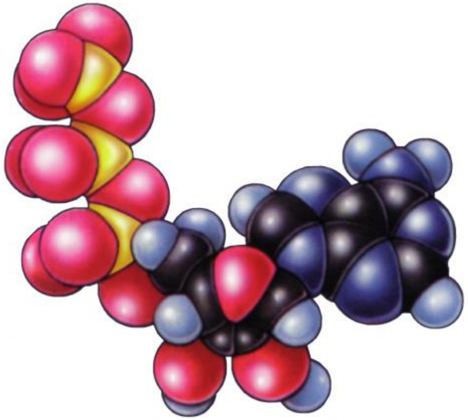
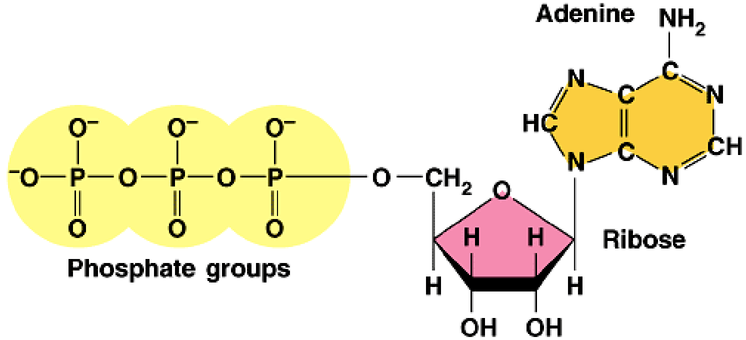
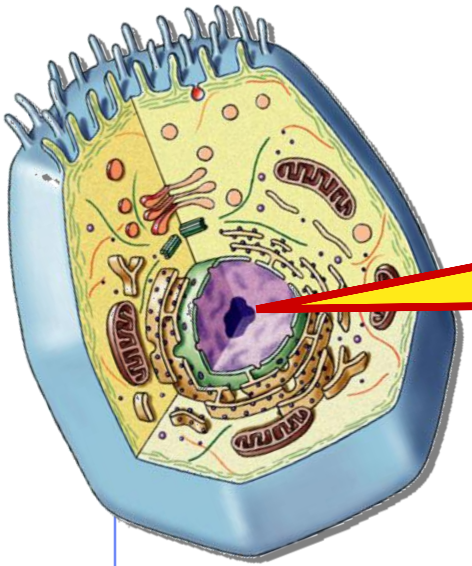


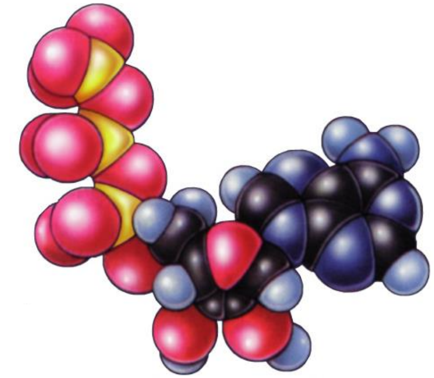


Cellular Respiration
Harvesting Chemical Energy

ATP

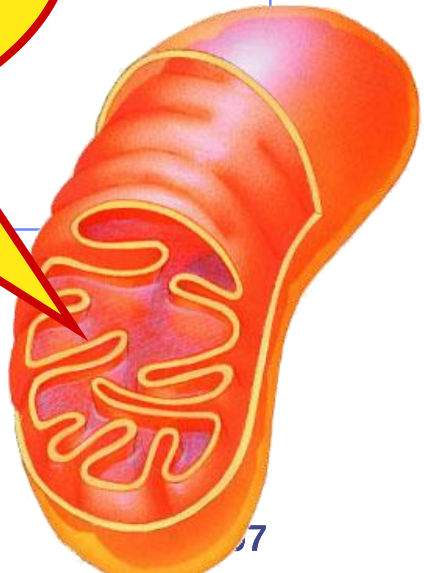


What's the point?



The point is to make **ATP!**

ATP



Harvesting stored energy

- Energy is stored in organic molecules
  - carbohydrates, fats, proteins
- Heterotrophs eat these organic molecules → food
  - digest organic molecules to get…
    - raw materials for synthesis
    - fuels for energy
      - controlled release of energy
      - "burning" fuels in a series of step-by-step enzyme-controlled reactions

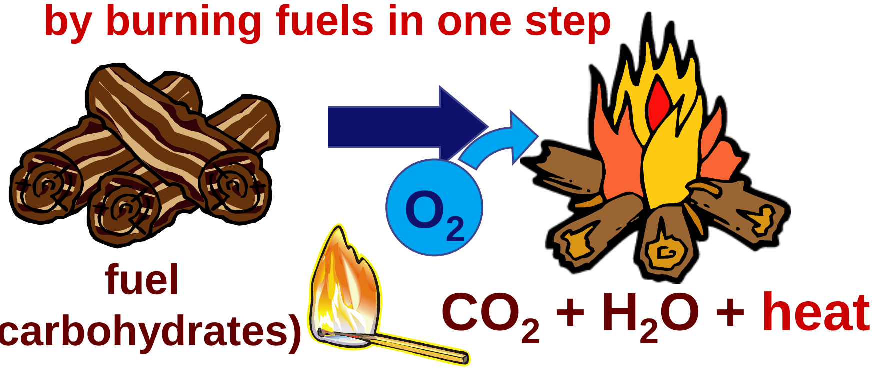

Harvesting stored energy

- **Glucose is the model**
  - **catabolism of glucose to produce ATP**

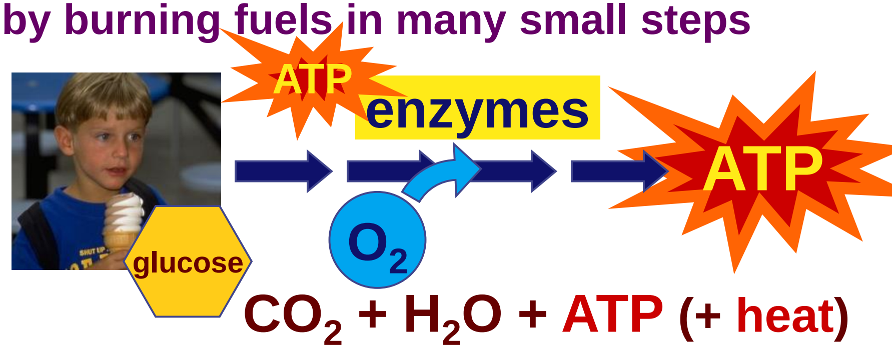
respiration

glucose + oxygen	→	**energy + water + carbon dioxide**		
$C_6H_{12}O_6$ + $6O_2$	→	ATP + $6H_2O$ + $6CO_2$ + heat		

COMBUSTION = making a lot of heat energy by burning fuels in one step

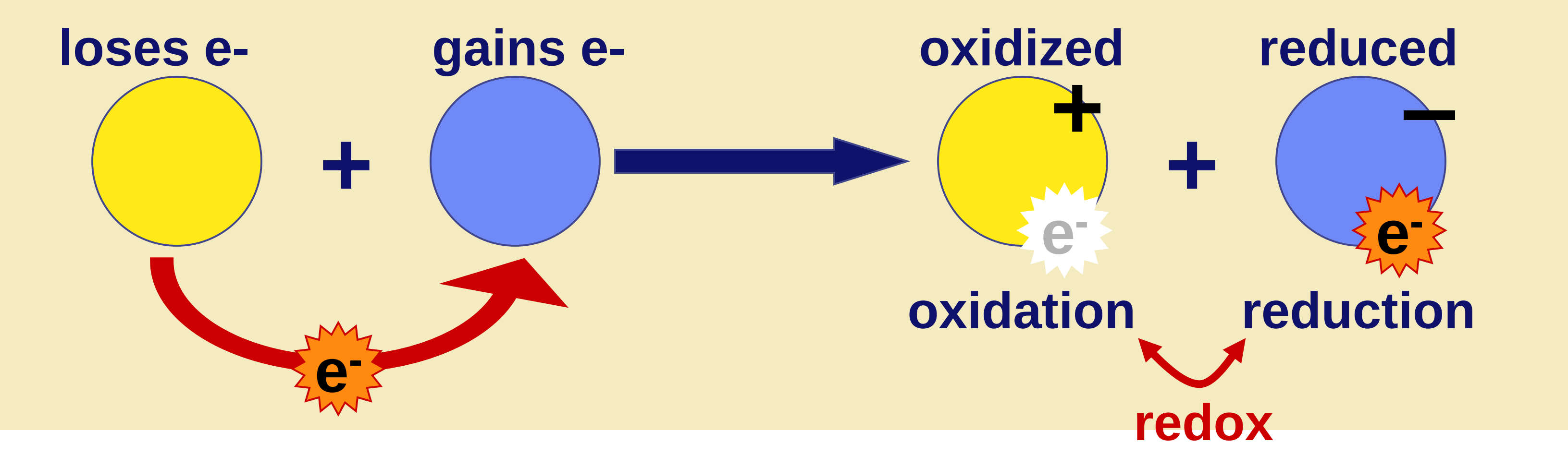


RESPIRATION = making ATP (& some heat) by burning fuels in many small steps



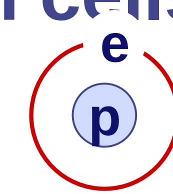
How do we harvest energy from fuels?

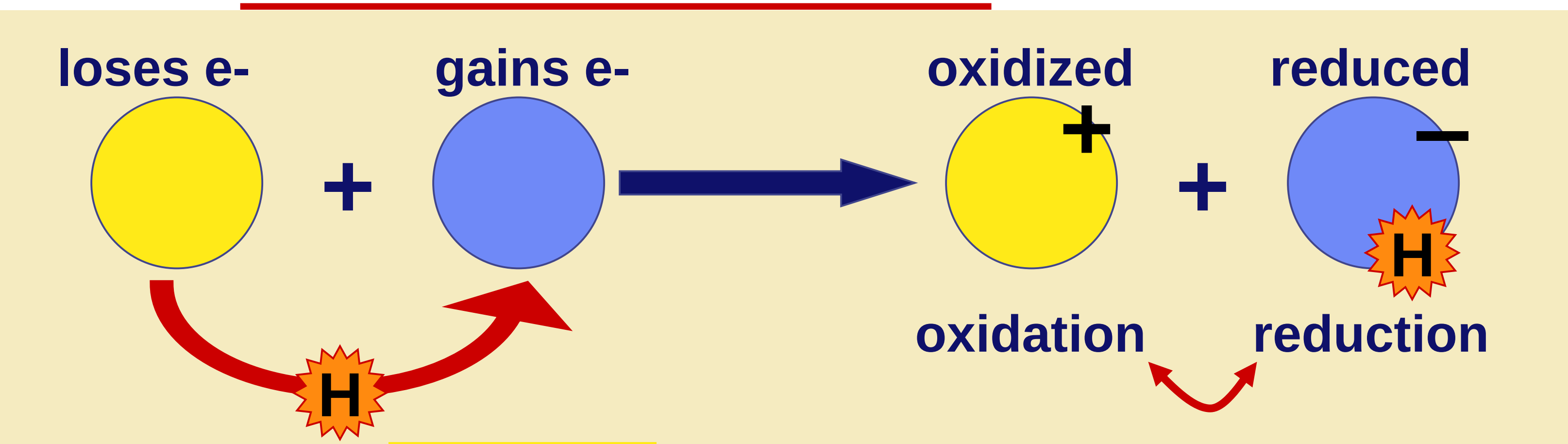
- **Digest large molecules into smaller ones**
  - break bonds & move electrons from one molecule to another
    - as electrons move they "carry energy" with them
    - that energy is stored in another bond, released as heat or harvested to make ATP

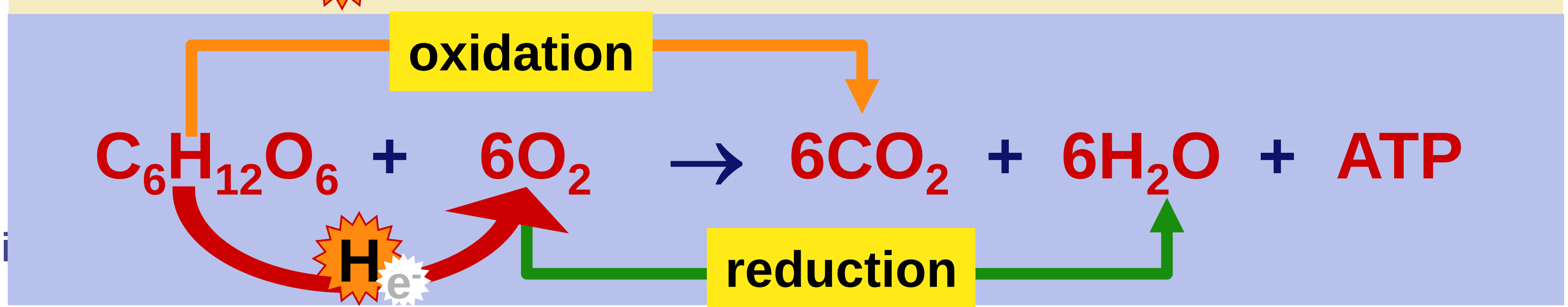


How do we move electrons in biology?

- Moving electrons in living systems
  - electrons cannot move alone in cells
    - electrons move as part of H atom
    - move H = move electrons







Coupling oxidation & reduction

- **REDOX reactions in respiration**
  - release energy as breakdown organic molecules
    - break C-C bonds
    - strip off electrons from C-H bonds by removing H atoms
      - $C_6H_{12}O_6 \rightarrow CO_2$ = the fuel has been <u>oxidized</u>
    - electrons attracted to more electronegative atoms
      - in biology, the most electronegative atom?
      - $O_2 \rightarrow H_2O$ = oxygen has been <u>reduced</u>

O_2

  - <u>couple REDOX reactions & use the released energy to synthesize ATP</u>

oxidation

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O + ATP$$

reduction

Oxidation & reduction

- **Oxidation**
  - adding O
  - removing H
  - loss of electrons
  - releases energy
  - <u>exergonic</u>
- **Reduction**
  - removing O
  - adding H
  - gain of electrons
  - stores energy
  - <u>endergonic</u>

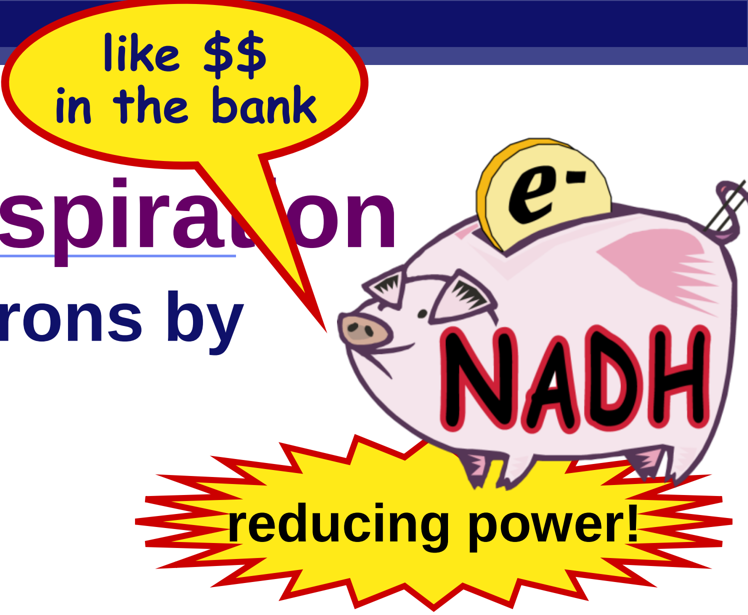
oxidation

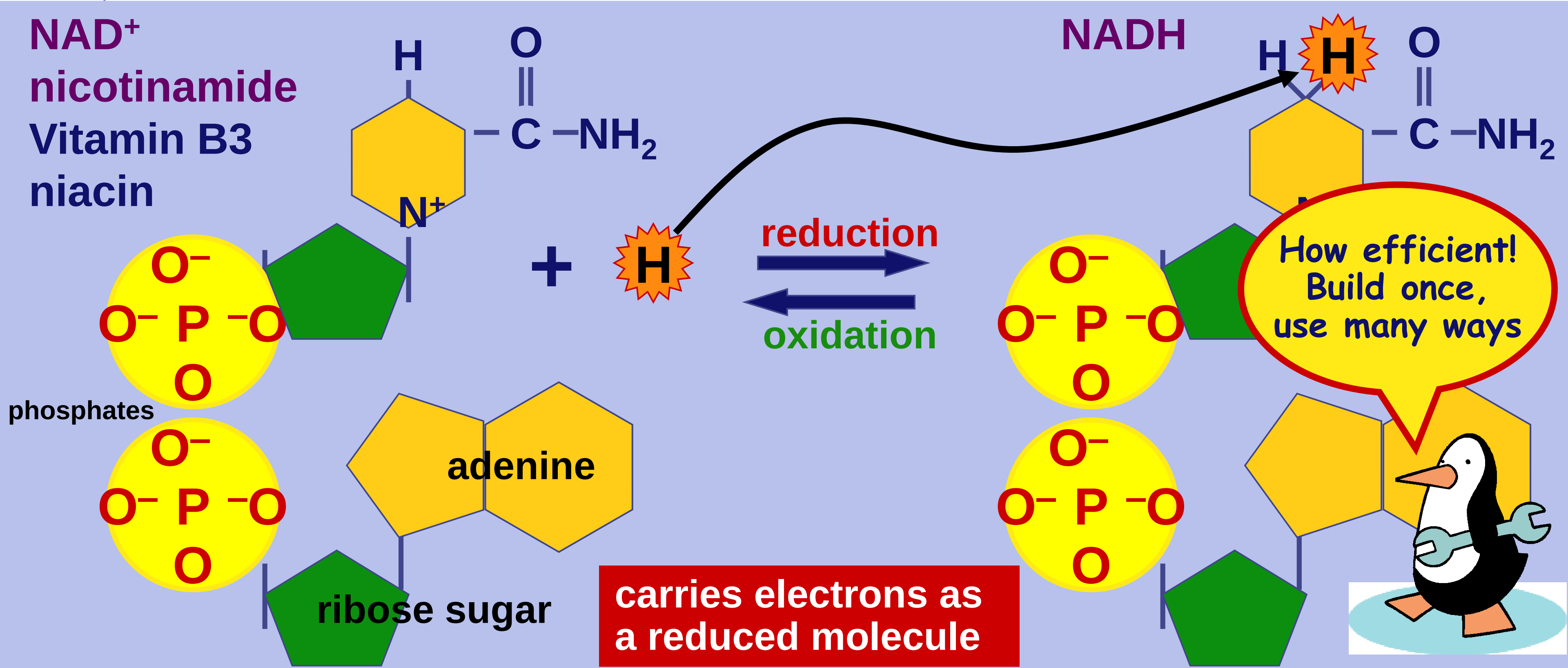
$$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O + ATP$$

reduction

Moving electrons in respiration

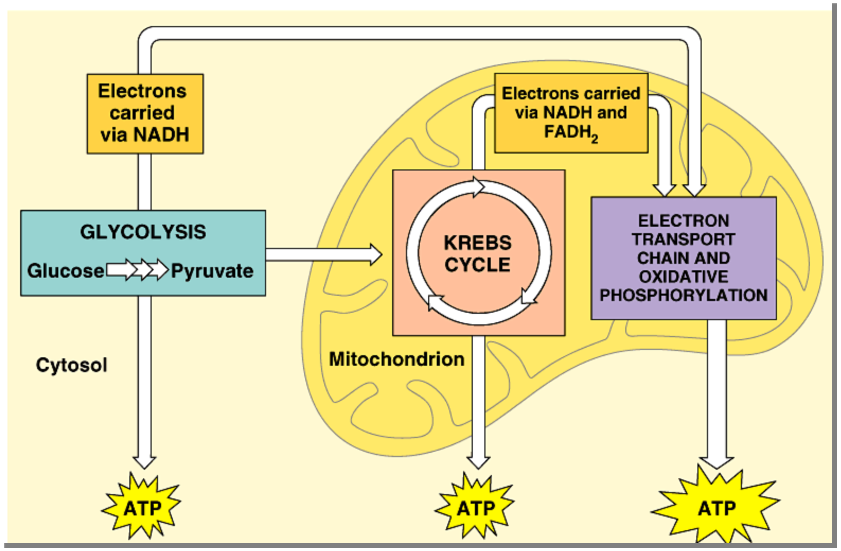
- <u>Electron carriers</u> move electrons by shuttling H atoms around
  - $NAD^+ \rightarrow$ NADH (reduced)
  - $FAD^{+2} \rightarrow FADH_2$ (reduced)



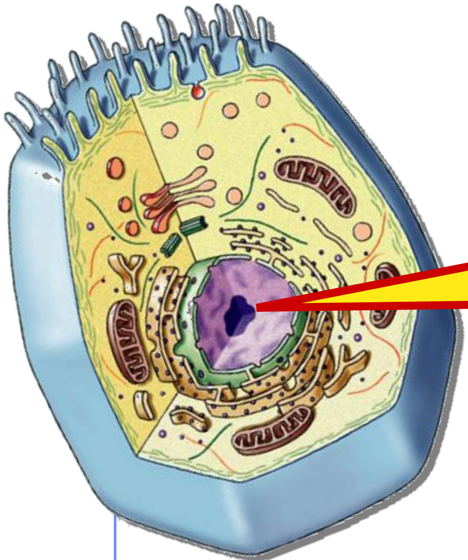


Overview of cellular respiration

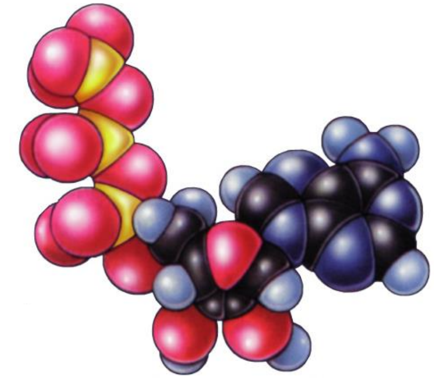
- 4 metabolic stages
  - Anaerobic respiration
    1. Glycolysis
       - respiration without O_2
       - in cytosol
  - Aerobic respiration
       - respiration using O_2
       - in mitochondria
    2. Pyruvate oxidation
    3. Krebs cycle
    4. Electron transport chain



$$C_6H_{12}O_6 + 6O_2 \rightarrow ATP + 6H_2O + 6CO_2 \text{ (+ heat)}$$

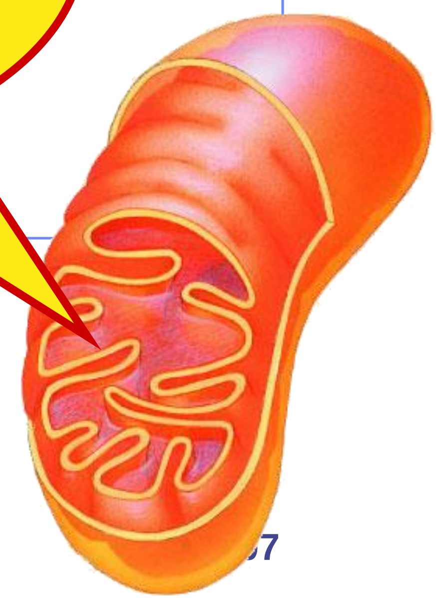


What's the point?



