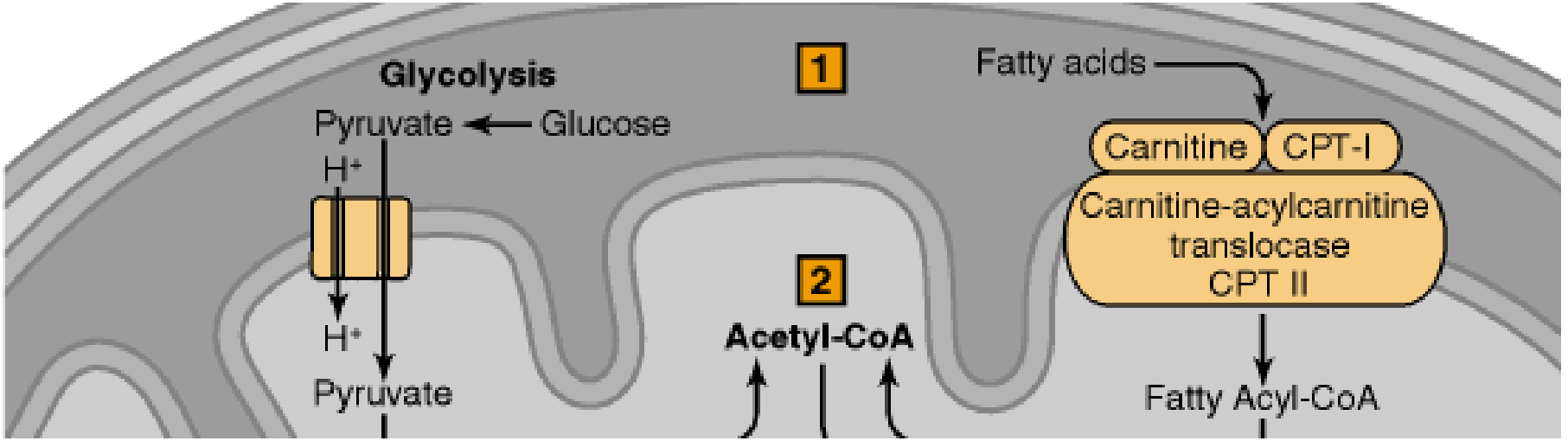
- Protons return through **ATP synthase (Complex V)**.
- This coupling of electron transport and proton flow drives **ATP synthesis**.

If a **deleterious mitochondrial mutation** occurs in any of these steps — such as defective transport, PDHC, TCA enzymes, or ETC complexes — energy production fails.
Tissues with high energy demands, like **muscle and nervous tissue**, are the most affected