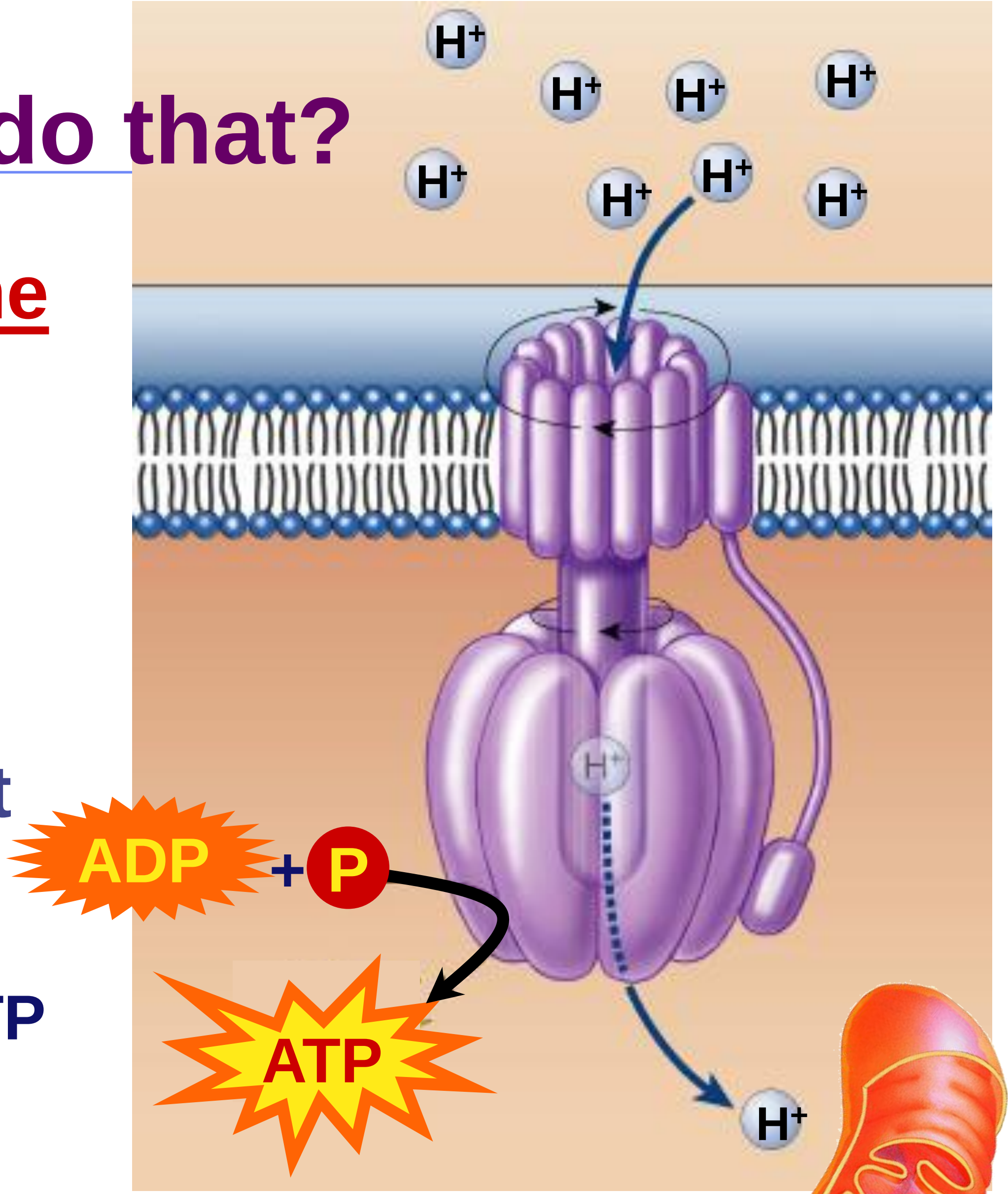
The point is to make ATP!

ATP



And how do we do that?

- <u>ATP synthase enzyme</u>
  - H^+ flows through it
    - conformational changes
    - bond P_i to ADP to make ATP
  - set up a H^+ gradient
    - allow the H^+ to flow down concentration gradient through ATP synthase
    - ADP + P_i → ATP

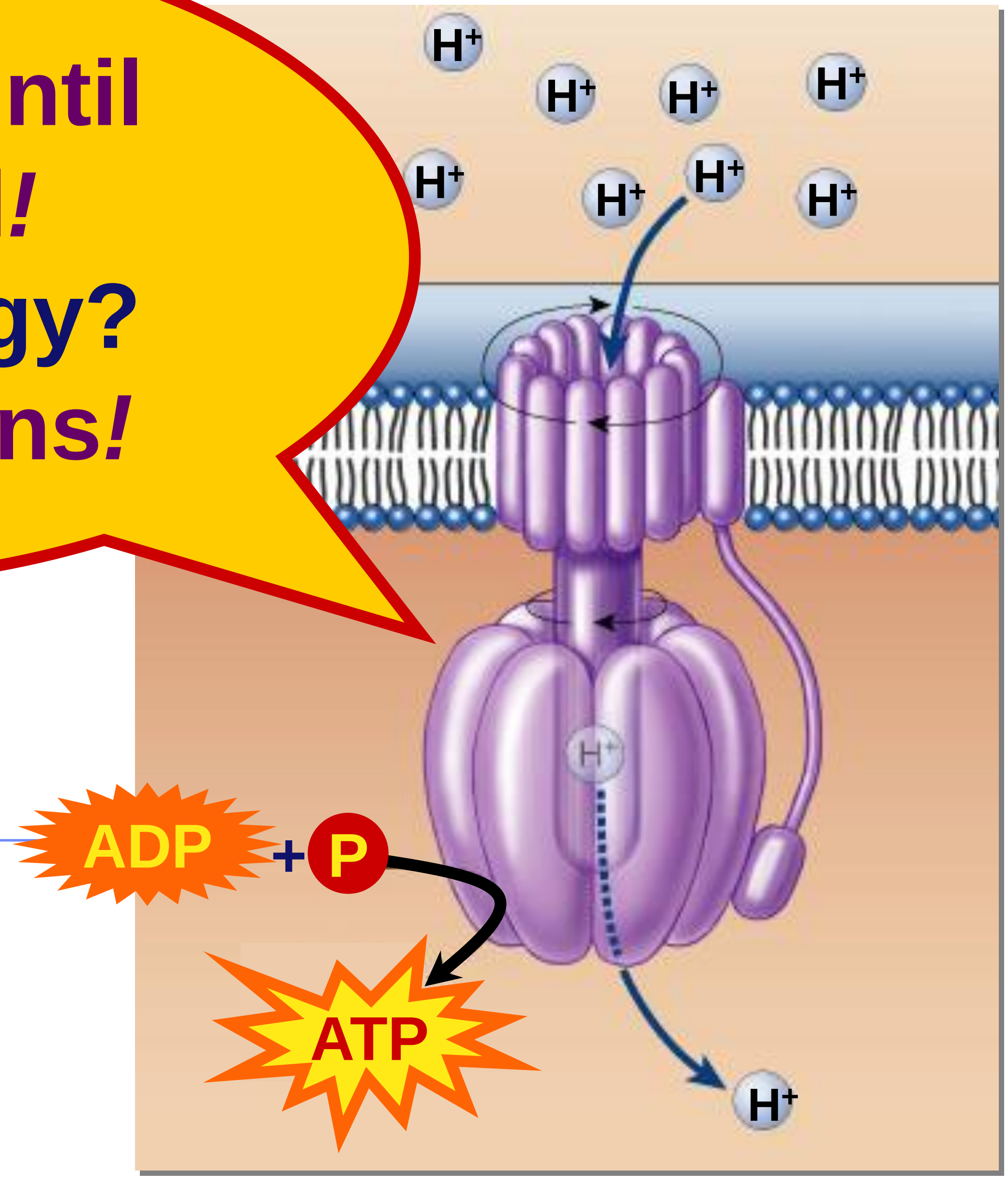


But… How is the proton (H^+) gradient formed?

Got to wait until the sequel!

Got the Energy?

Ask Questions!



Cellular Respiration

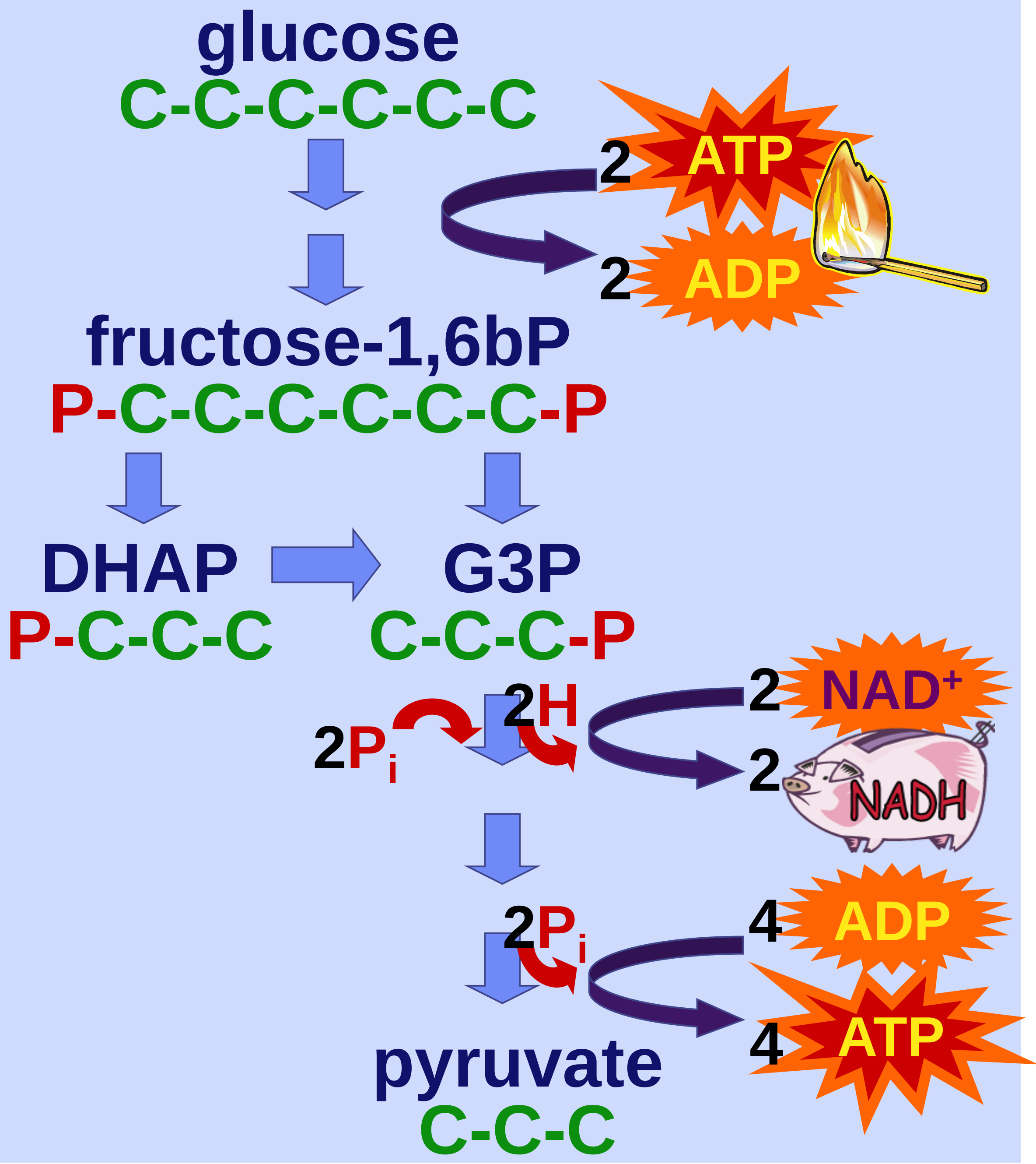
Stage 2 & 3:

Oxidation of Pyruvate
Krebs Cycle

Overview

10 reactions

- convert
  glucose (6C) to
  2 pyruvate (3C)
- produces:
  4 ATP & 2 NADH
- consumes:
  2 ATP
- net:
  2 ATP & 2 NADH



Glycolysis is only the start

- **Glycolysis**

$$\text{glucose} \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \text{pyruvate}$$

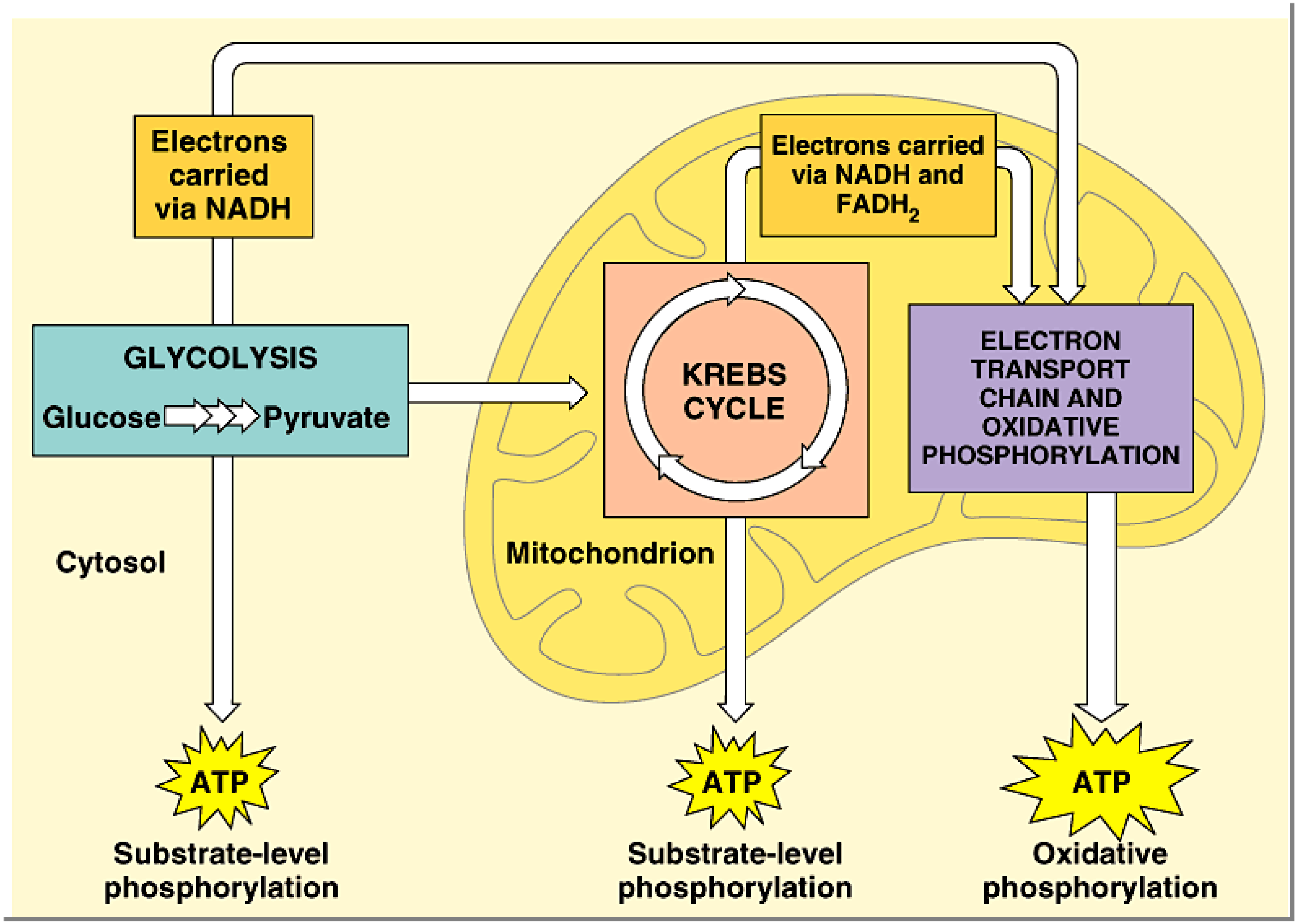
6C → 2x 3C

- **Pyruvate has more energy to yield**
  - 3 more C to strip off (to oxidize)
  - if O_2 is available, pyruvate enters mitochondria
  - enzymes of Krebs cycle complete the full oxidation of sugar to CO_2

$$\text{pyruvate} \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow CO_2$$

3C → 1C

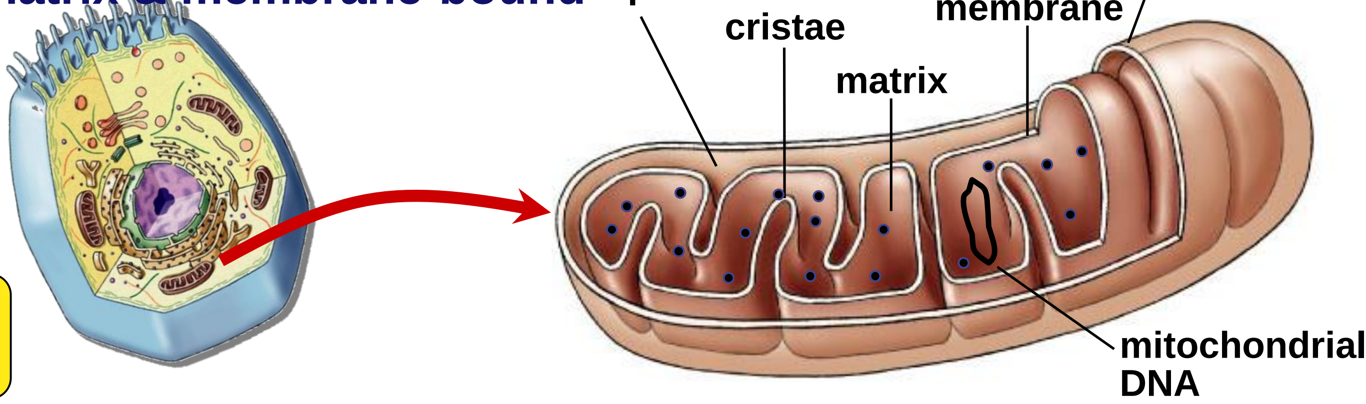
Cellular respiration



Mitochondria — Structure

- Double membrane energy harvesting organelle
  - smooth outer membrane
  - highly folded inner membrane
    - cristae
  - intermembrane space
    - fluid-filled space between membranes
  - matrix
    - inner fluid-filled space
  - DNA, ribosomes
  - enzymes
    - free in matrix & membrane-bound

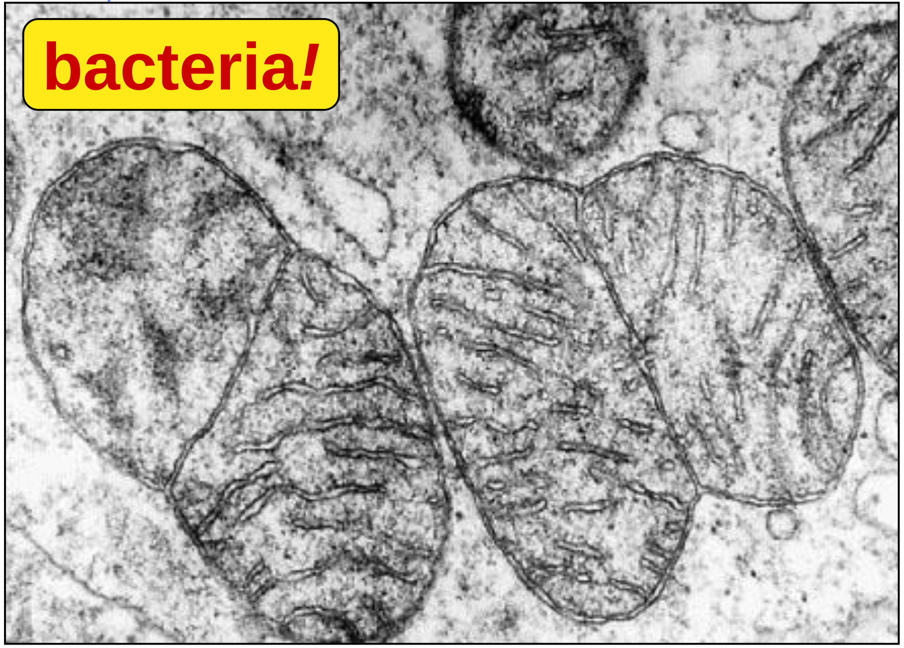
What cells would have a lot of mitochondria?



Mitochondria – Function

Dividing mitochondria

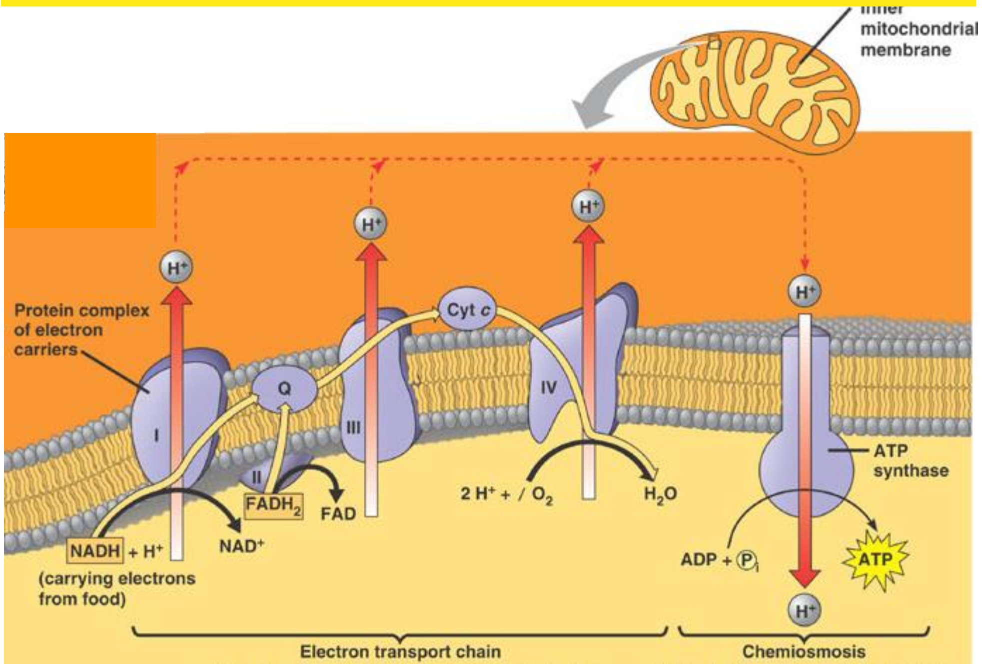
Who else divides like that?



bacteria!

Membrane-bound proteins

Enzymes & permeases



What does this tell us about the evolution of eukaryotes?

Endosymbiosis!

Advantage of highly folded inner membrane?

More surface area for membrane-bound enzymes & permeases

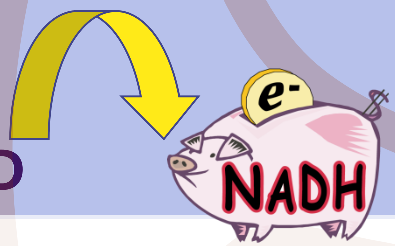
Oxidation of pyruvate

- Pyruvate enters mitochondrial matrix

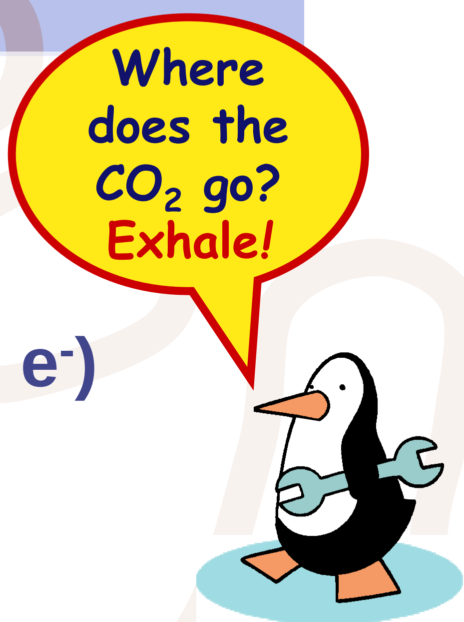
2x [pyruvate → → → acetyl CoA + CO_2]

3C 2C 1C

NAD

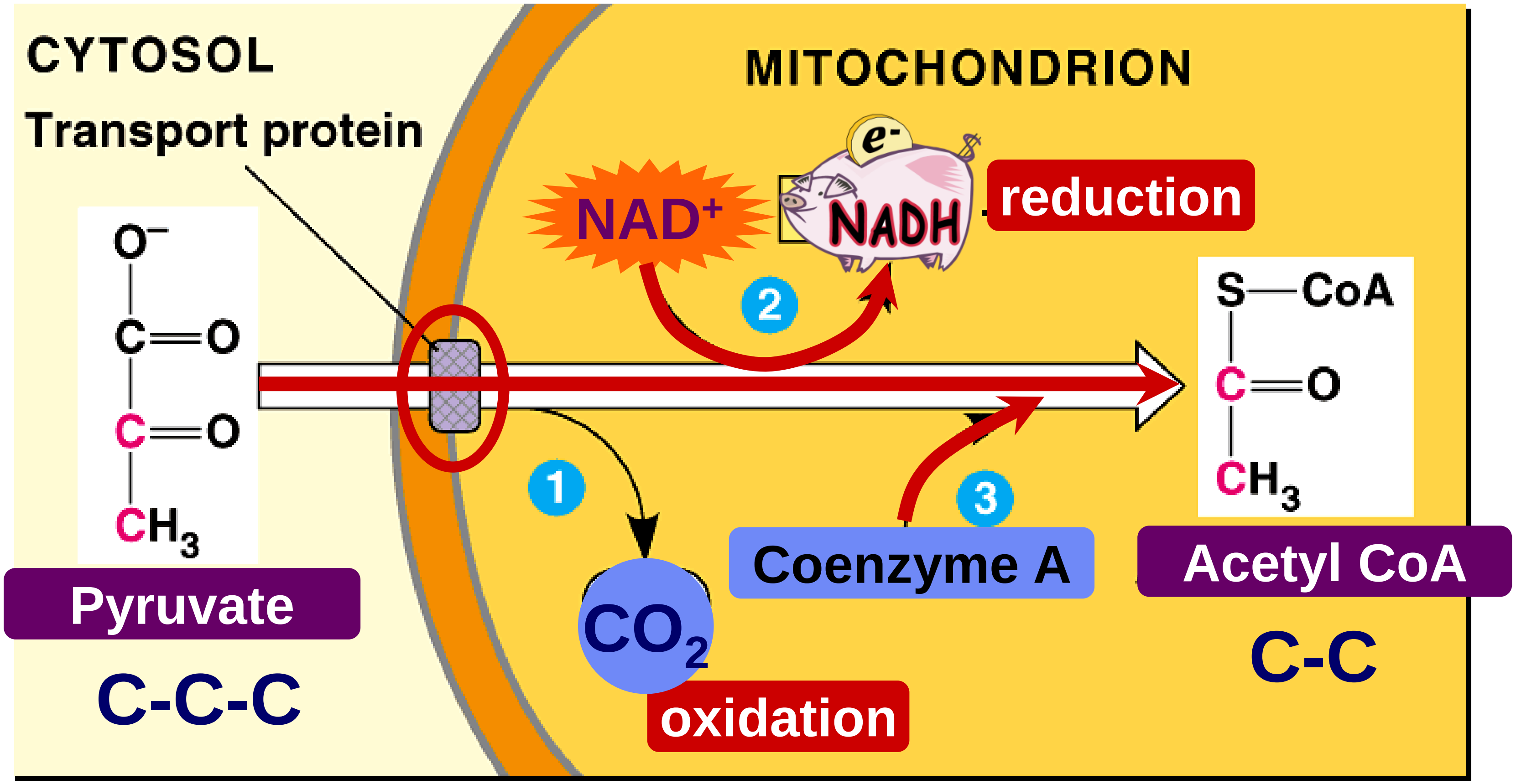


- 3 step **oxidation** process
- releases **2 CO_2** (count the carbons!)
- reduces **2 NAD → 2 NADH** (moves e^-)
- produces **2 acetyl CoA**



- Acetyl CoA enters **Krebs cycle**

Pyruvate oxidized to Acetyl CoA



2 x [Yield = 2C sugar + NADH + CO_2]

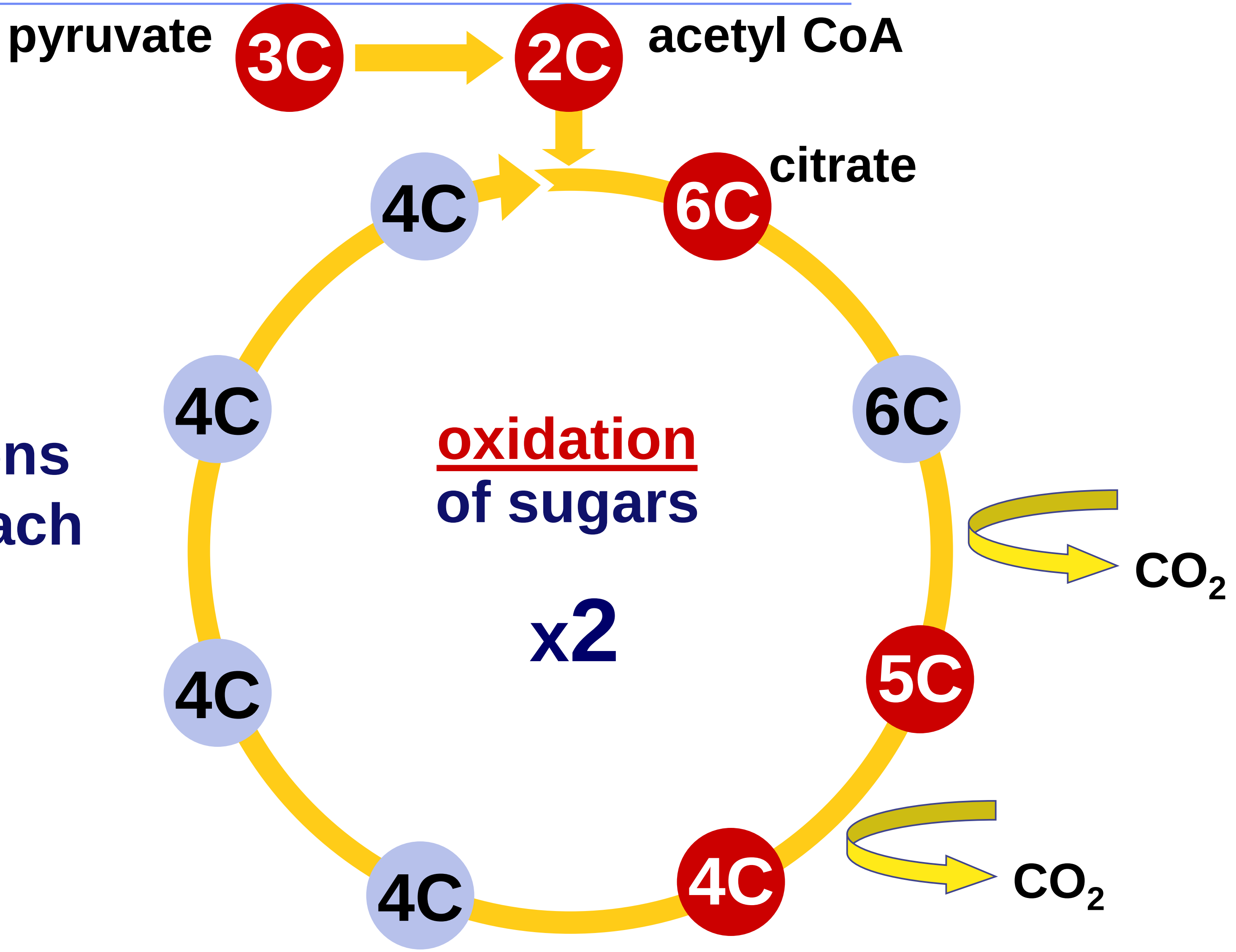
1937 | 1953

Krebs cycle

Hans Krebs
1900-1981

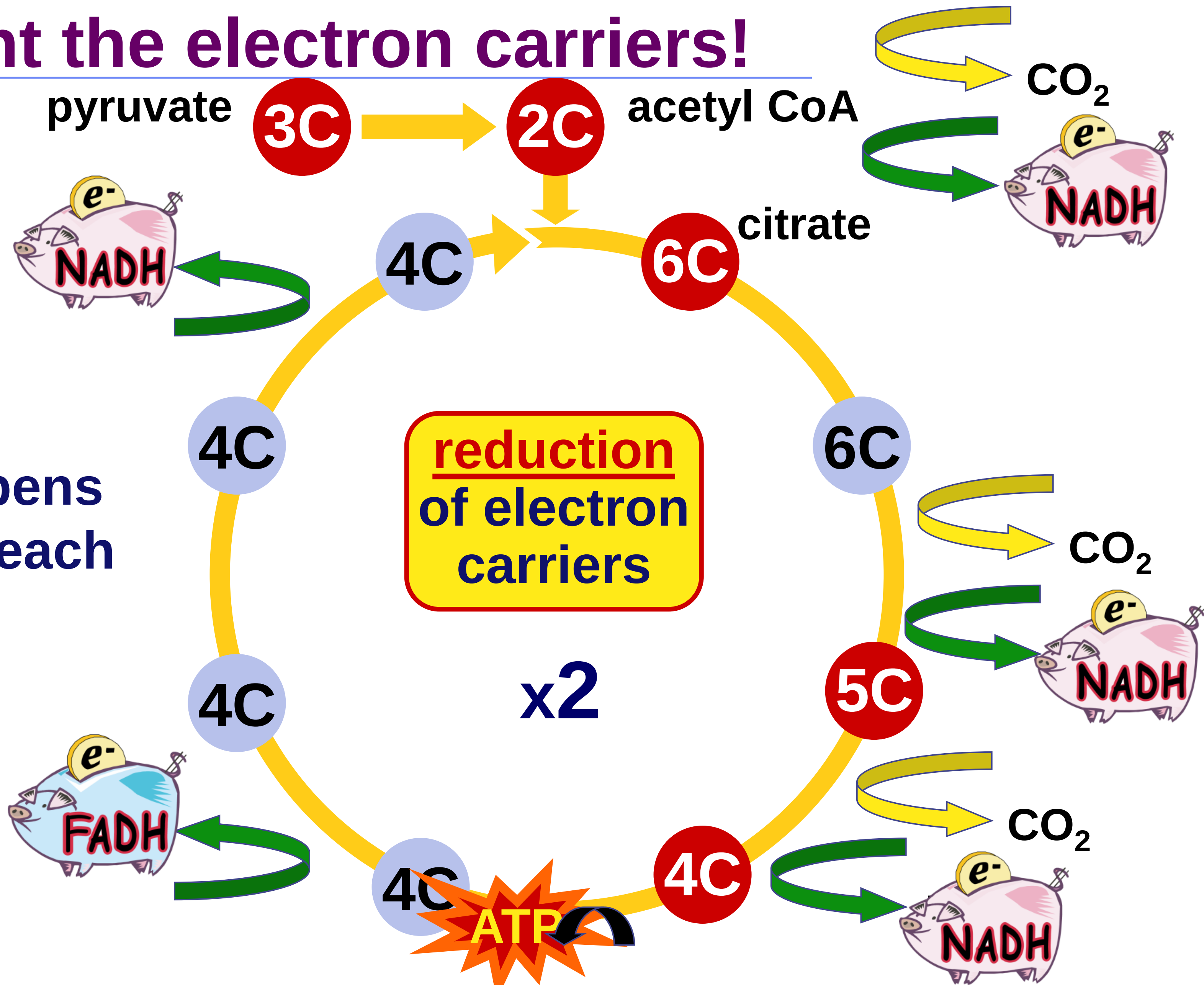
- aka Citric Acid Cycle
  - in mitochondrial matrix
  - 8 step pathway
    - each catalyzed by specific enzyme
    - step-wise catabolism of 6C citrate molecule
- Evolved later than glycolysis
  - does that make evolutionary sense?
    - bacteria →3.5 billion years ago (glycolysis)
    - free O_2 →2.7 billion years ago (photosynthesis)
    - eukaryotes →1.5 billion years ago (aerobic respiration = organelles → mitochondria)

Count the carbons!



This happens <u>twice</u> for each glucose molecule

Count the electron carriers!



This happens twice for each glucose molecule

Whassup?

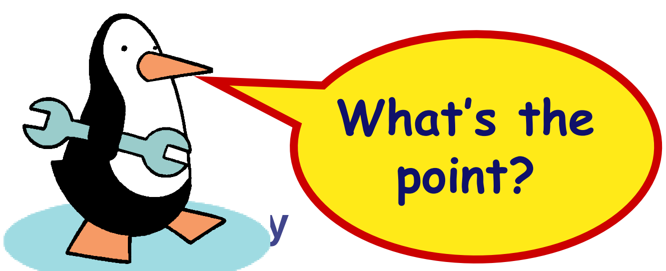
So we fully oxidized glucose

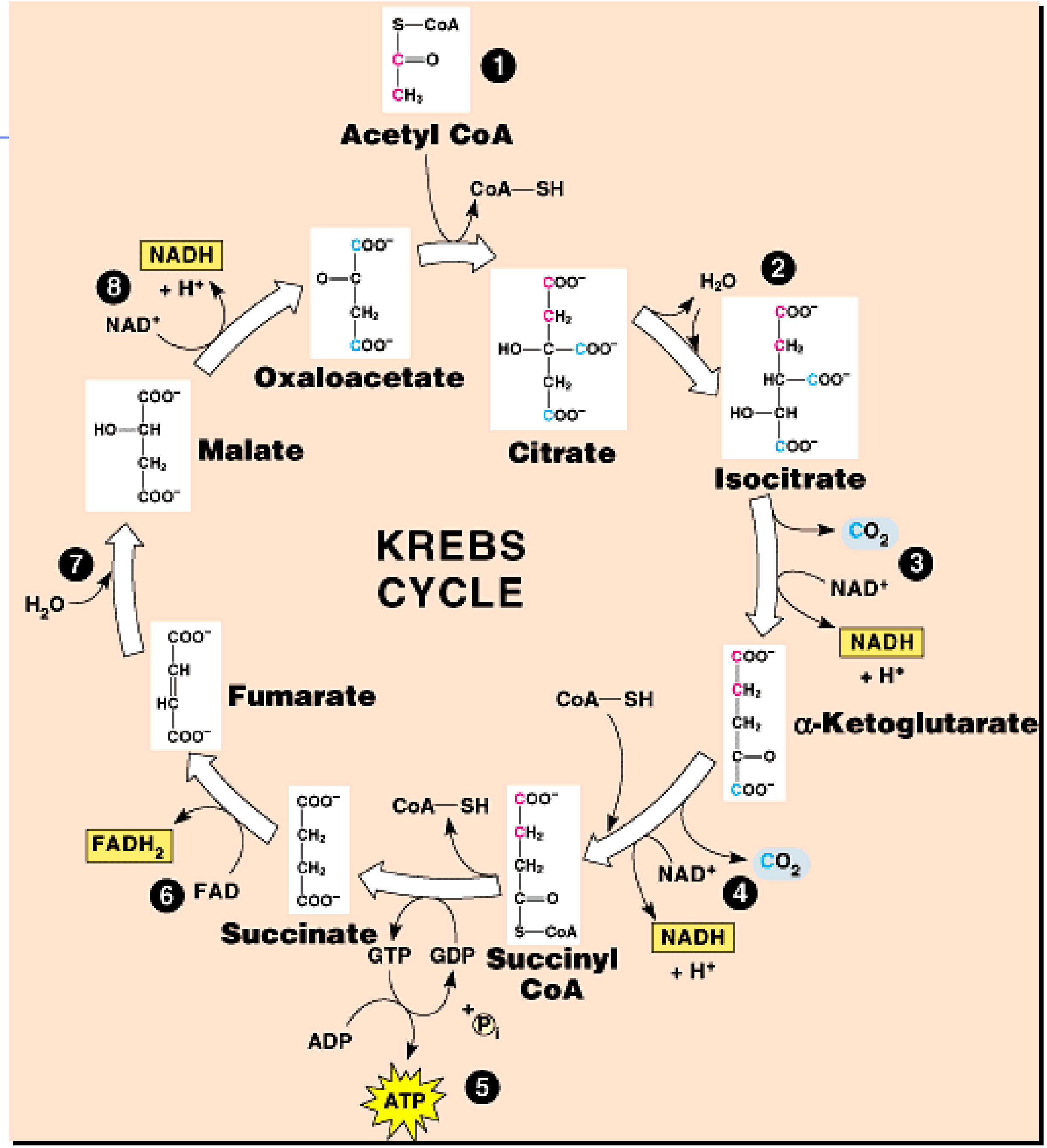
$C_6H_{12}O_6$

↓

CO_2

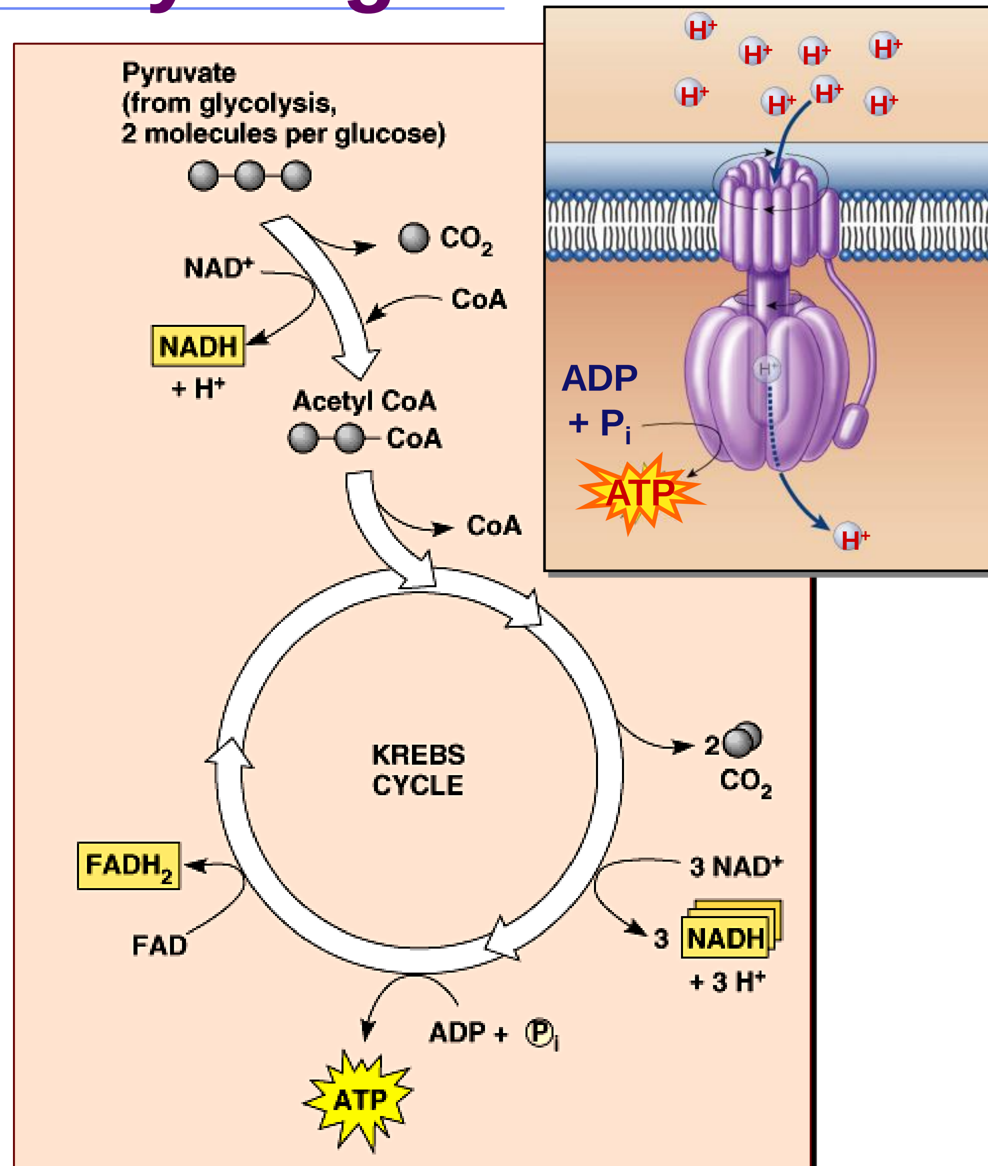
& ended up with **4 ATP!**

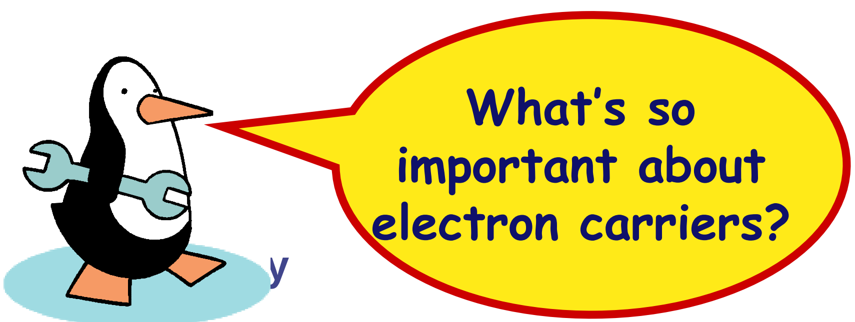




Electron Carriers = Hydrogen Carriers

- Krebs cycle produces large quantities of **electron carriers**
  - NADH
  - $FADH_2$
  - go to **Electron Transport Chain!**





Energy accounting of Krebs cycle

4 NAD + 1 FAD → 4 NADH + 1 $FADH_2$

2x [pyruvate → → → → → → → → → CO_2]

3C → 3x 1C

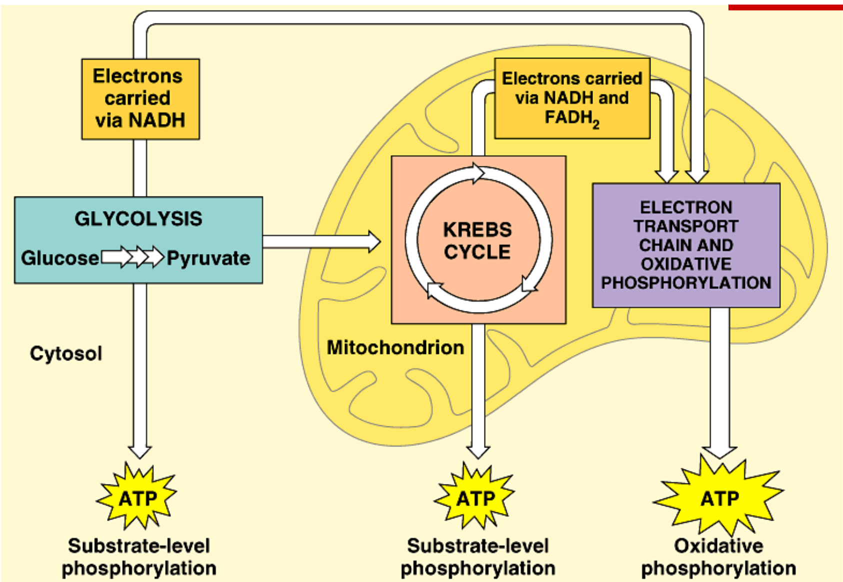
1 ADP → 1 ATP

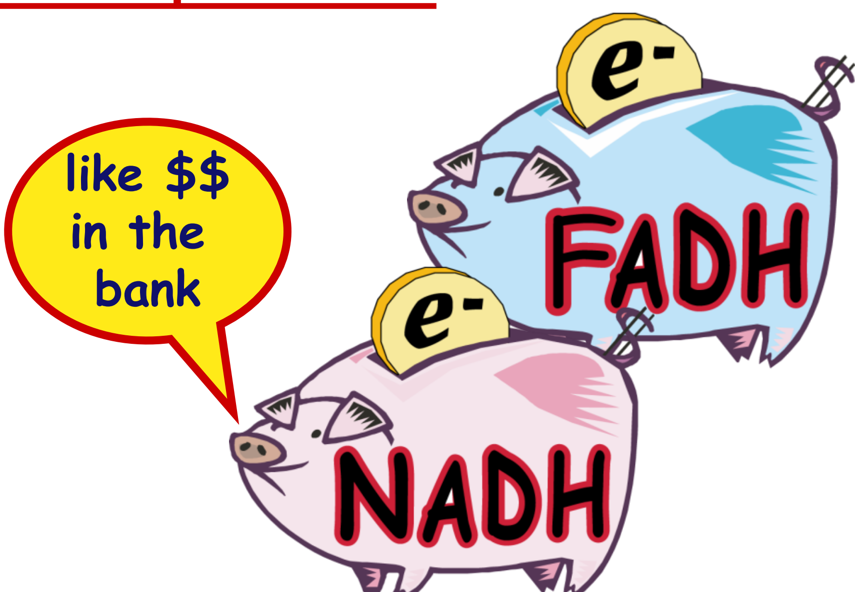
Net gain = 2 ATP

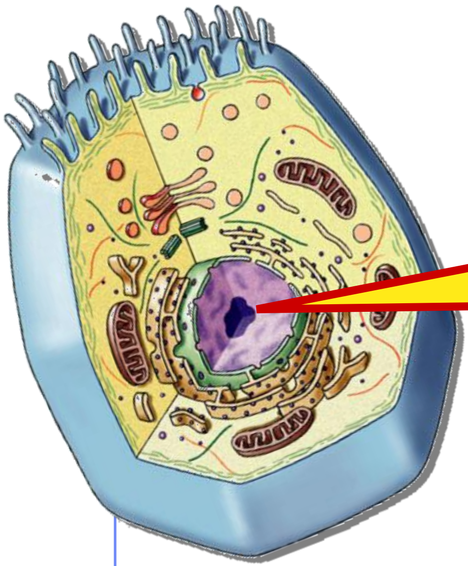
= 8 NADH + 2 $FADH_2$

Value of Krebs cycle?