Defects of mitochondrial transport

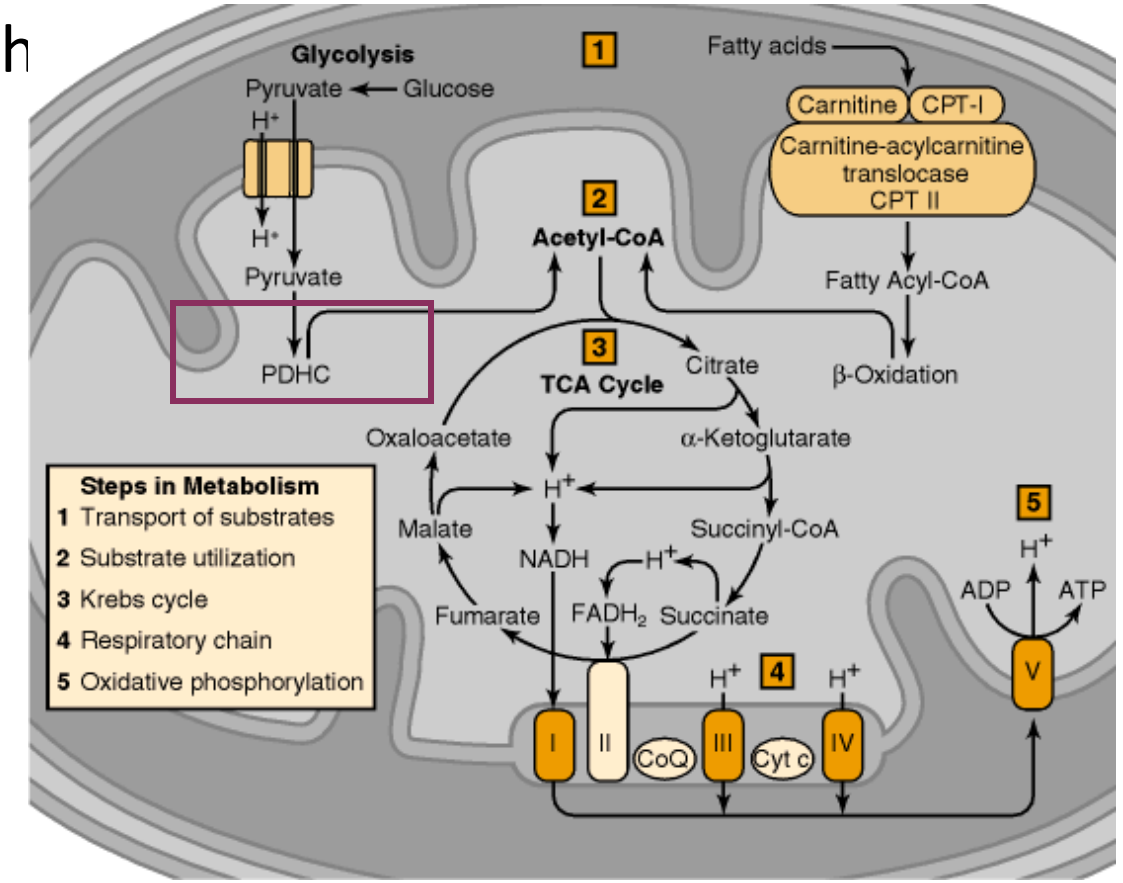
The transport system can be defective

- interfere with the movement of molecules across the inner mitochondrial membrane, which is tightly regulated by specific translocation systems.



Substrate utilization

- Pyruvate dehydrogenase (PDH) deficiency can cause alterations of pyruvate metabolism.
- The PDH complex (PDHC) catalyzes th to acetyl-CoA.



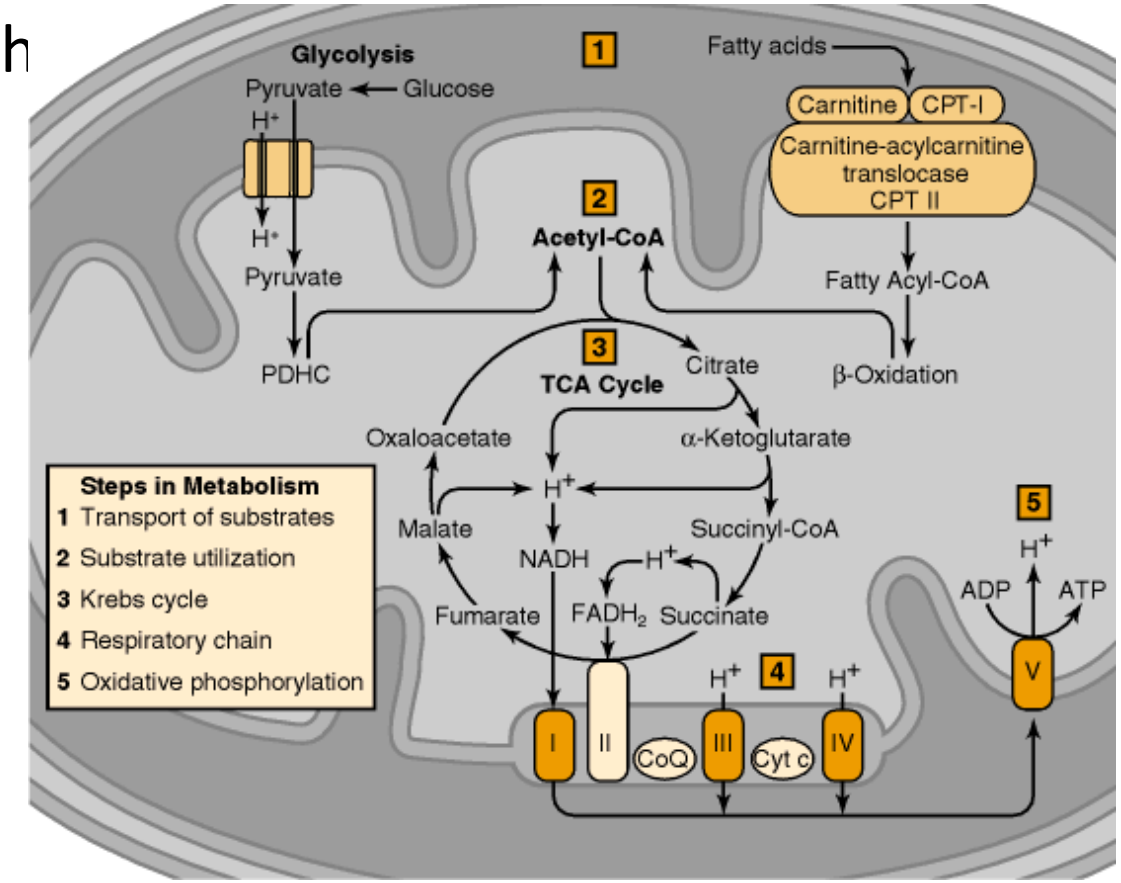
If a defect occurs in this complex (PDHC) , aerobic metabolism cannot be completed. As a result, pyruvate accumulates and is converted to lactate.