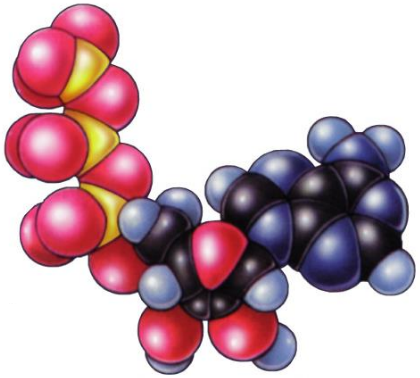
- If the yield is only 2 ATP then how was the Krebs cycle an adaptation?
  - value of NADH & $FADH_2$
    - electron carriers & H carriers
      - reduced molecules move electrons
      - reduced molecules move H^+ ions
    - to be used in the Electron Transport Chain







What's the point?

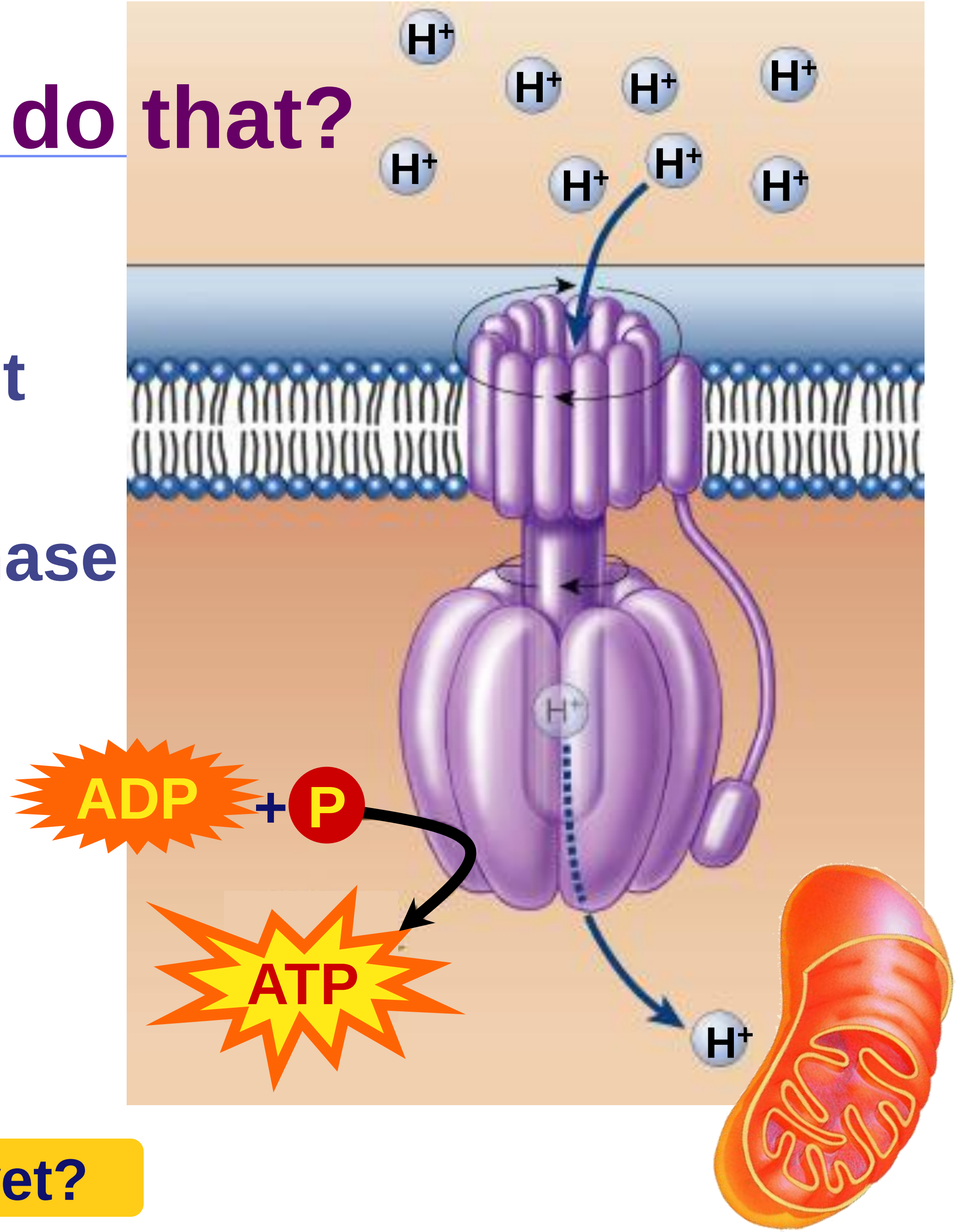


The point is to make **ATP!**

ATP

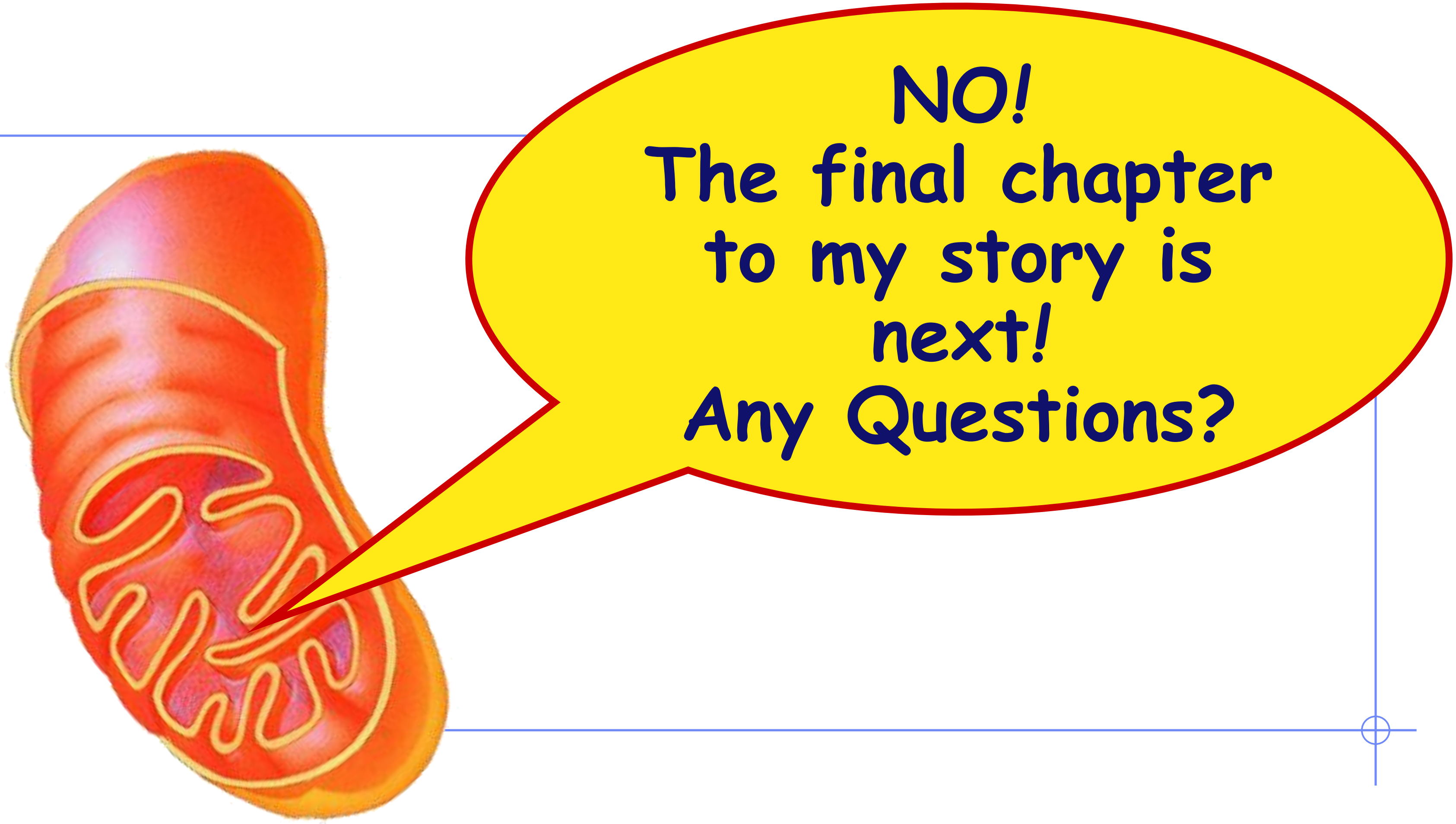
And how do we do that?

- ATP synthase
  - set up a H^+ gradient
  - allow H^+ to flow through ATP synthase
  - powers bonding of P_i to ADP



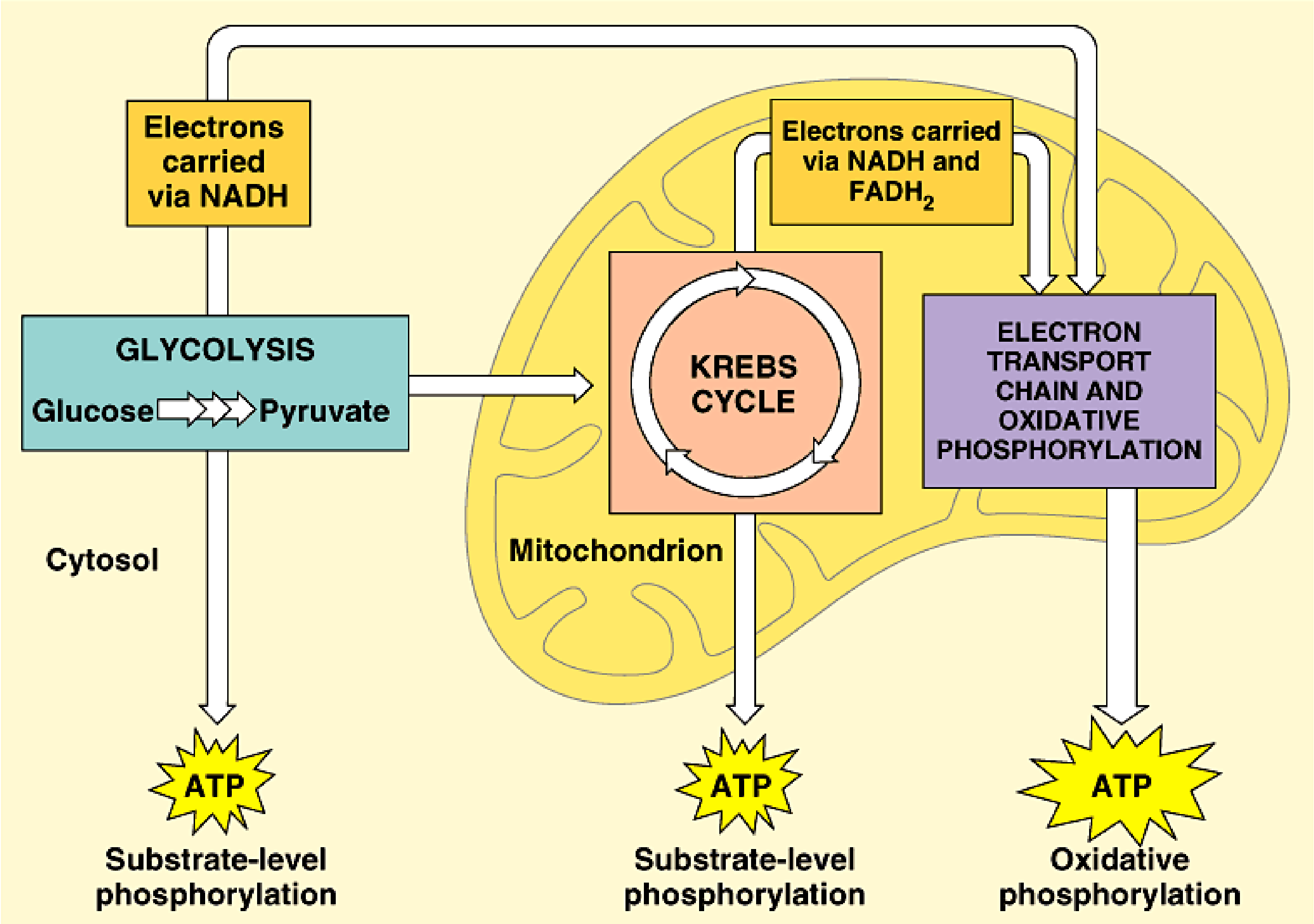
$$ADP + P_i \rightarrow ATP$$

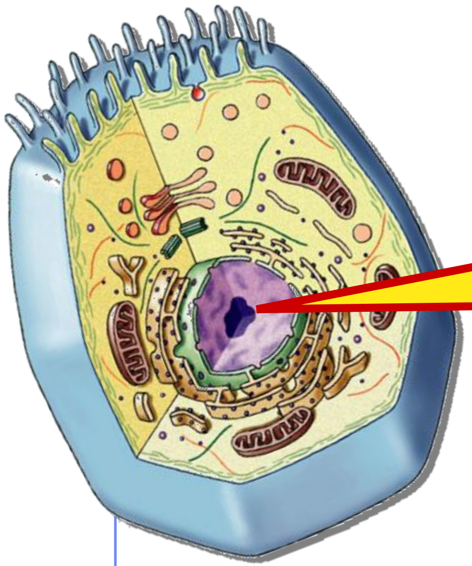
But… Have we done that yet?


NO!
The final chapter to my story is next!
Any Questions?

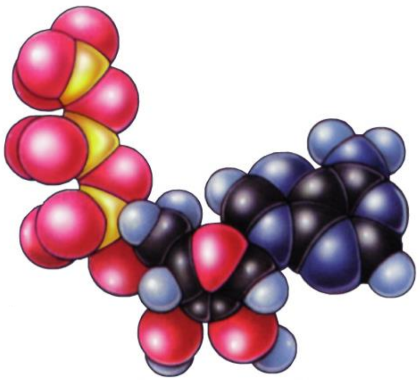
Cellular Respiration
Stage 4:
Electron Transport Chain

Cellular respiration



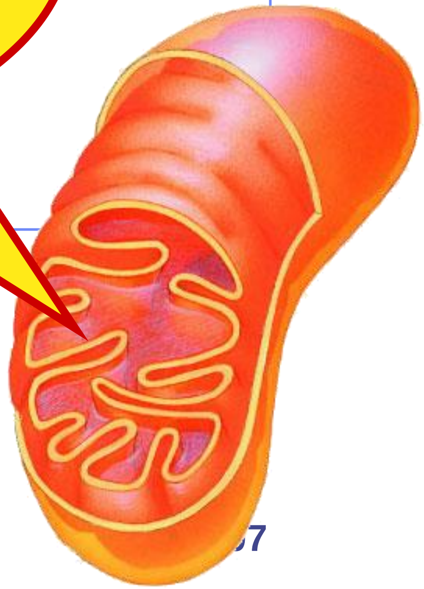


What's the point?



The point is to make **ATP!**

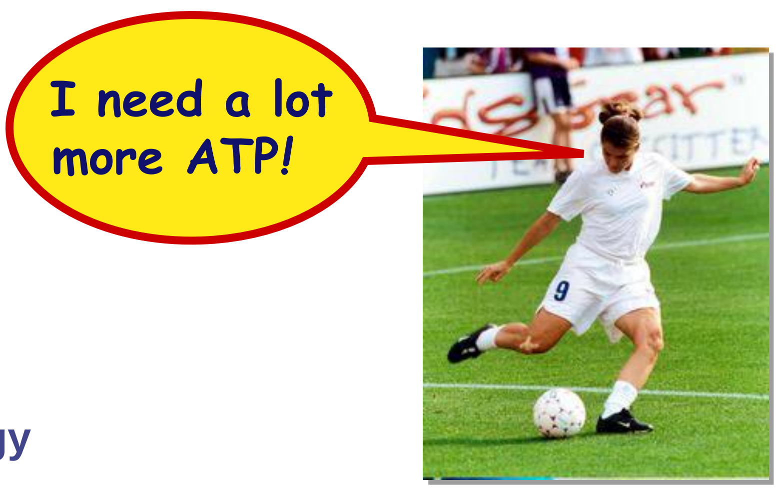
ATP

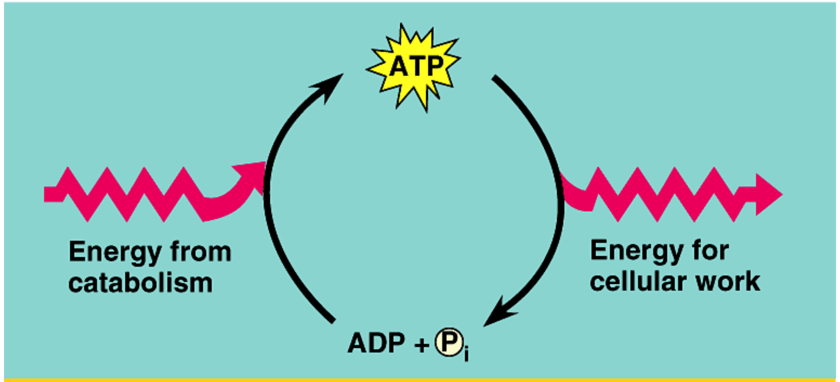


ATP accounting so far…

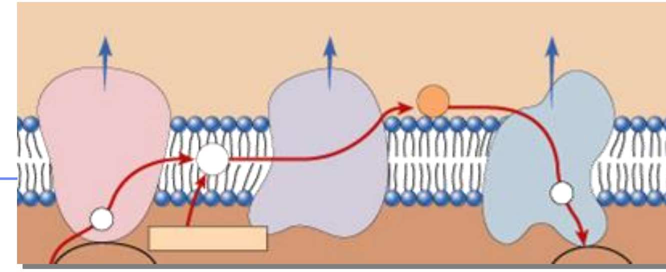
- Glycolysis → 2 ATP
- Kreb's cycle → 2 ATP
- Life takes a lot of energy to run, need to extract more energy than 4 ATP!

There's got to be a better way!



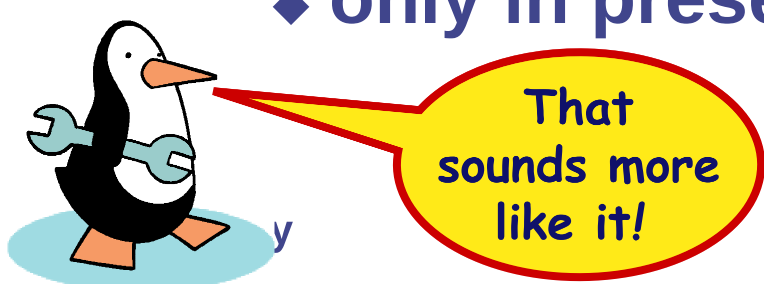


A working muscle recycles over 10 million ATPs per second



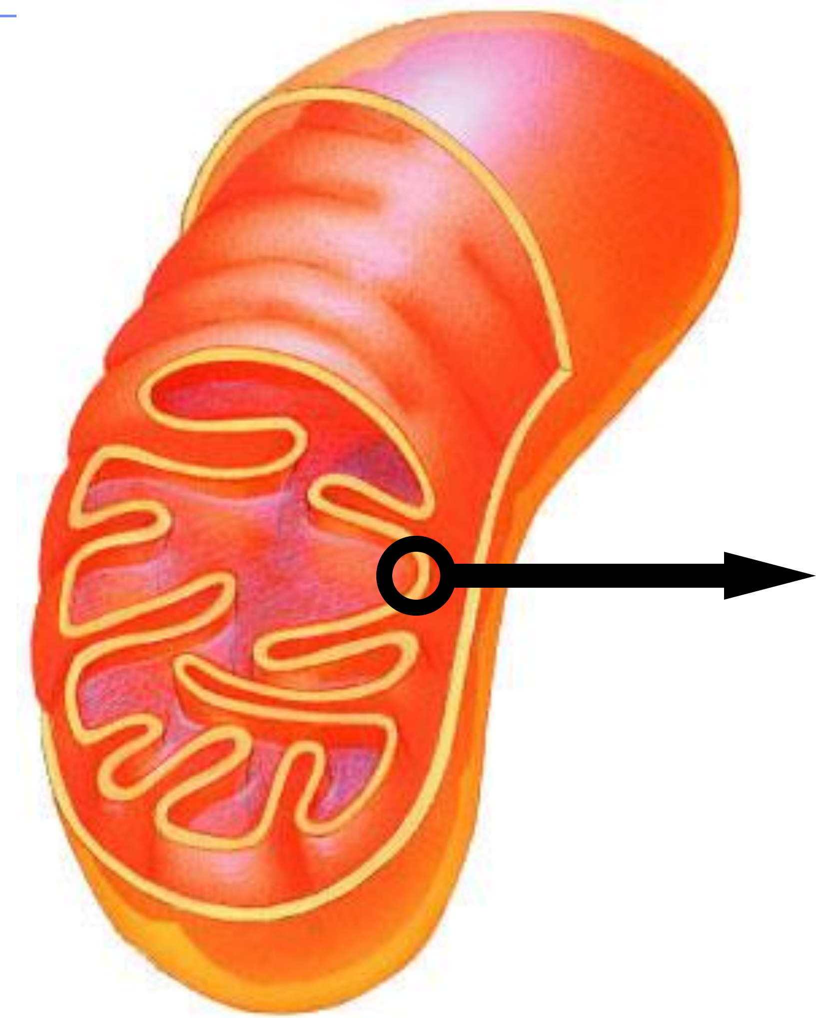
There *is* a better way!

- **Electron Transport Chain**
  - series of proteins built into **inner mitochondrial membrane**
    - along **cristae**
    - transport proteins & enzymes
  - transport of electrons down ETC linked to pumping of H^+ to create H^+ gradient
  - yields **~36 ATP** from 1 glucose*!*
  - only in presence of O_2 (**aerobic respiration**)

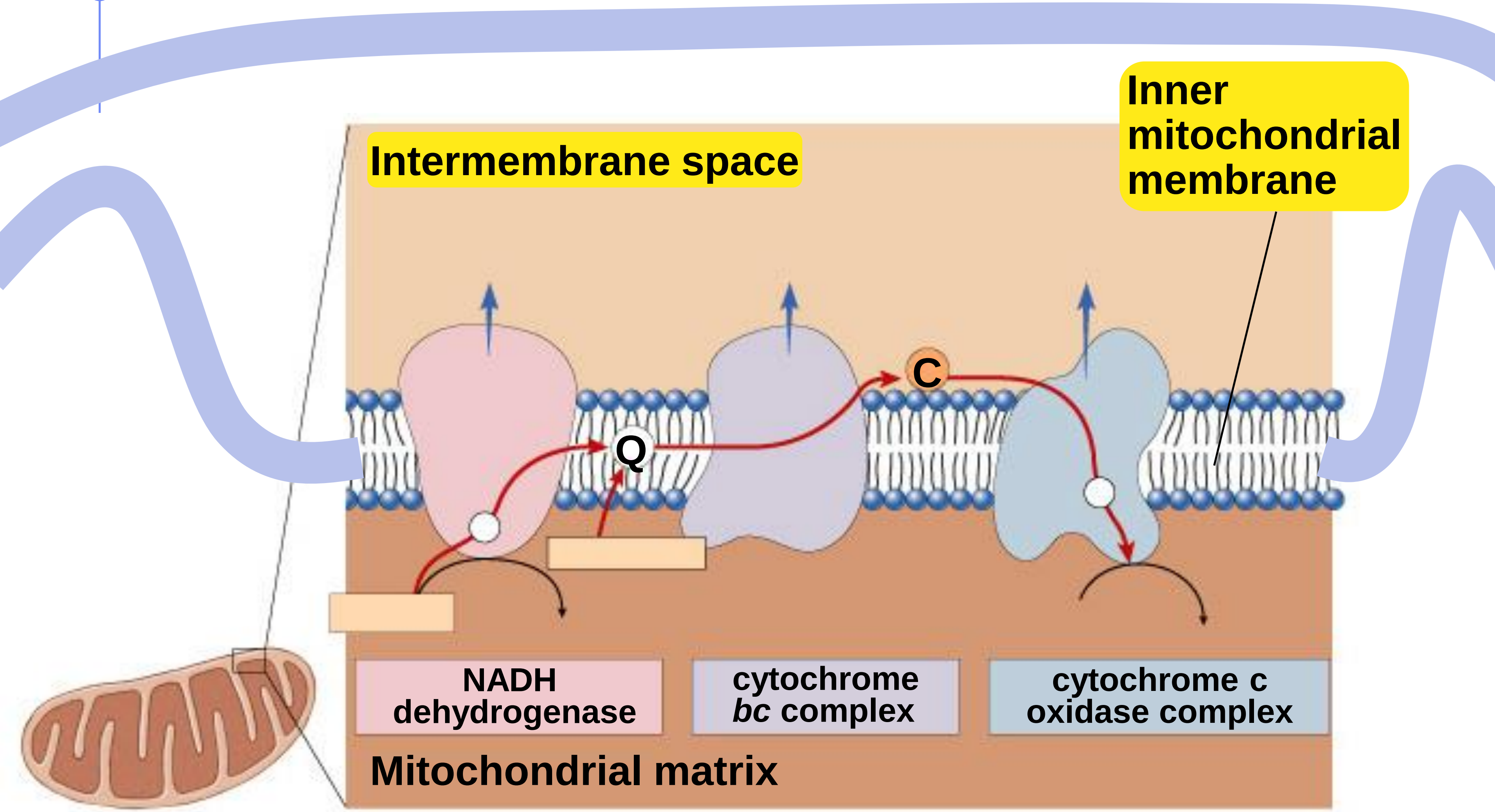


Mitochondria

- **Double membrane**
  - outer membrane
  - <u>inner membrane</u>
    - highly folded <u>cristae</u>
    - enzymes & transport proteins
  - <u>intermembrane space</u>
    - fluid-filled space between membranes



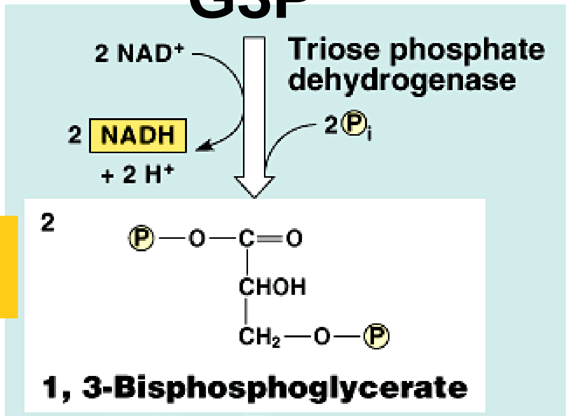
Electron Transport Chain



Remember the Electron Carriers?

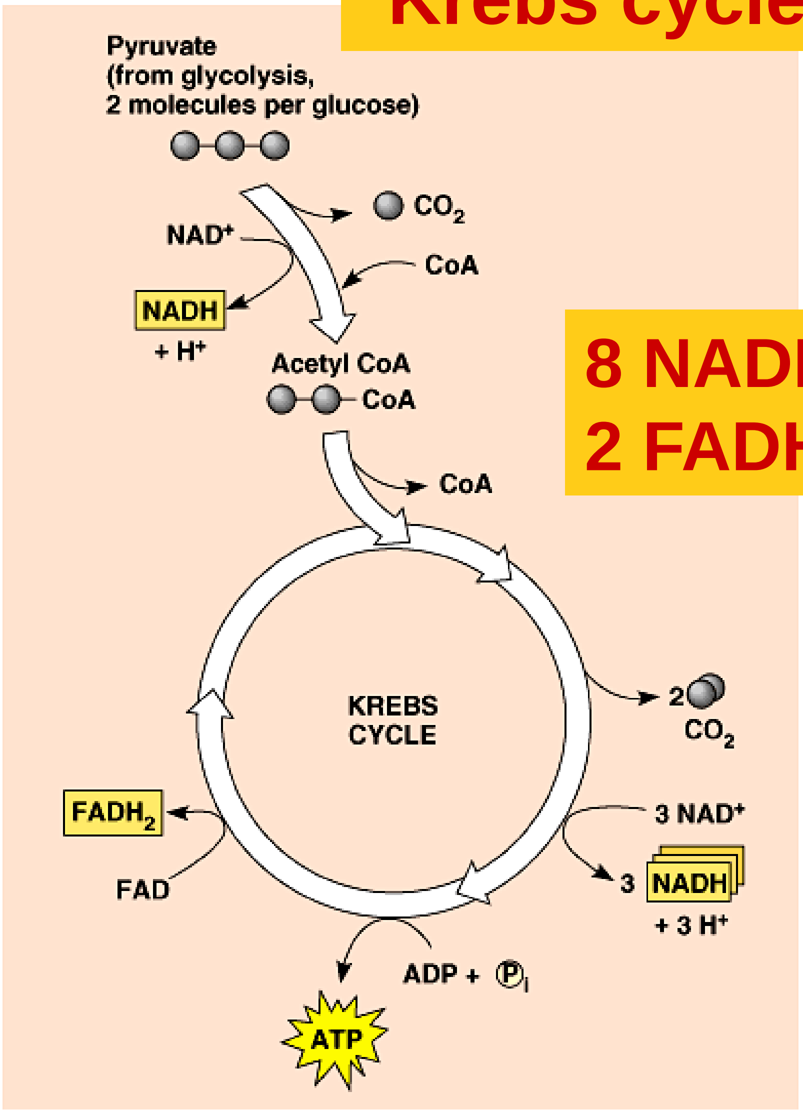
Glycolysis

glucose
↓
G3P

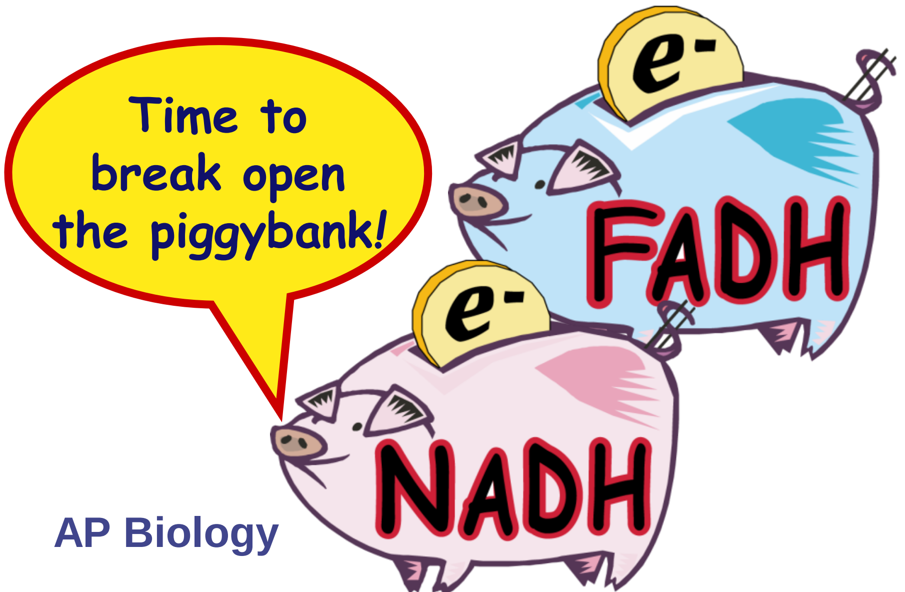


2 NADH

Krebs cycle



8 NADH
2 $FADH_2$

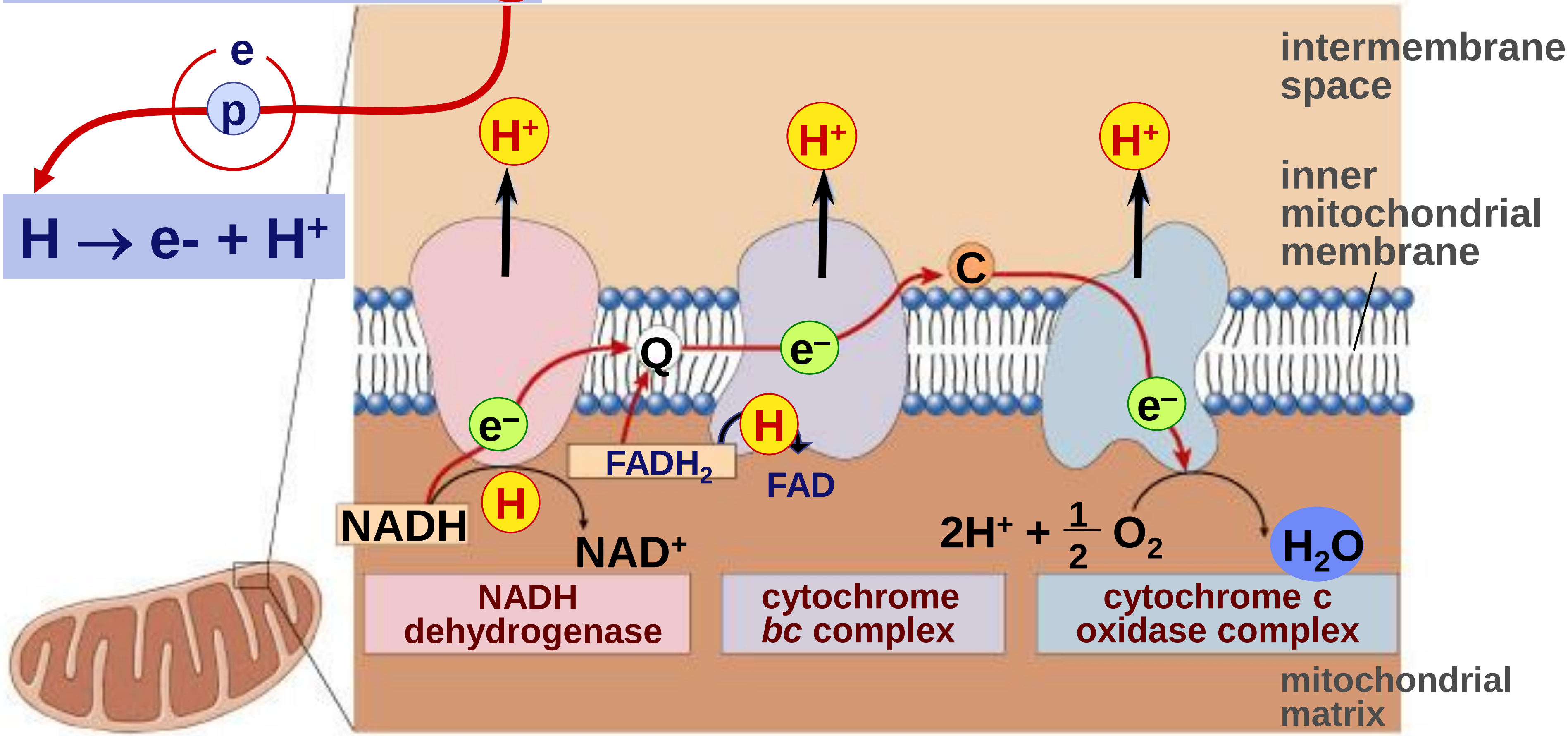


Electron Transport Chain

Building proton gradient!

NADH → NAD^+ + H

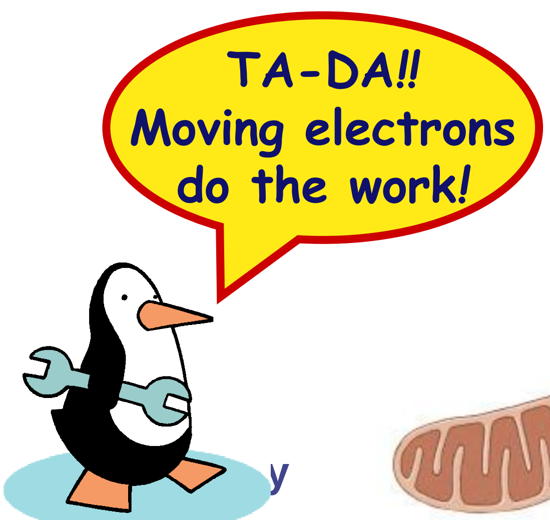
H → e- + H^+

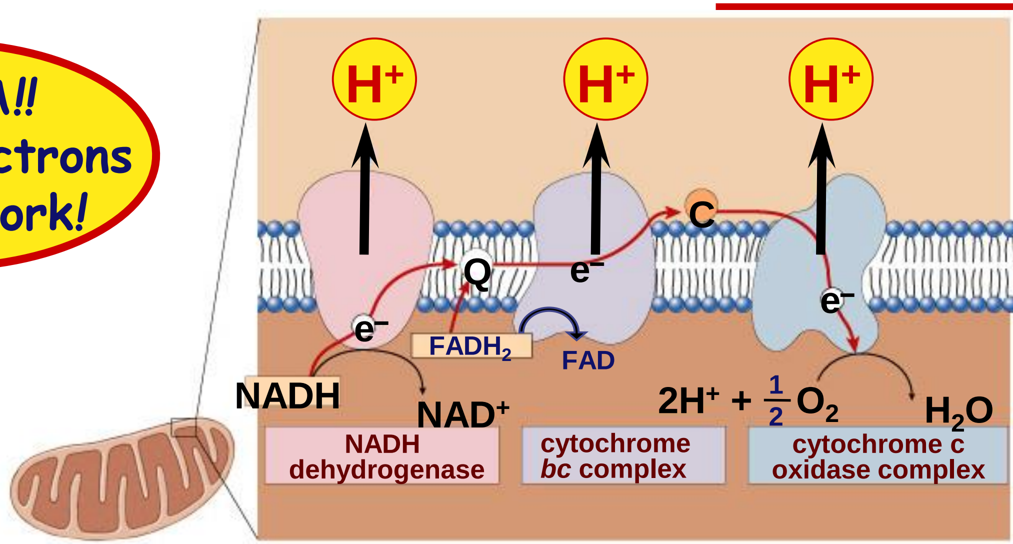


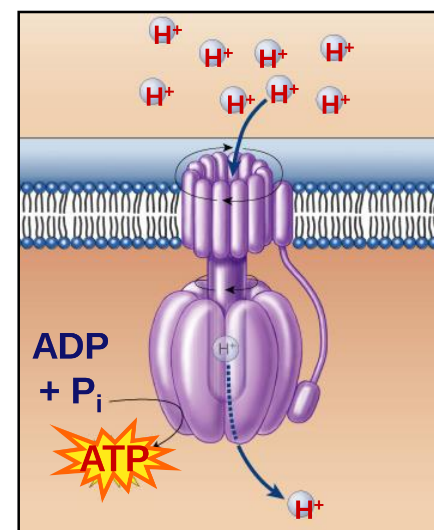
What powers the proton (H^+) pumps?…

Stripping H from Electron Carriers

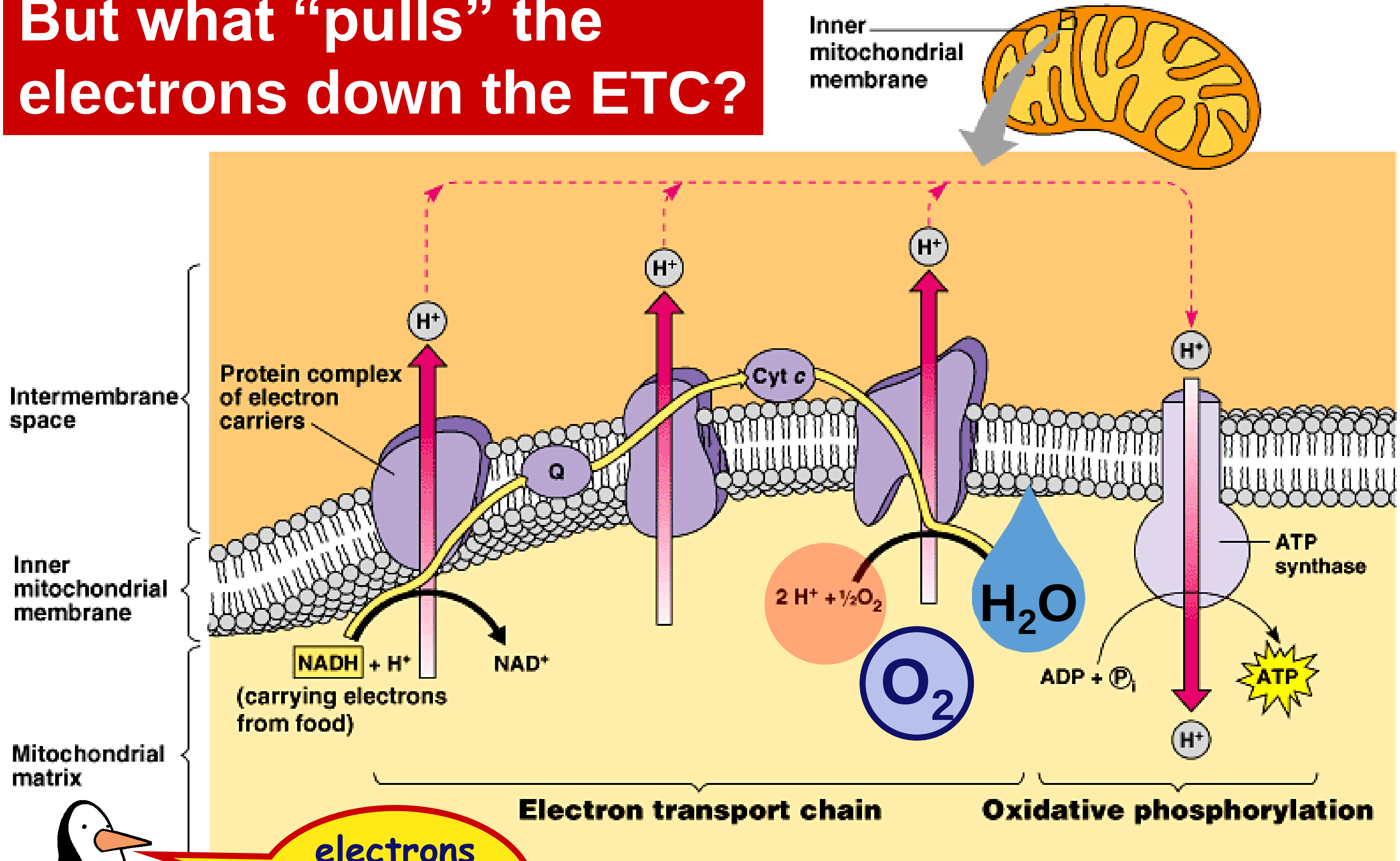
- **Electron carriers pass electrons & H^+ to ETC**
  - H cleaved off NADH & $FADH_2$
  - electrons stripped from H atoms → H^+ (protons)
    - electrons passed from one electron carrier to next in mitochondrial membrane (ETC)
    - flowing electrons = energy to do work
  - transport proteins in membrane pump H^+ (protons) across inner membrane to intermembrane space

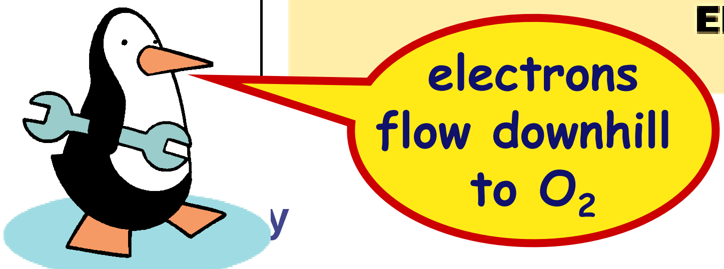






But what "pulls" the electrons down the ETC?

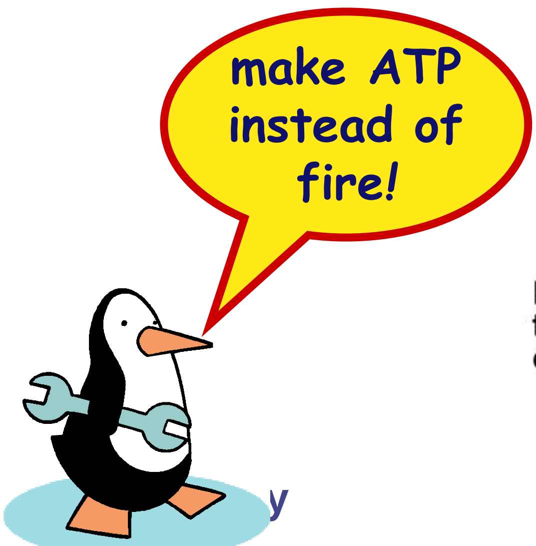


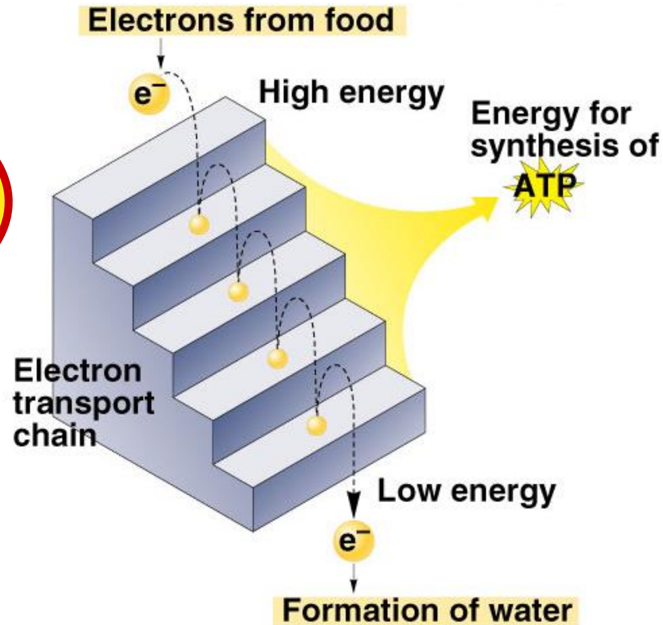


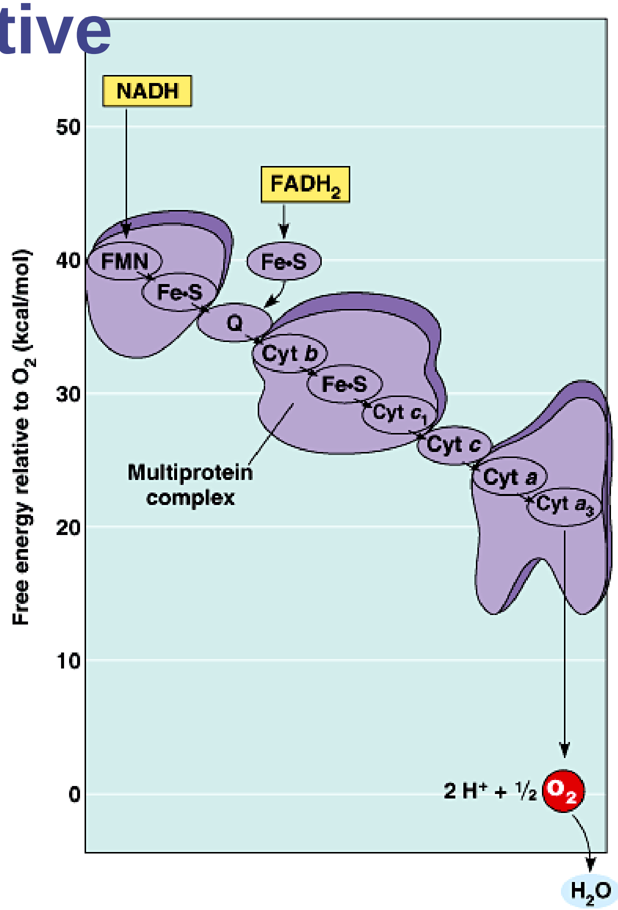
oxidative phosphorylation

Electrons flow downhill

- Electrons move in steps from carrier to carrier downhill to oxygen
  - each carrier more electronegative
  - controlled oxidation
  - controlled release of energy