The purpose of this conversion is to regenerate NAD^+. However, since lactate is an acidic molecule, this leads to increased levels of pyruvate, lactate, and alanine.
Alanine increases because pyruvate is converted to alanine via transaminase enzymes.
Even in the case of fatty acid metabolism, the cell must have an alternative plan to produce energy."

Substrate utilization

- Pyruvate dehydrogenase (PDH) deficiency can cause alterations of pyruvate metabolism.
- The PDH complex (PDHC) catalyzes th to acetyl-CoA.

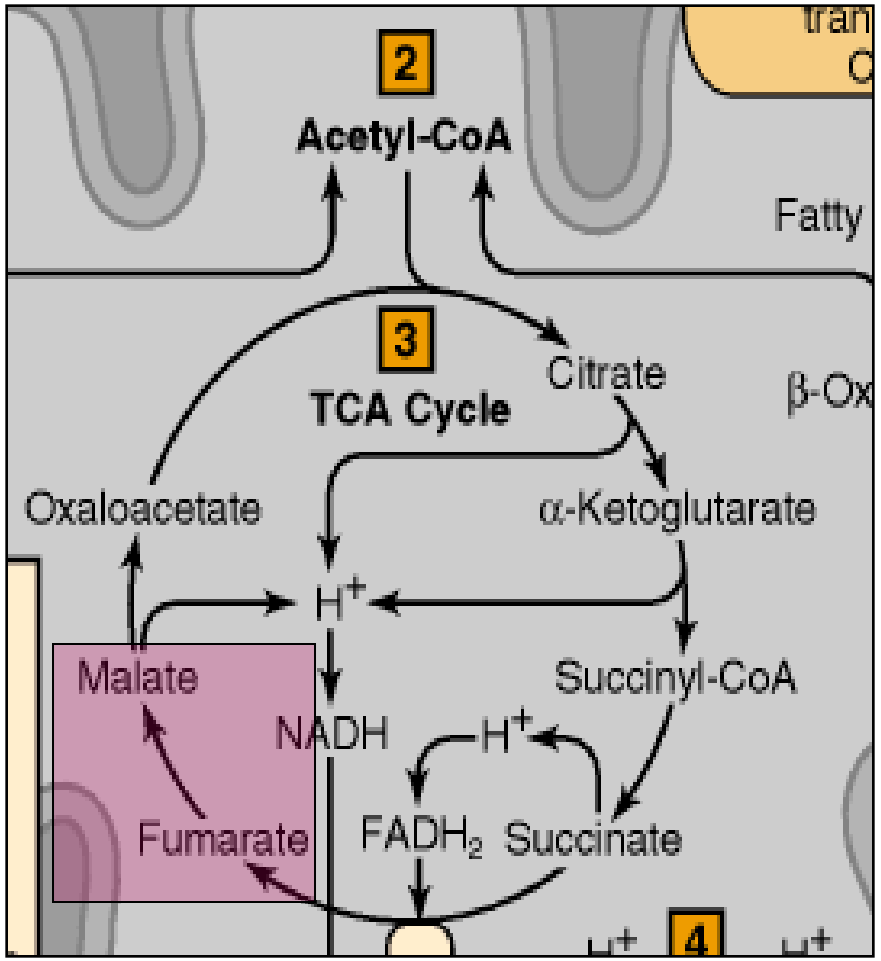
- **The most devastating phenotype of PDH deficiency presents in the newborn period.**
- **The majority of patients are male with severe metabolic acidosis, elevated lactate in blood or CSF, and associated elevations of pyruvate and alanine.**