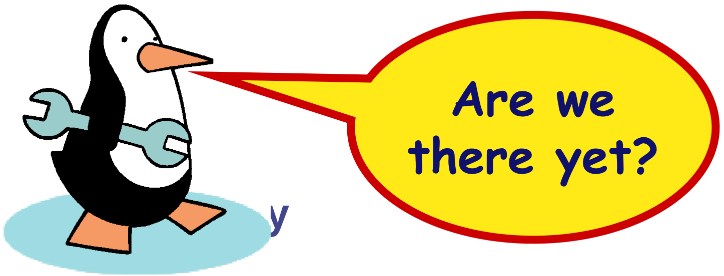


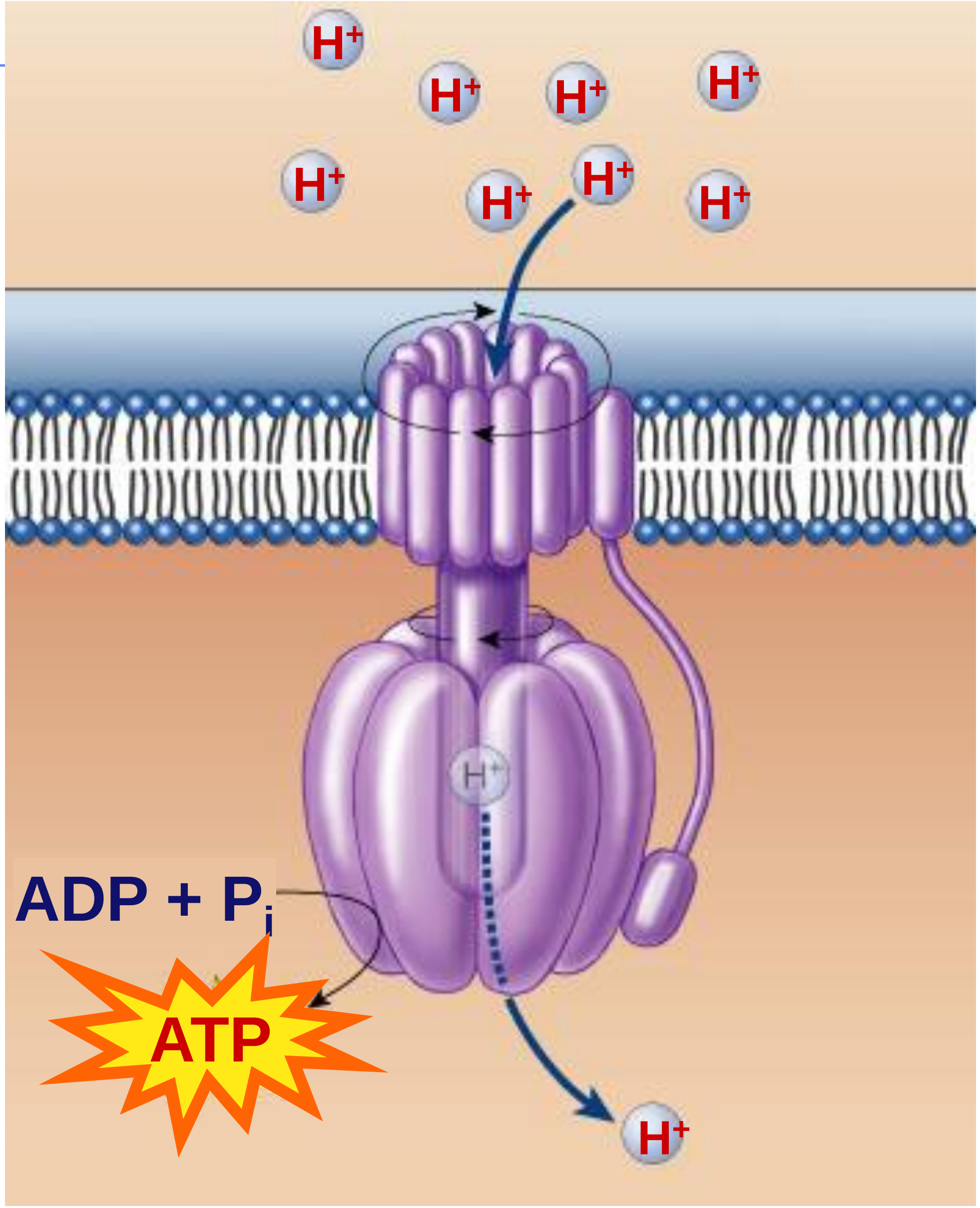
“proton-motive” force

We did it!

- Set up a H^+ gradient
- Allow the **protons** to flow through ATP synthase
- Synthesizes ATP

$ADP + P_i \rightarrow ATP$

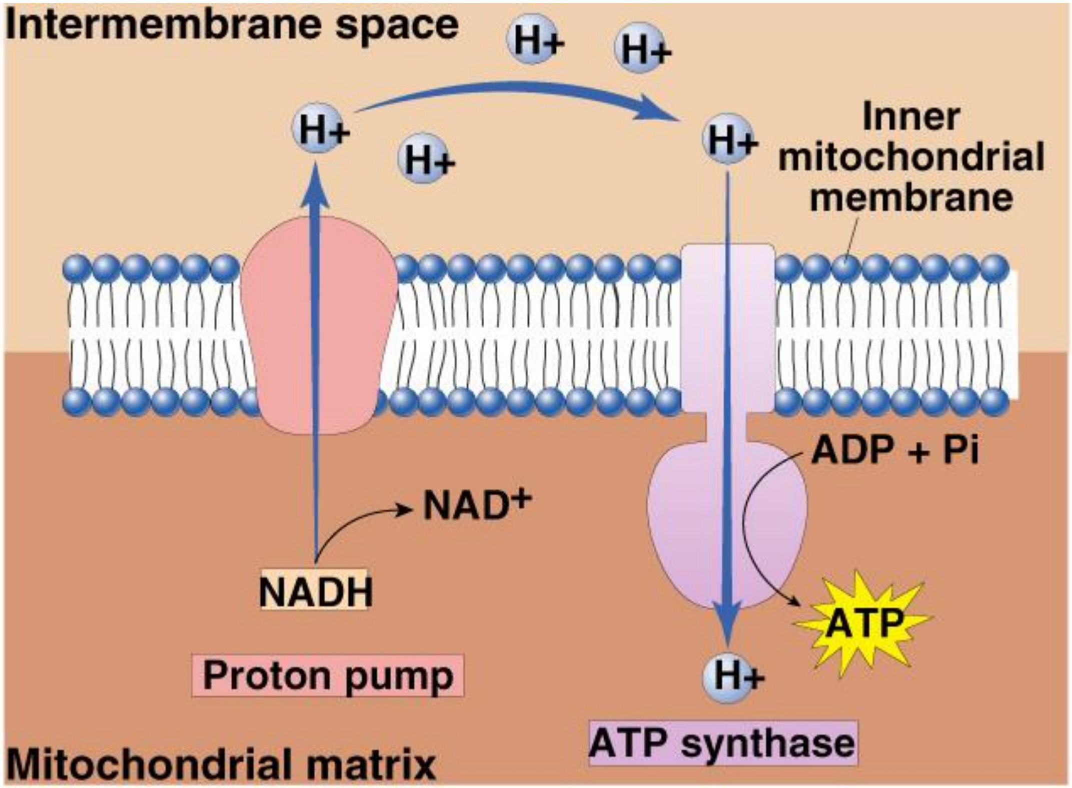


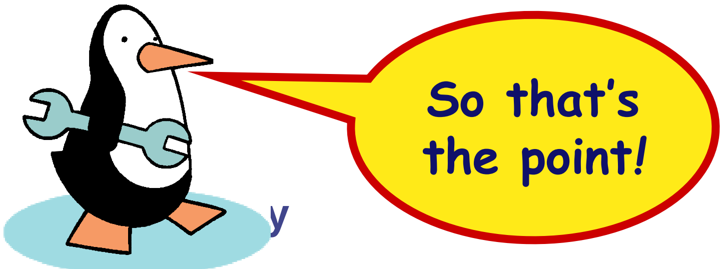


Chemiosmosis

- The diffusion of ions across a membrane
  - build up of proton gradient just so H+ could flow through ATP synthase enzyme to build ATP

Chemiosmosis links the Electron Transport Chain to ATP synthesis

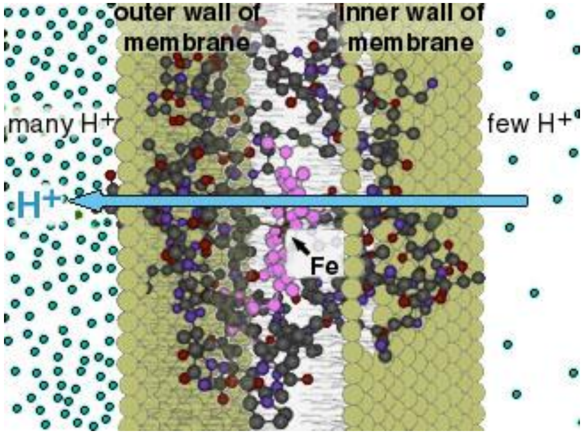




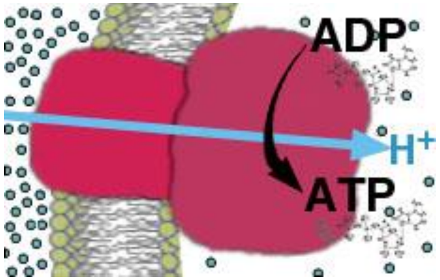
Peter Mitchell

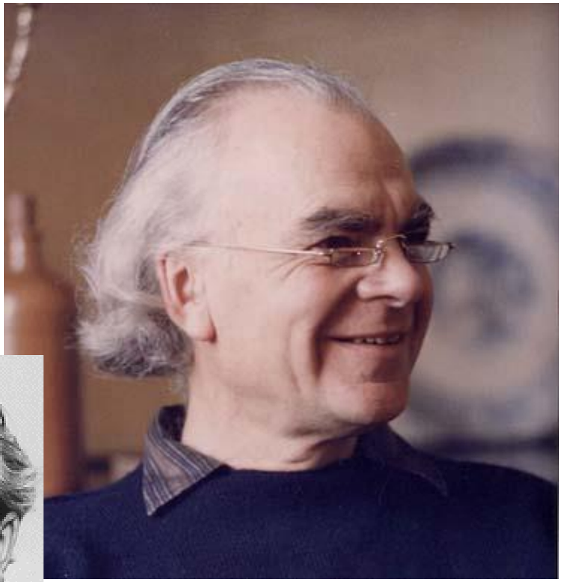
1961 | 1978

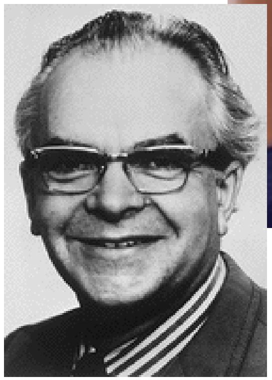
- Proposed chemiosmotic hypothesis
  - revolutionary idea at the time



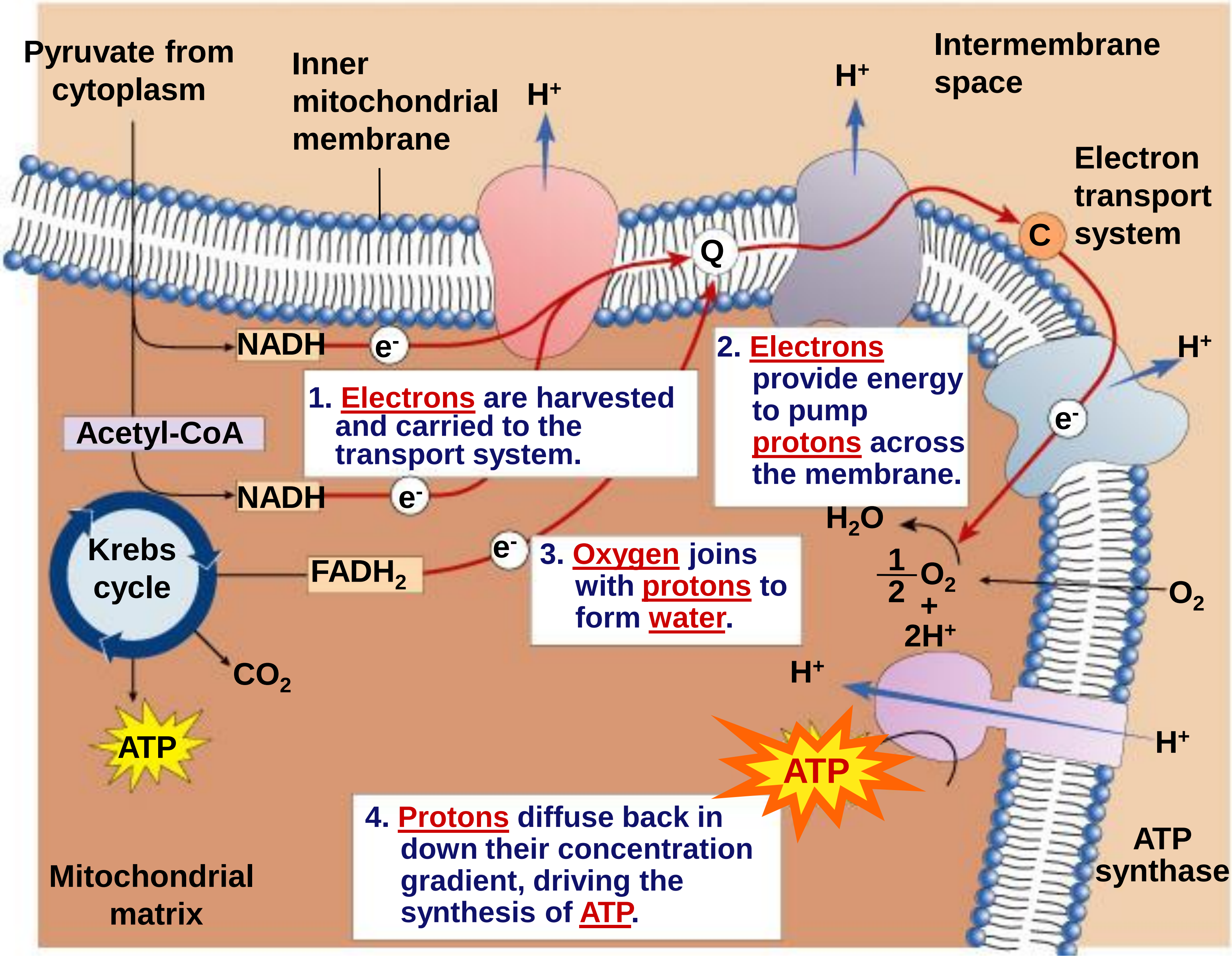
proton motive force





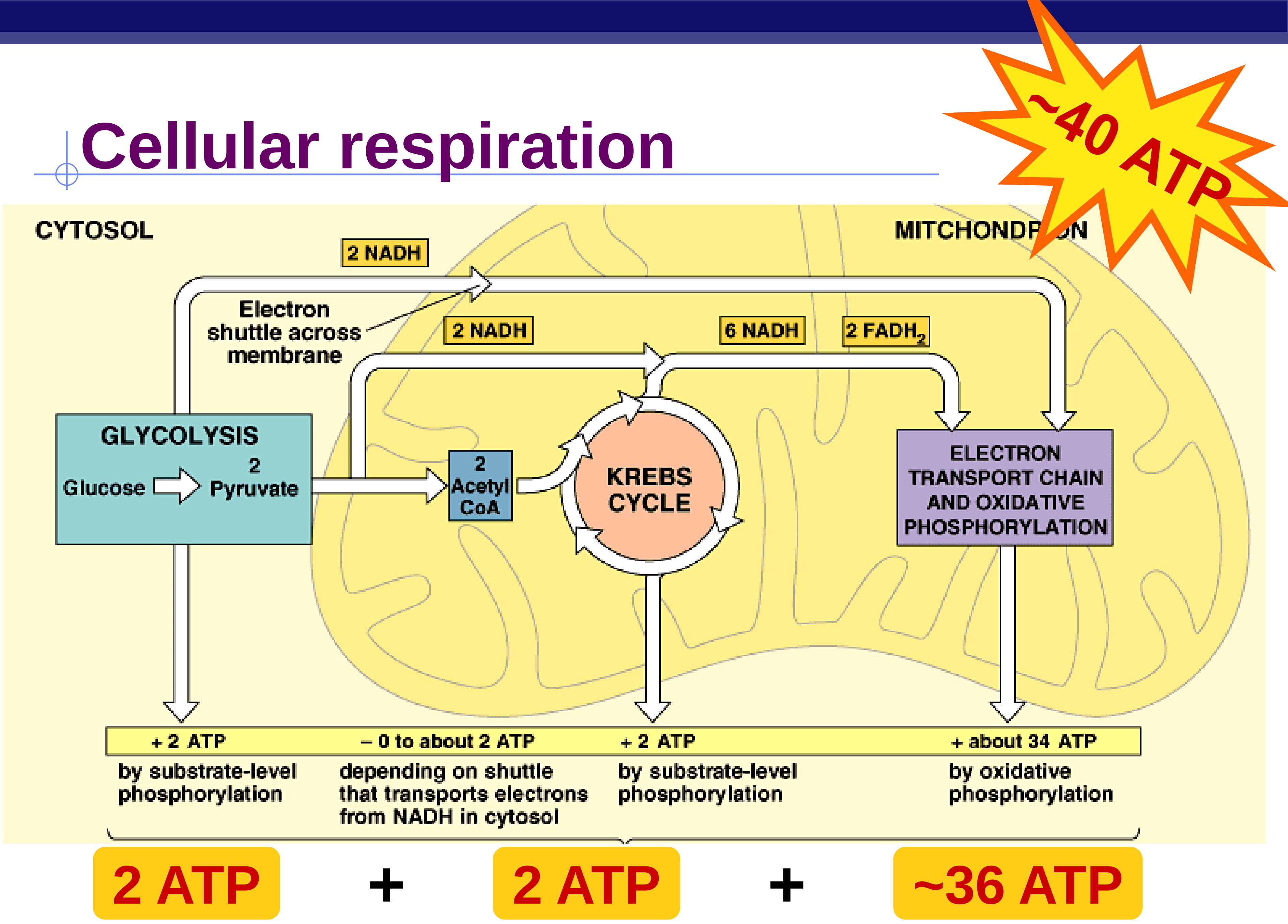


1920-1992



Pyruvate from cytoplasm
Inner mitochondrial membrane
H^+
H^+
Intermembrane space
Electron transport system
C
Q
NADH
e^-
1. Electrons are harvested and carried to the transport system.
2. Electrons provide energy to pump protons across the membrane.
H^+
e^-
Acetyl-CoA
NADH
e^-
Krebs cycle
$FADH_2$
e^-
3. Oxygen joins with protons to form water.
H_2O
$\frac{1}{2} O_2$
+
$2H^+$
O_2
CO_2
H^+
ATP
ATP
H^+
4. Protons diffuse back in down their concentration gradient, driving the synthesis of ATP.
ATP synthase
Mitochondrial matrix

Cellular respiration



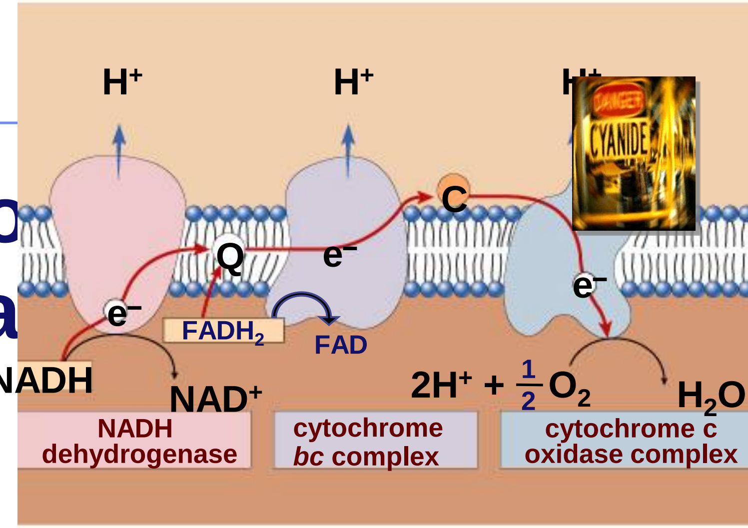
Summary of cellular respiration

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O + \sim 40\ ATP$$

- Where did the glucose come from?
- Where did the O_2 come from?
- Where did the CO_2 come from?
- Where did the CO_2 go?
- Where did the H_2O come from?
- Where did the ATP come from?
- What else is produced that is not listed in this equation?
- Why do we breathe?

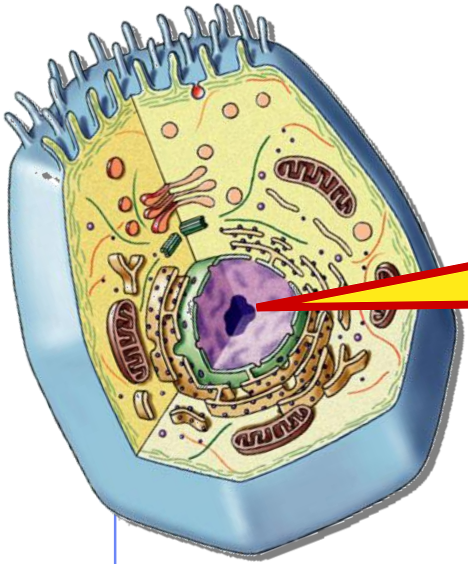
Taking it beyond…

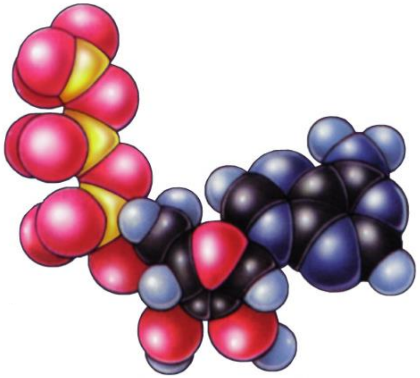
- What is the final electro
  Electron Transport Cha



O_2

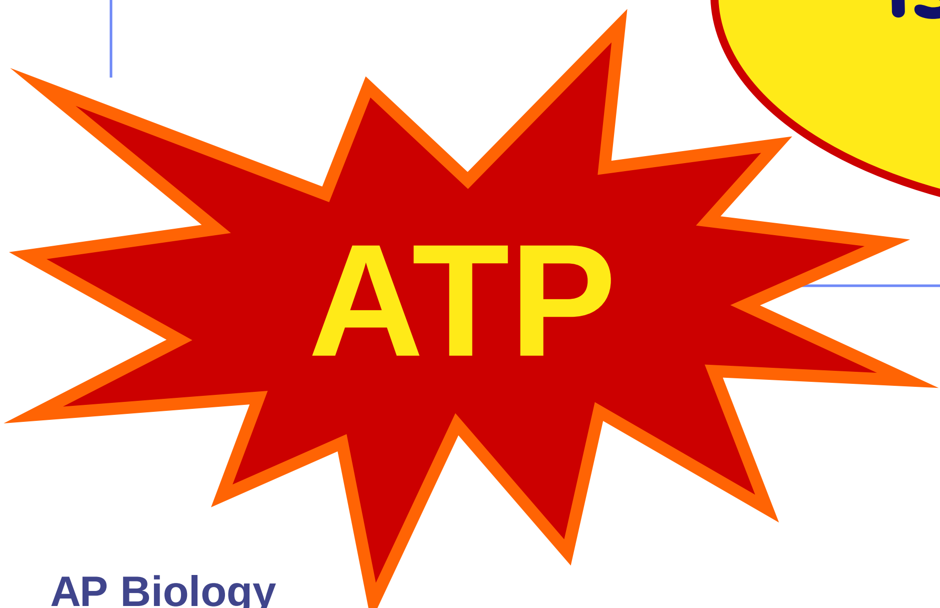
- So what happens if O_2 unavailable?
  - ETC backs up
    - nothing to pull electrons down chain
    - NADH & $FADH_2$ can't unload H
  - ATP production ceases
  - cells run out of energy
  - and you die!