Defects of the Krebs cycle

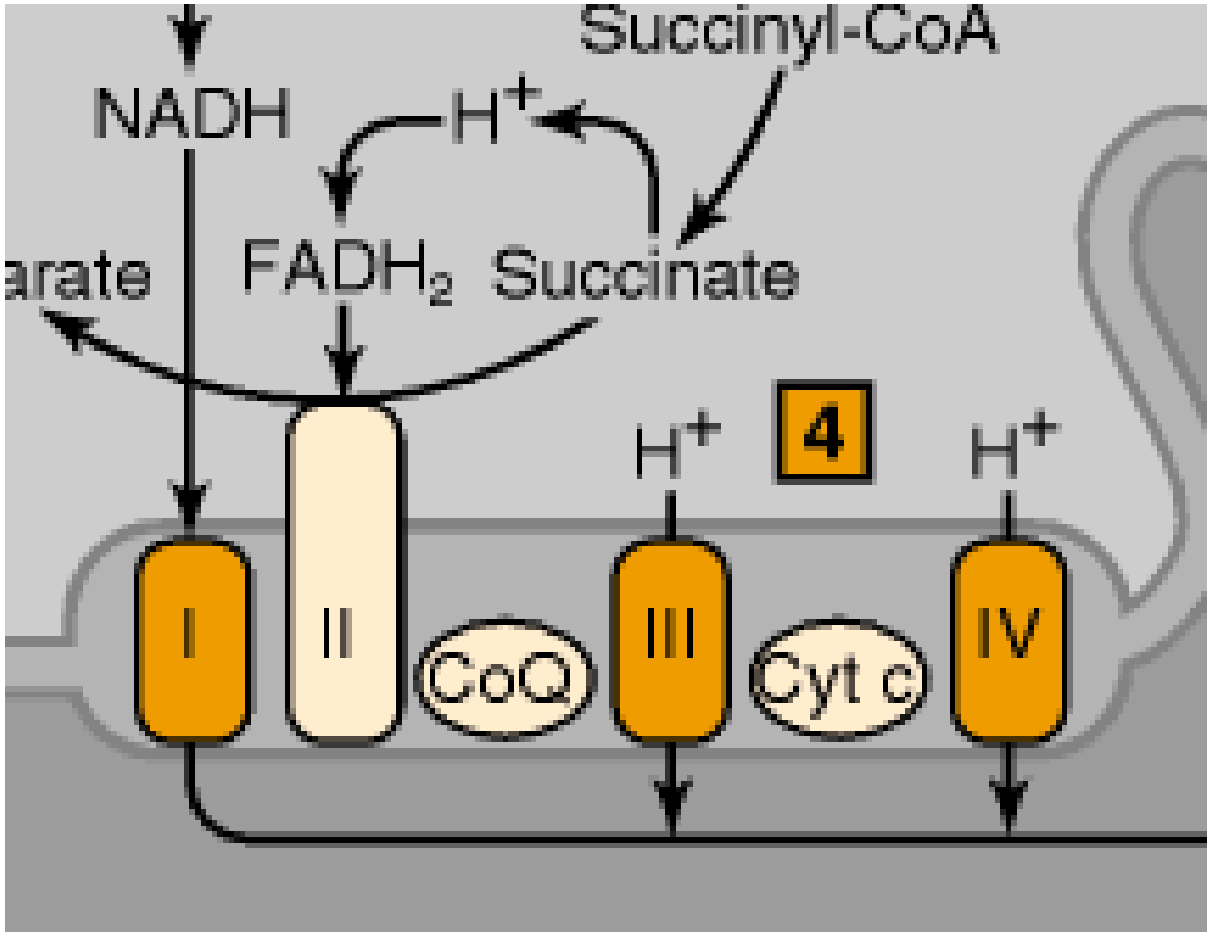
Each step in the Krebs cycle is catalyzed by an enzyme, so defects can occur in any of them.
One important defect is **fumarase deficiency**, which converts fumarate to malate.
When fumarase is defective, **fumarate and succinate accumulate** and are excreted in the urine.

- Fumarase deficiency is reported in patients having mitochondrial encephalomyopathy.
- Features: excretion of large amounts of fumarate and, to a lesser extent, succinate in the urine.



Abnormalities of the respiratory chain reaction

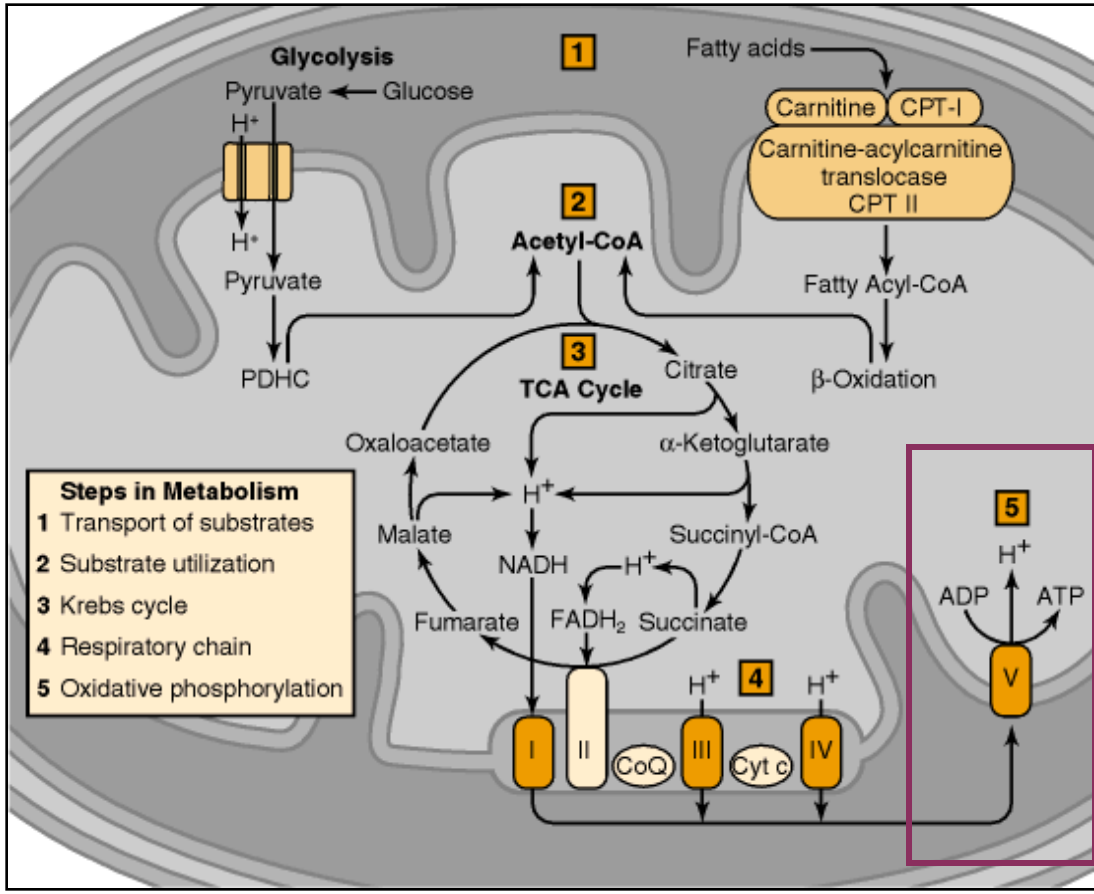
- Defect in any of the 4 electron chain complexes have been reported.