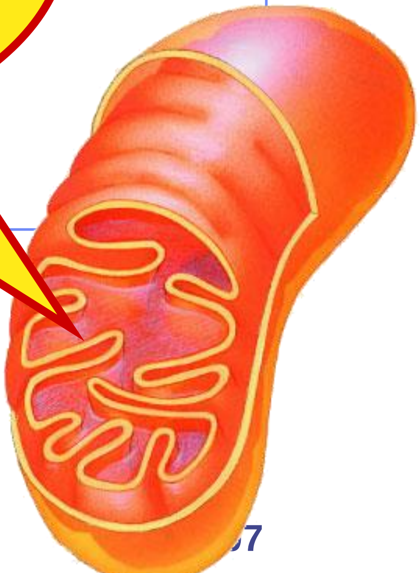




What's the point?

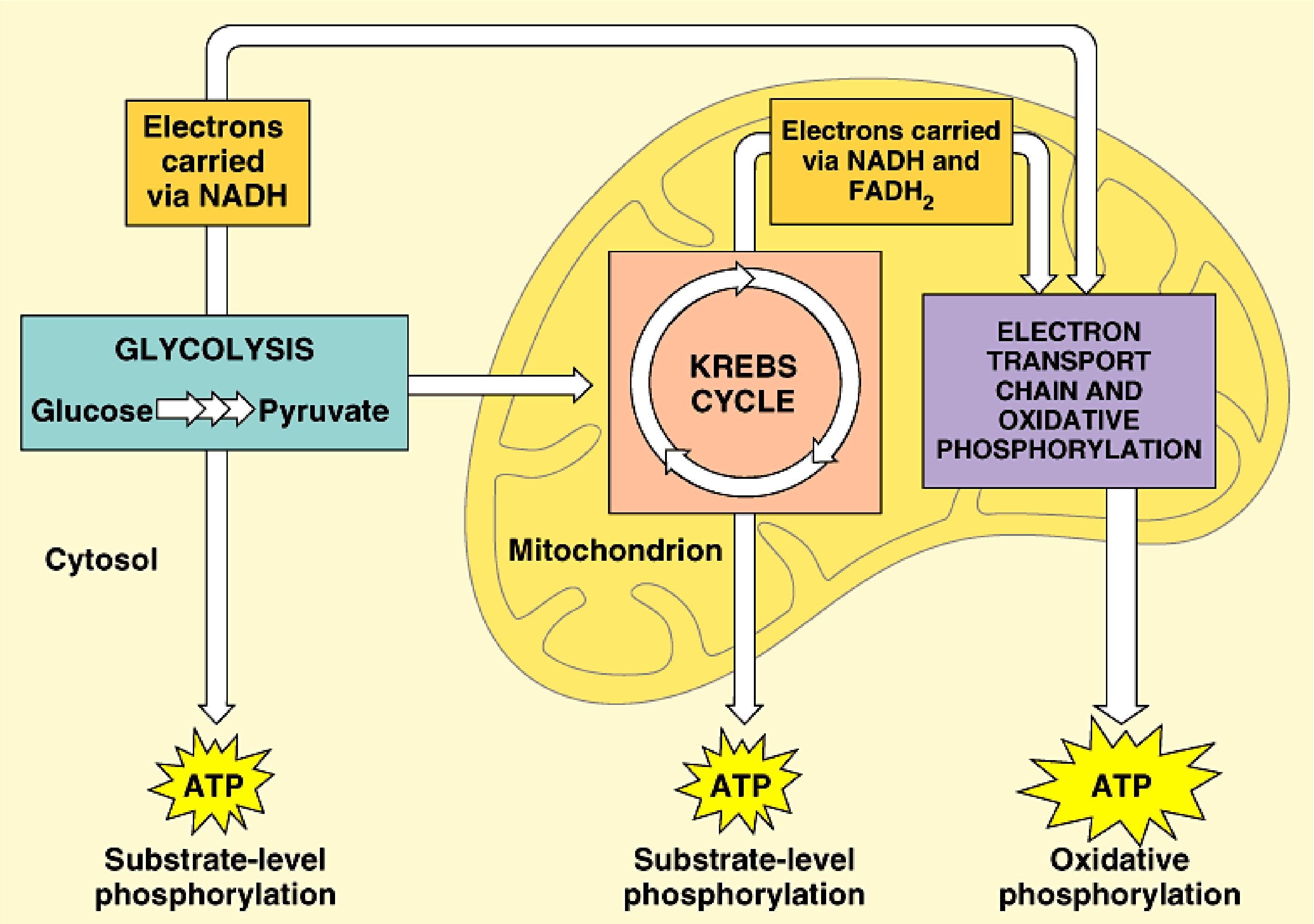
The point is to make **ATP!**





Chapter 9.
Cellular Respiration
Other Metabolites & Control of Respiration

Cellular respiration

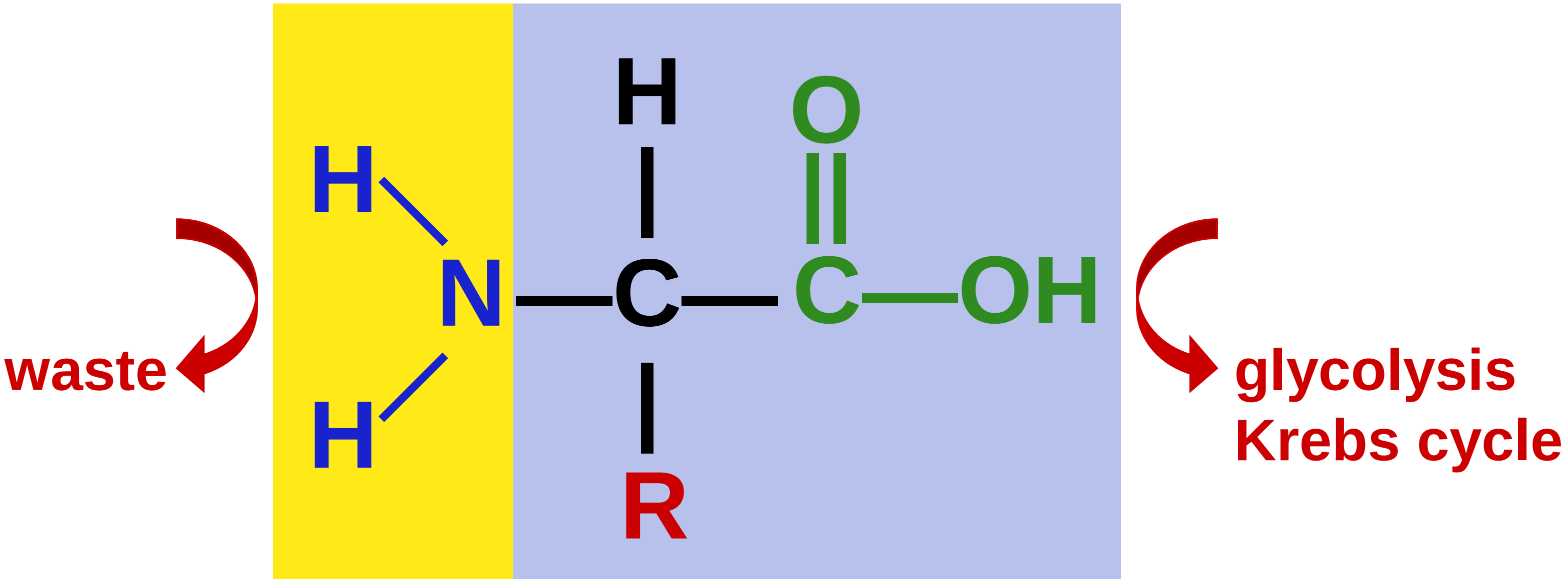


Beyond glucose: Other carbohydrates

- **Glycolysis accepts a wide range of carbohydrates fuels**
  - polysaccharides → → → glucose
    hydrolysis
    - ex. starch, glycogen
  - other 6C sugars → → → glucose
    modified
    - ex. galactose, fructose

Beyond glucose: Proteins

- Proteins → → → → → amino acids
  hydrolysis



amino group = waste product excreted as ammonia, urea, or uric acid

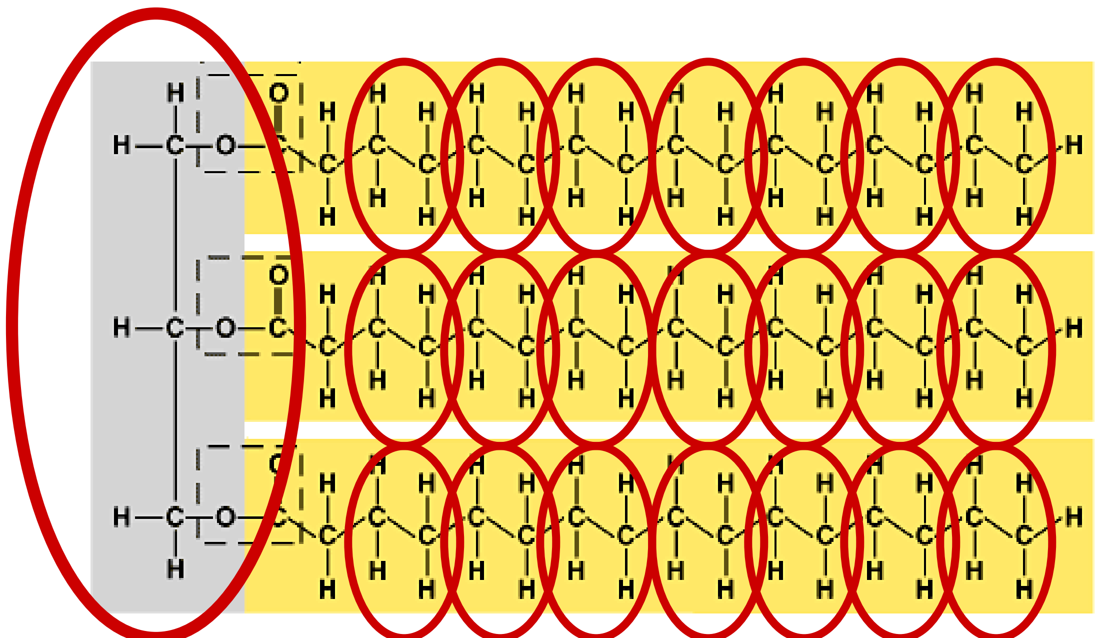
carbon skeleton = enters glycolysis or Krebs cycle at different stages

Beyond glucose: Fats

- Fats → → → → → glycerol & fatty acids
  hydrolysis
  - glycerol (3C) → → PGAL → → glycolysis
  - fatty acids → 2C acetyl groups → acetyl coA → Krebs cycle

glycerol

enters glycolysis as PGAL



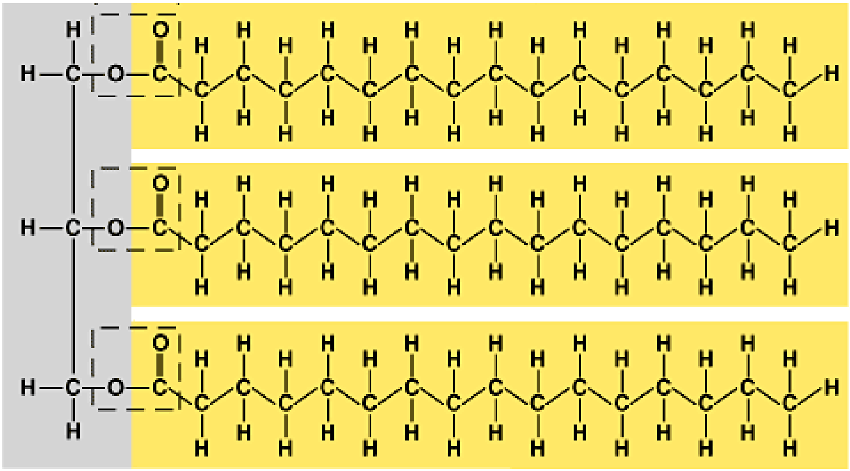
fatty acids

enter Krebs cycle as acetyl CoA

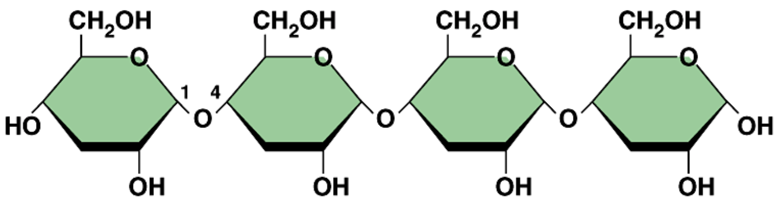
Carbohydrates vs. Fats

- **Fat generates 2x ATP vs. carbohydrate**
  - more C in gram of fat
  - more O in gram of carbohydrate
    - so it's already partly oxidized

fat

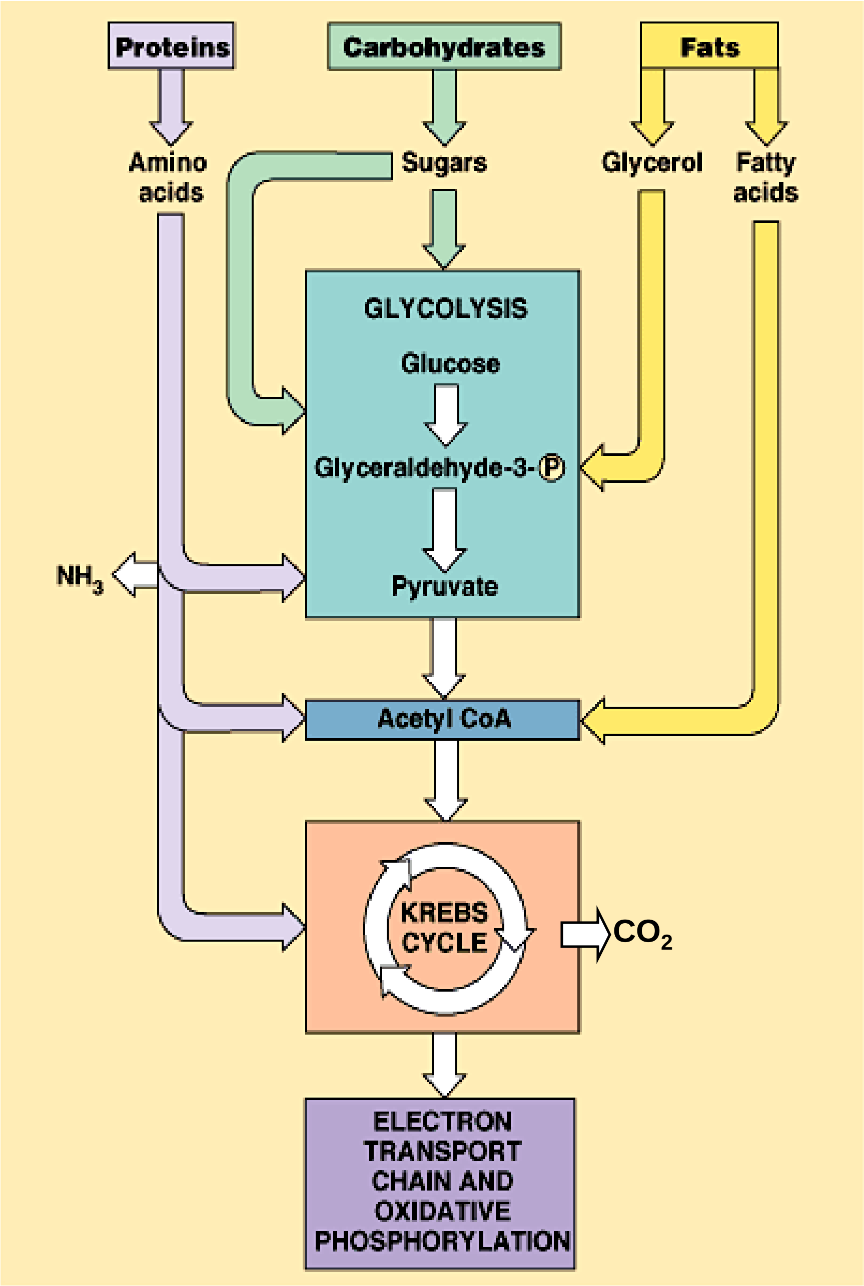


carbohydrate



Metabolism

- Coordination of digestion & synthesis
  - by regulating enzyme
- Digestion
  - digestion of carbohydrates, fats & proteins
    - all catabolized through same pathways
    - enter at different points
  - cell extracts energy from every source



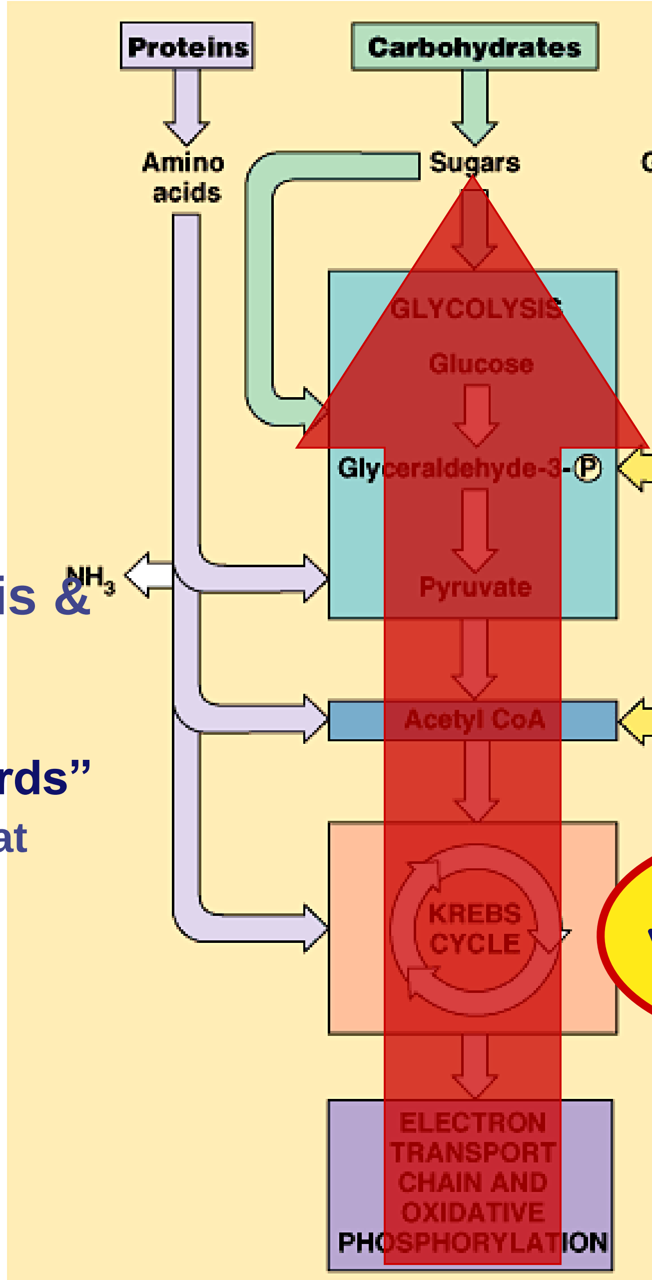
Metabolism

- Coordination of digestion & synthesis
  - by regulating enzyme
- Synthesis
  - enough energy?
    build stuff!
  - cell uses points in glycolysis & Krebs cycle as links to pathways for synthesis
    - run the pathways "backwards"
      - eat too much fuel, build fat

pyruvate → → glucose

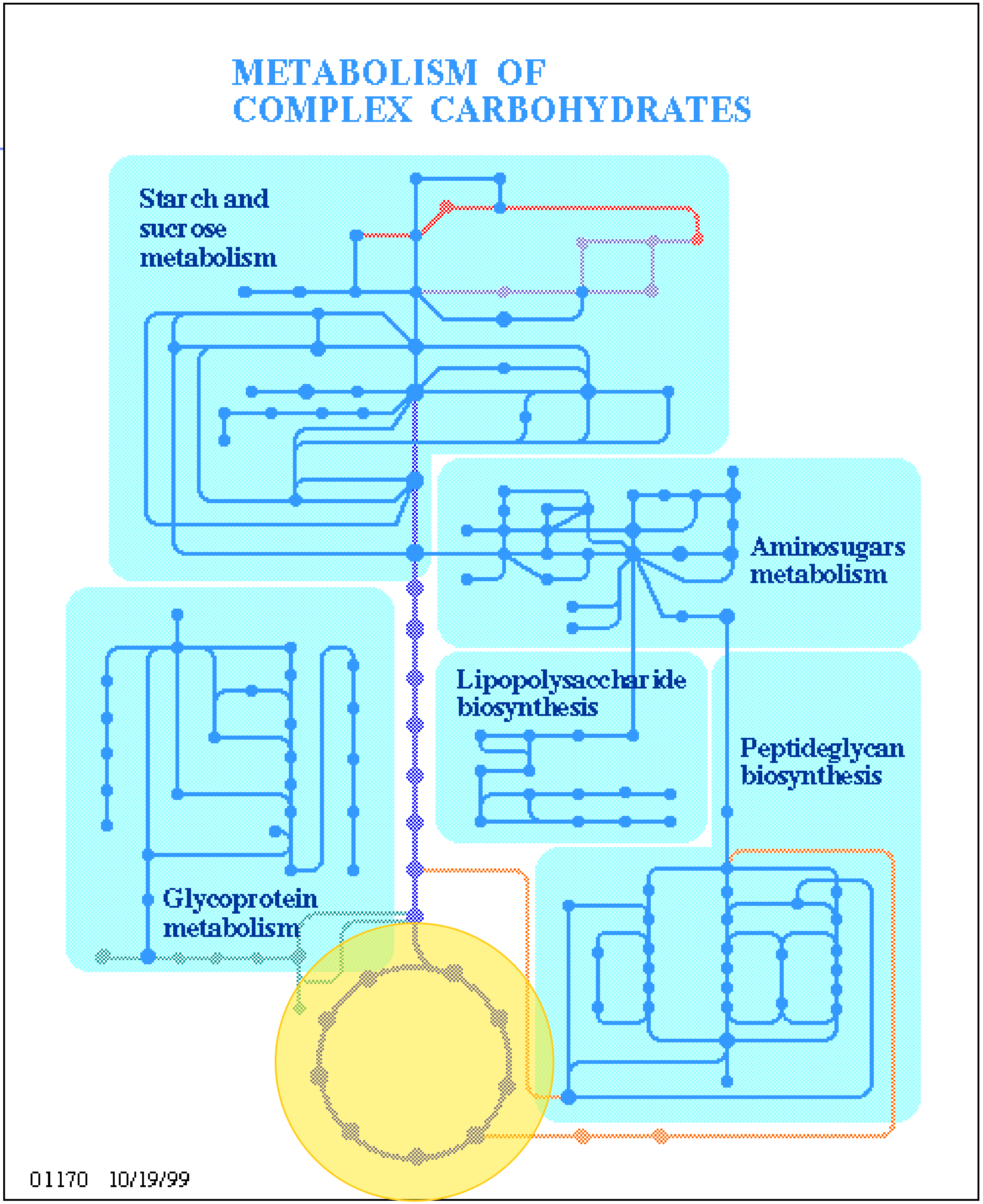
Krebs cycle intermediaries → → amino acids