Defects of oxidation-phosphorylation coupling

- *The coupling of phosphorylation and oxidation involves the transport of electrons and the formation of a proton gradient across the inner mitochondrial membrane to form ATP.*
- *If the defect is in ATPase, the electron transport chain continues working nonstop, but ATP will not be produced.*

- The best-known example of such a defect is Luft's disease, or nonthyroidal hypermetabolism.
- Respiratory rate is at a maximal rate even in the absence of ADP, an indication that respiratory control is lost.
  The continuous proton gradient formation leads to heat production and increased metabolism (hypermetabolism) since the energy is released as heat instead of stored as ATP.
- Respiration proceeds at a high rate independently of phosphorylation, and energy is lost as heat, causing hypermetabolism and hyperthermia.



These are the biochemical causes of mitochondrial diseases.

The genetic classification of mitochondrial diseases

Defects of mitochondrial DNA (mtDNA)

- As we know mitochondria has its own DNA (circular) and there is more than one copy of mtDNA inside each mt .
- The 13 subunits encoded by mtDNA are involved in the electron transport chain complexes I,II, III, and IV.
- These disorders are associated with dysfunction of the respiratory chain because all 13 subunits encoded by mtDNA are subunits of respiratory chain complexes.
- Diseases due to point mutations are transmitted by maternal inheritance. Transmitted by mitochondrial inheritance pattern not x-linked inheritance pattern .

MERRF and others

- One main syndrome is myoclonic epilepsy and ragged red fiber disease (MERRF), which can be caused by a mutation in one of the mitochondrial transfer RNA genes required for the synthesis of the mitochondrial proteins responsible for electron transport and production of ATP.
- Other syndromes include
  - Lactic acidosis and stroke-like episodes (MELAS)
  - Leber's hereditary optic neuropathy (LHON),
  - Neurogenic atrophy, ataxia and retinitis pigmentosa (NARP)
- Memorize the abbreviations of the diseases. You don't have to know the full name.

Leber's hereditary optic neuropathy (LHON)

- caused by a defect in the respiratory chain complexes
- Females (10%) are affected less frequently than males (50%), but males never transmit LHON to their offspring ;because the oocyte is the one that transmits mt and not all individuals with mutations develop the disease.
  - Inheritance is mitochondrial (cytoplasmic) not nuclear.
- The mutations reduce the efficiency of oxidative phosphorylation and ATP generation.