acetyl CoA → → fatty acids



Carbohydrate Metabolism

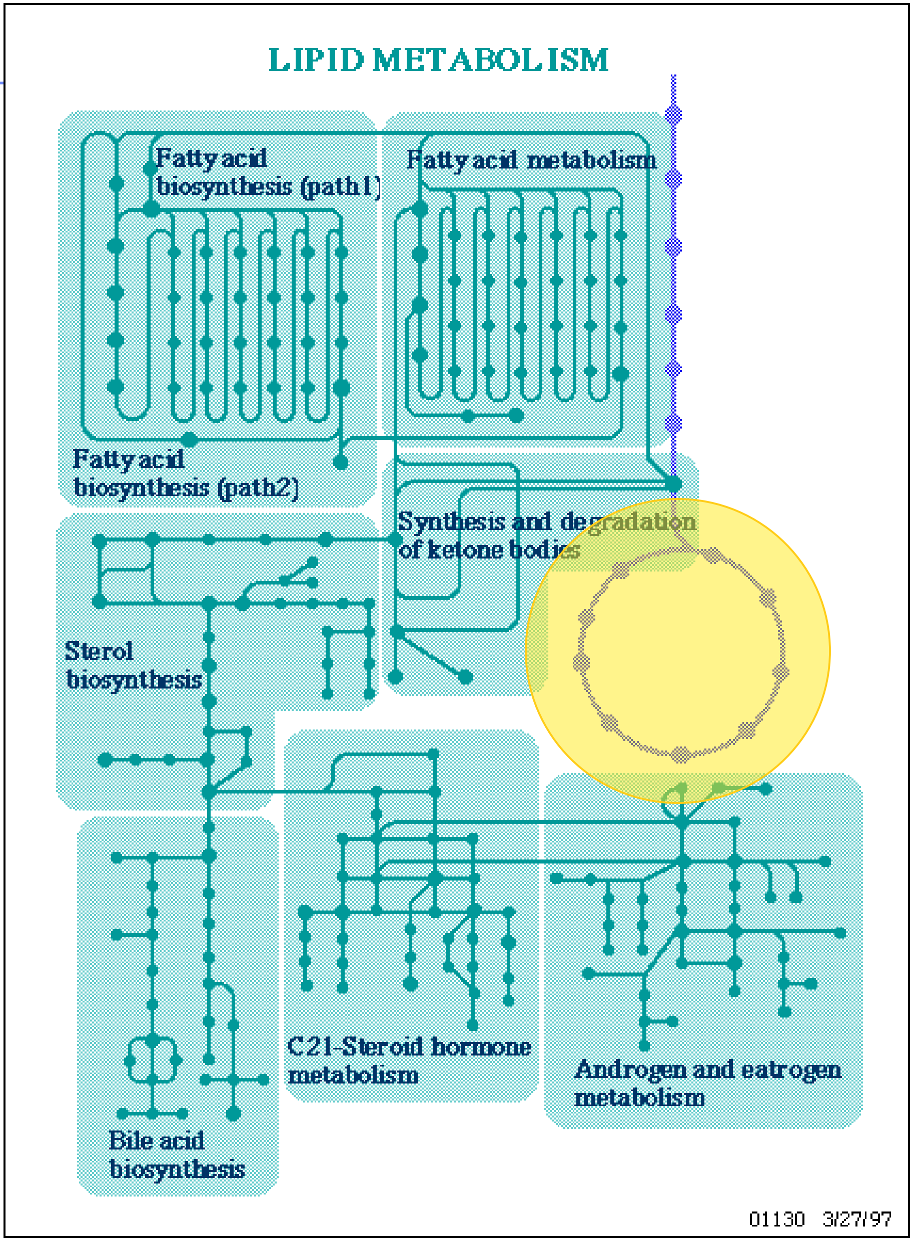
- The many stops on the Carbohydrate Line



gluconeogenesis

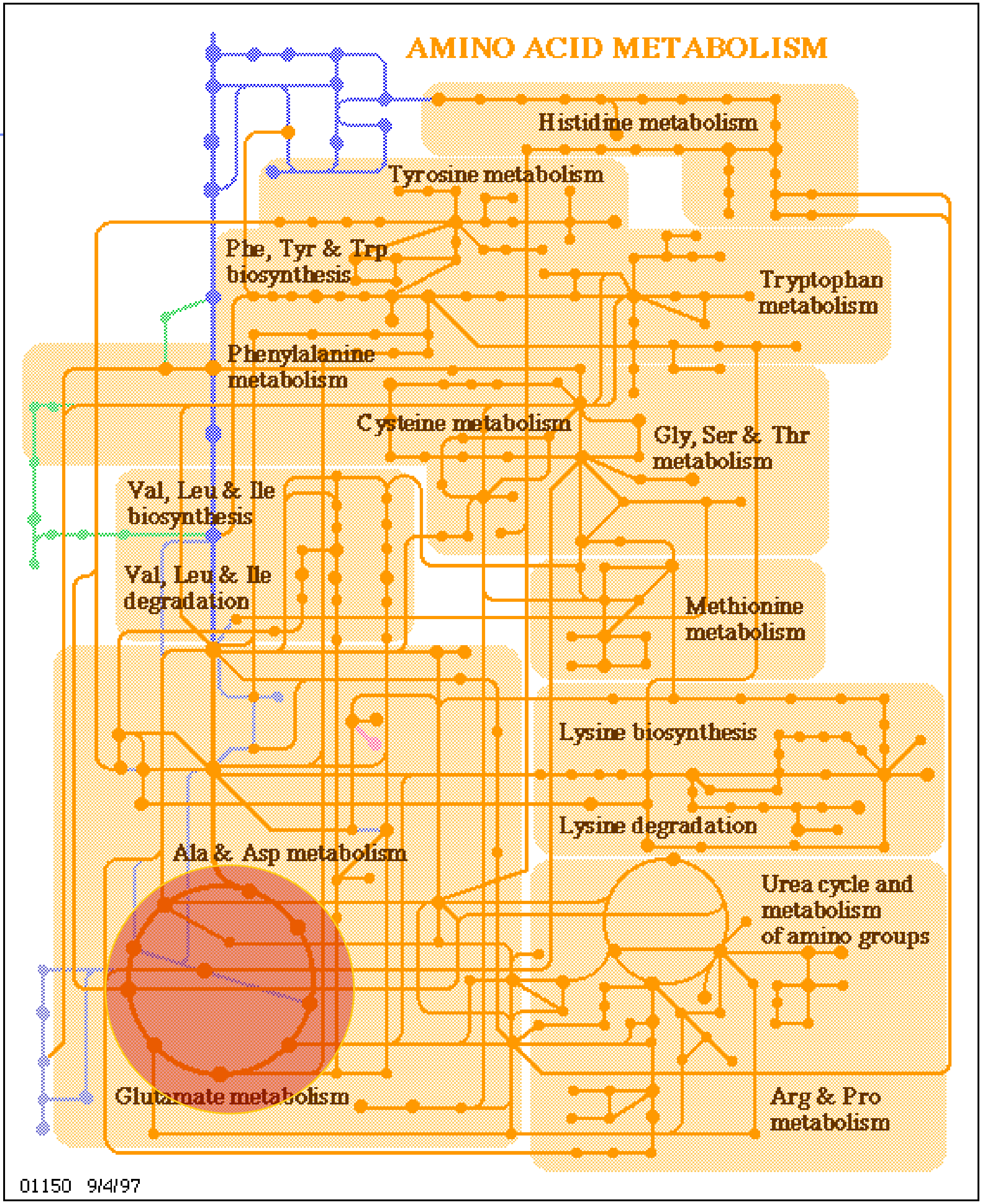
Lipid Metabolism

- The many stops on the Lipid Line



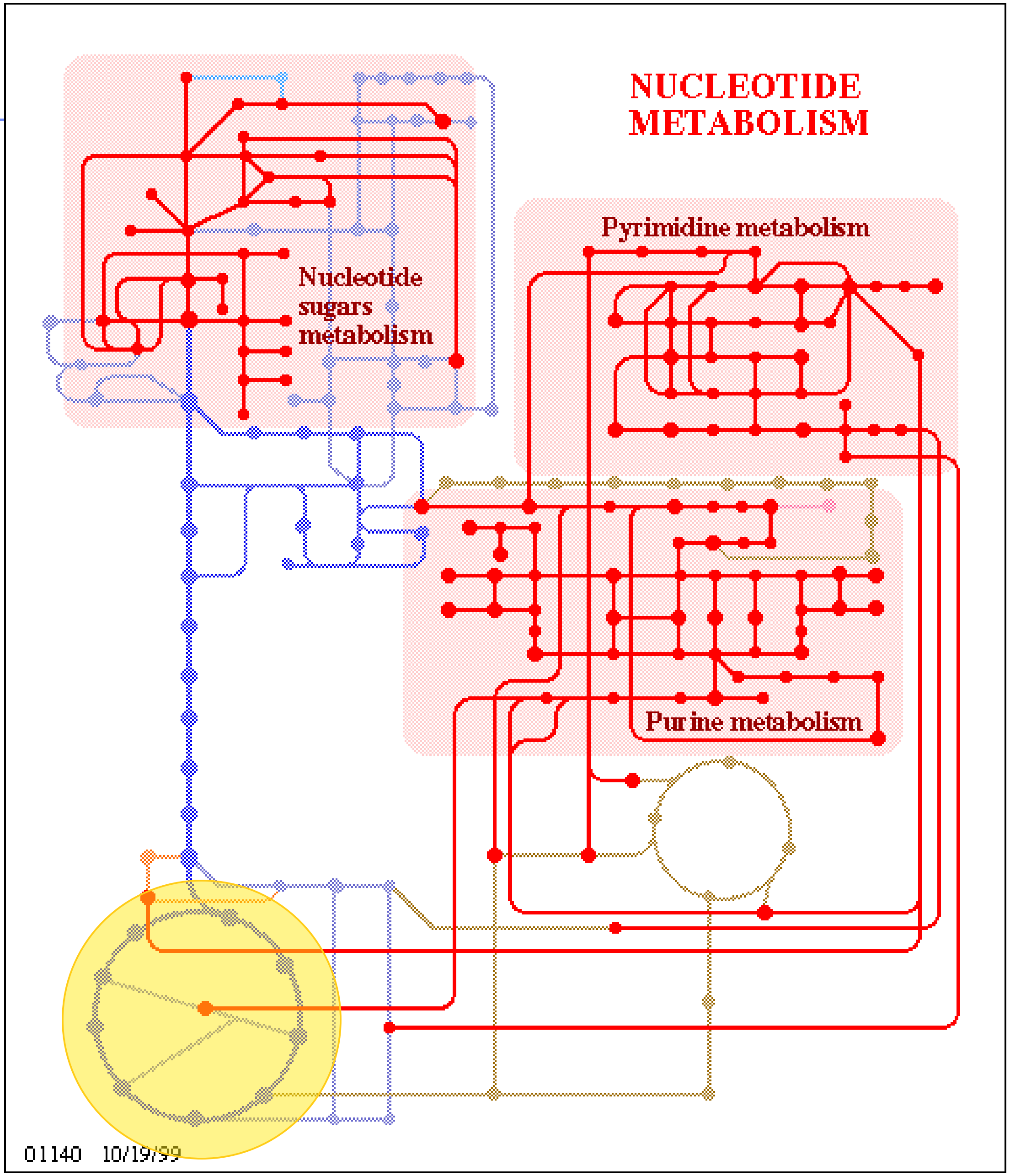
Amino Acid Metabolism

- The many stops on the AA Line



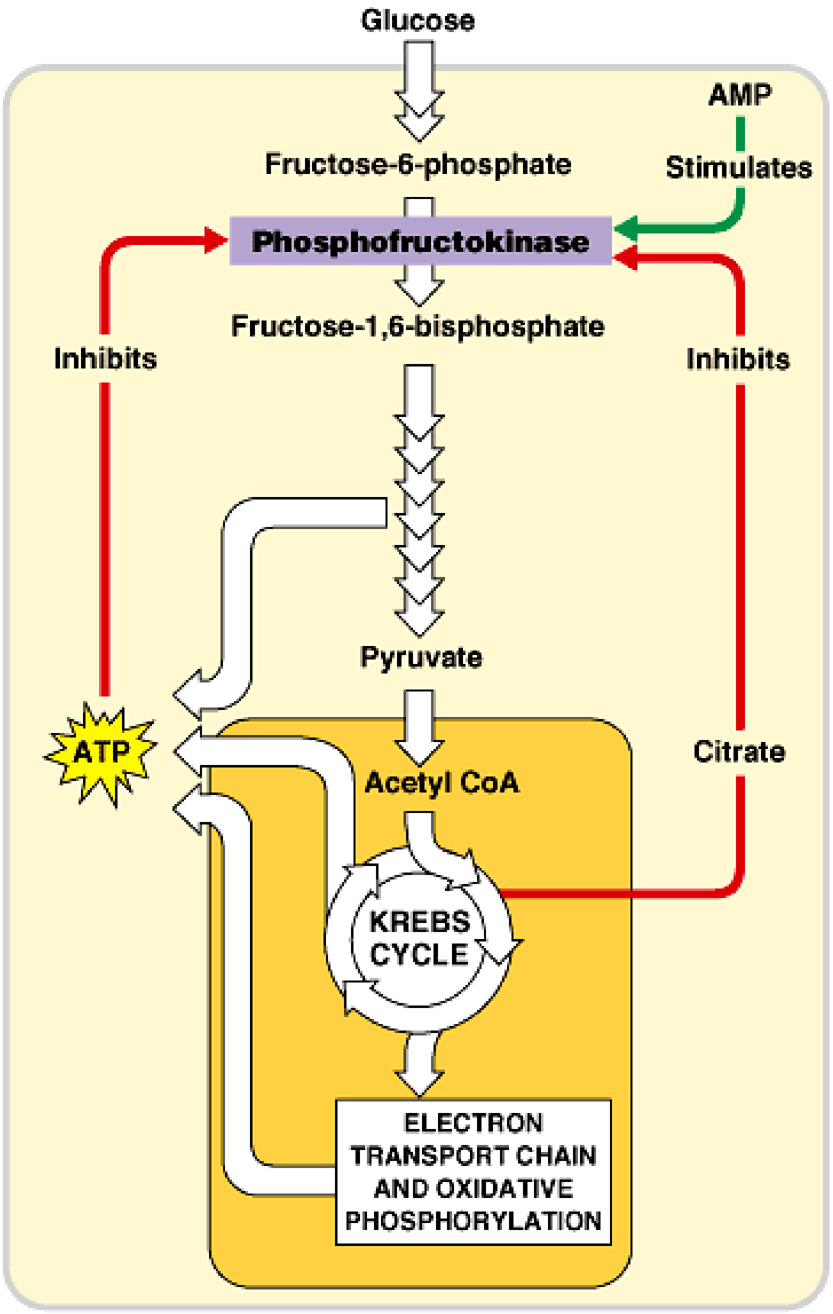
Nucleotide Metabolism

- The many stops on the GATC Line



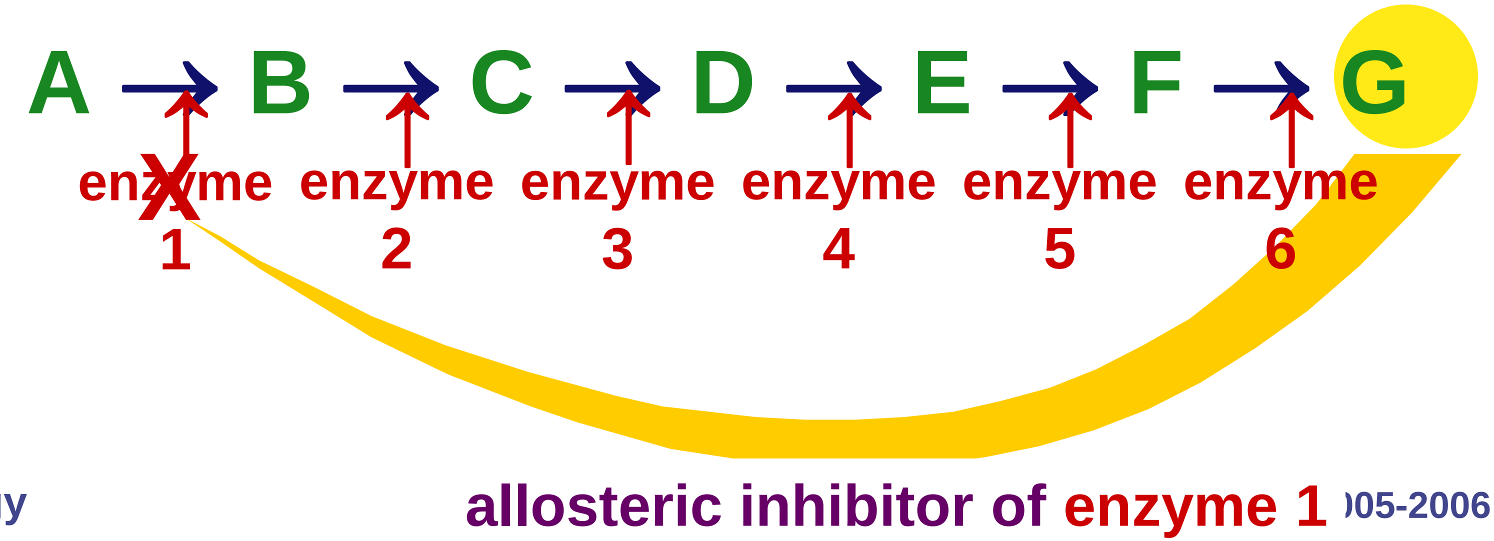
Control of Respiration

Feedback Control



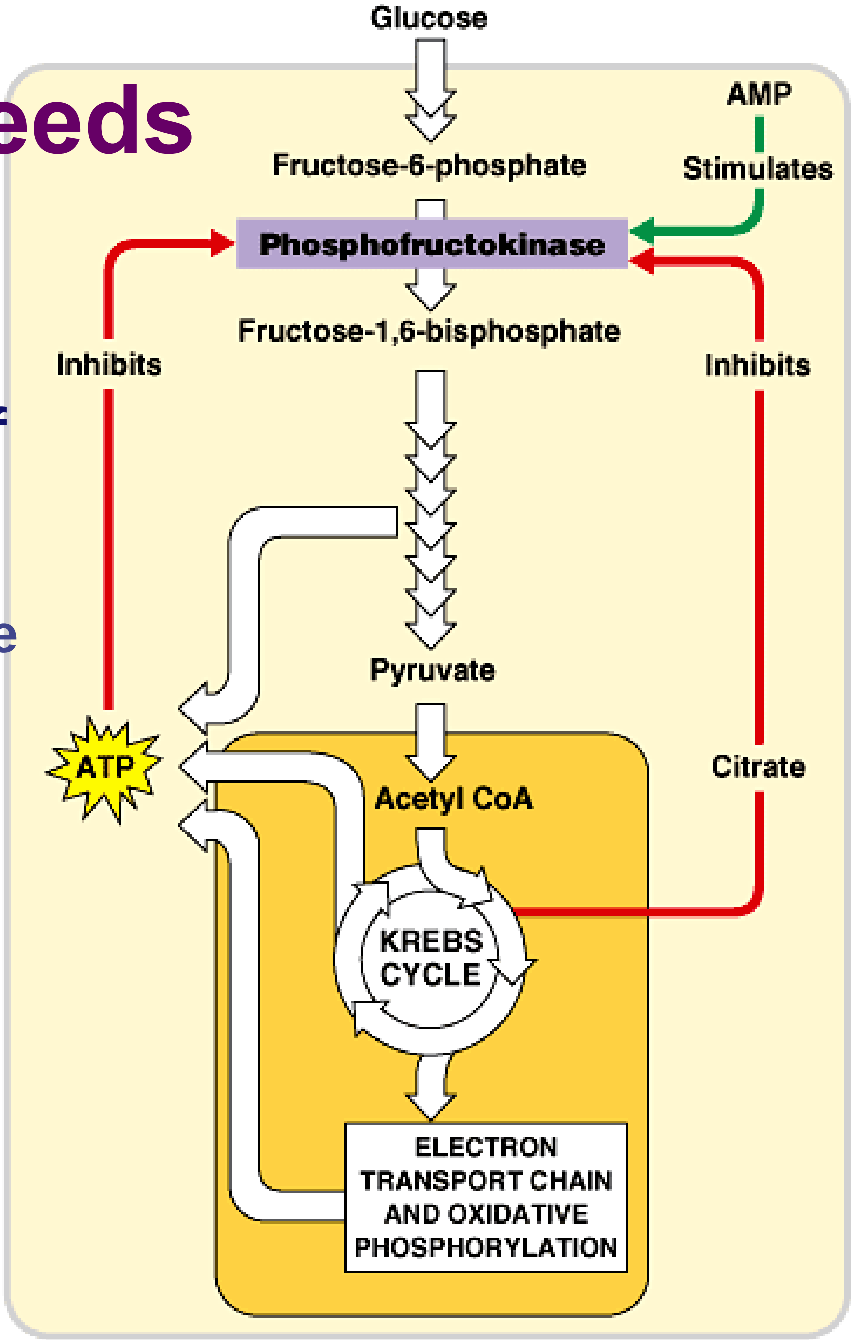
Feedback Inhibition

- **Regulation & coordination of production**
  - production is self-limiting
  - final product is inhibitor of earlier step
    - allosteric inhibitor of earlier enzyme
  - no unnecessary accumulation of product



Respond to cell's needs

- Key points of control
  - phosphofructokinase
    - allosteric regulation of enzyme
      - "can't turn back" step before splitting glucose
    - AMP & ADP stimulate
    - ATP inhibits
    - citrate inhibits



Why is this regulation important?

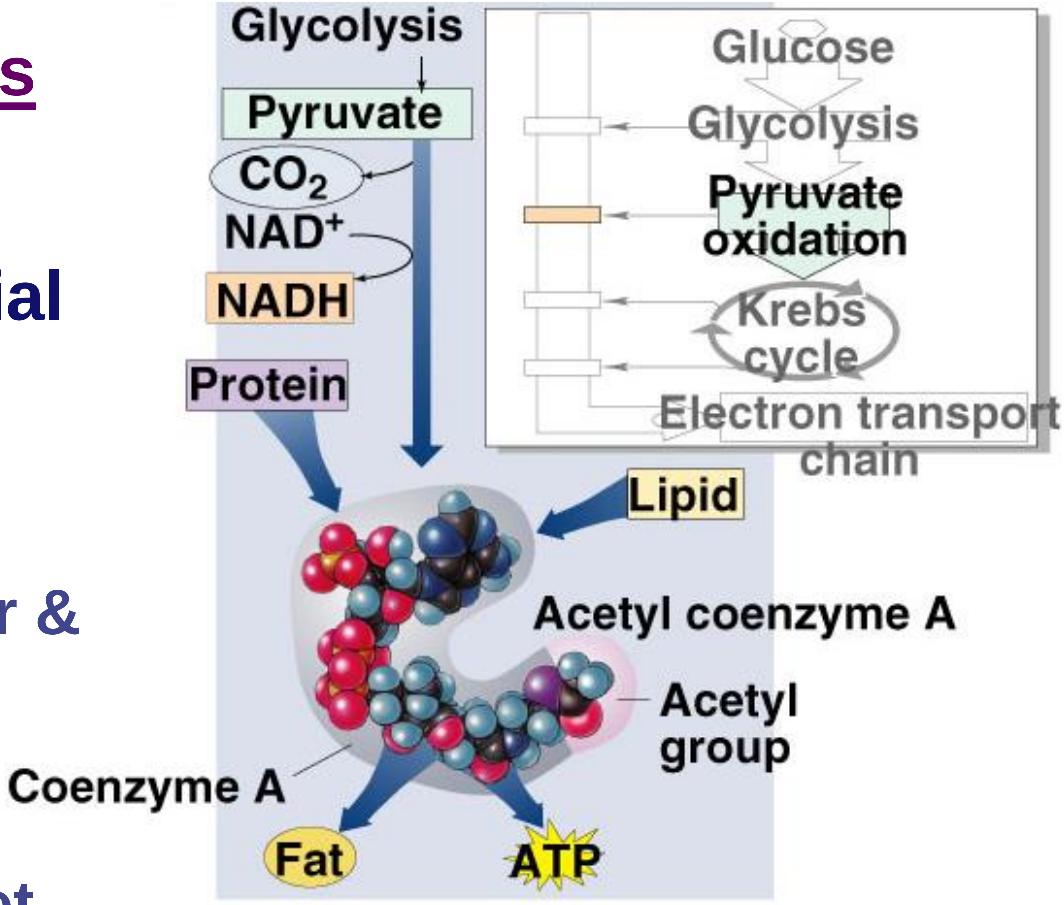
Balancing act:
availability of raw materials vs. energy demands vs. synthesis

A Metabolic economy

- **Basic principles of supply & demand regulate metabolic economy**
  - **balance the supply of raw materials with the products produced**
  - **these molecules become feedback regulators**
    - **they control enzymes at strategic points in glycolysis & Krebs cycle**
      - **AMP, ADP, ATP**
        - **regulation by final products & raw materials**
      - **levels of intermediates compounds in the pathways**
        - **regulation of earlier steps in pathways**
      - **levels of other biomolecules in body**
        - **regulates rate of siphoning off to synthesis pathways**

It's a Balancing Act

- Balancing synthesis with availability of both energy & raw materials is essential for survival!
  - do it well & you survive longer
  - you survive longer & you have more offspring
  - you have more offspring & you get to "take over the world"



Acetyl CoA is central to both energy production & synthesis
make ATP or store it as fat

Any Questions??