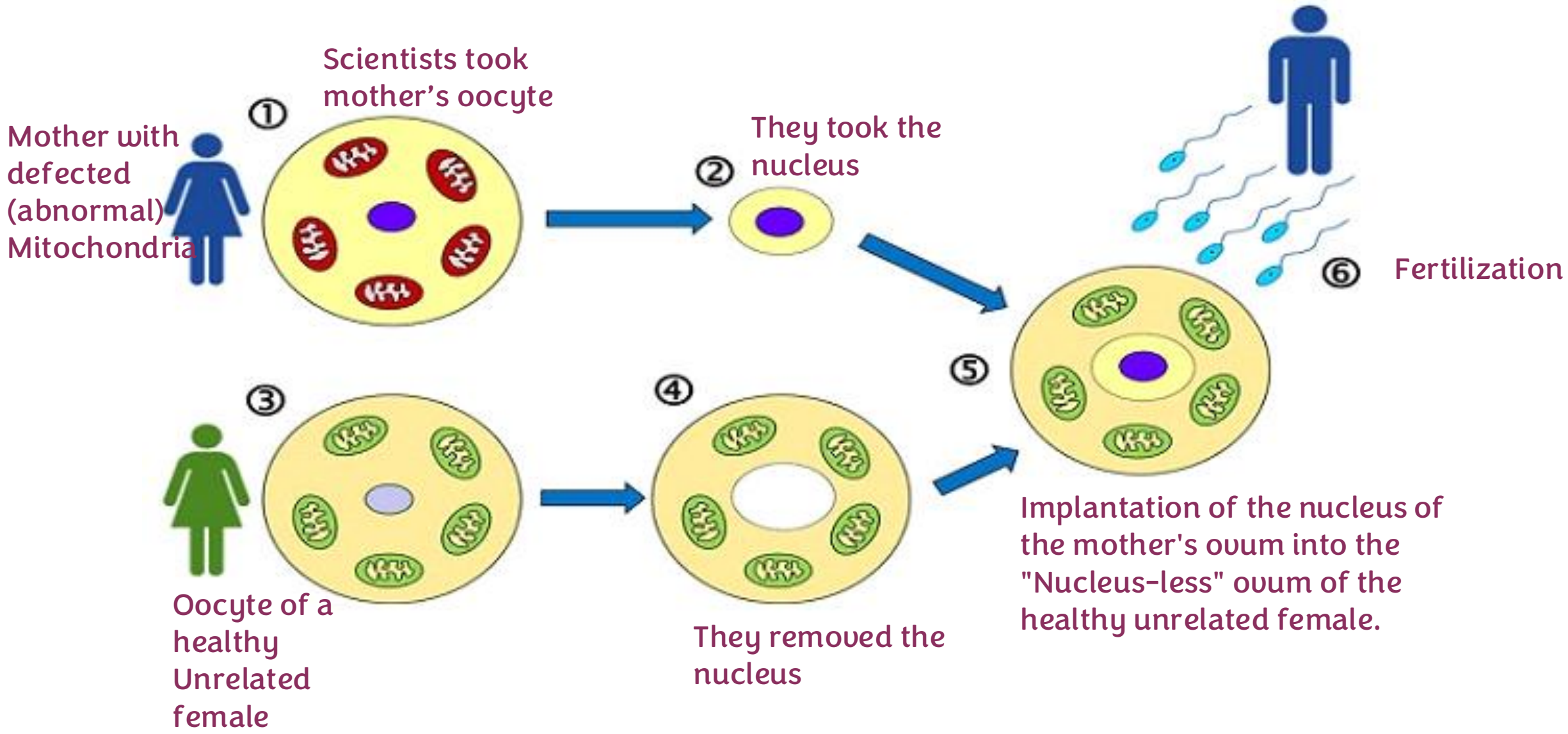
- **A rare inherited disease that results in blindness because of degeneration of the optic nerve.**
- **Vision loss is only manifestation, occurs between 15-35.**

Defects of nuclear DNA

- The vast majority of mitochondrial proteins (1500) are encoded by nuclear DNA.
- **mt diseases are mainly caused by nuclear DNA mutations .**
- **These diseases follow the inheritance pattern (autosomal , X-linked , Y-linked)**
- All areas of mitochondrial metabolism can be affected.

Mitochondrial Replacement Therapy

The baby will have 3 genetic systems (father mother, donor)



Not secure | nationalpost.com/news/world/jordanian-couple-has-baby-using-three-parent-genetic-engineering-but-its-actually-abou

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*The **British**-developed technique was performed in **Mexico** by a **Chinese-American** physician who worked in New York*

Jordanian couple has baby using 'three parent' genetic engineering — but it's actually about 2.001 parents

The Jordanian newborn represents the first successful birth in a new wave of "three parent" techniques, although the procedure is illegal in most countries

This Jordanian newborn represents the first successful birth in a new wave of "three parent" techniques — ones that are more sophisticated, and that will likely stick around much longer.

Additional Resources:

رسالة من الفريق العلمي:

ثم تأتي إرادةُ الله؛ فتتيسّر معسراتك، وتتمهّد الطرق، وتُفتح مغاليقها، وتُهيئ أسبابها، وتتجمّل لتأتيك كاملة تامة مصحوبة بجميل عطاء ربّك.. فلا يغرنك تشتّتها الآن، ولا تحزن لاستحالتها، فوالله لو كان بينك وبينها عوامق البحار، وشواهق الجبال، يأتِ بها الله إنّ الله لطيفٌ خبير.

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	Slide 14	the electron transport chain complexes I, III, IV, and V.	the electron transport chain complexes I,II, III, and IV.
V1 → V2			