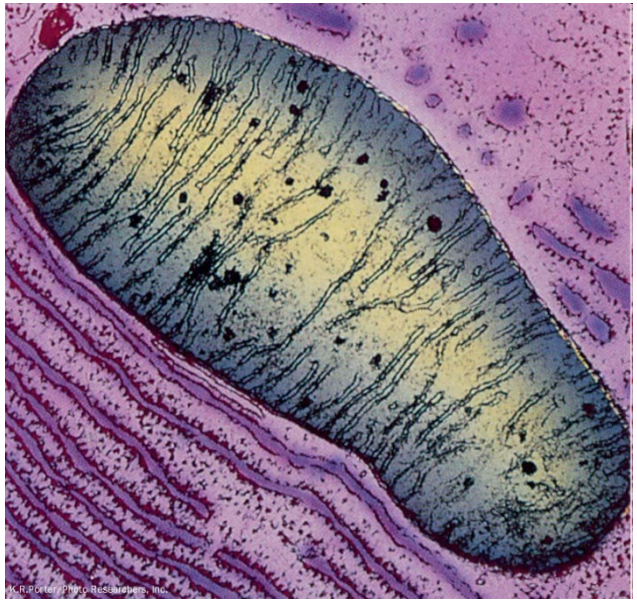
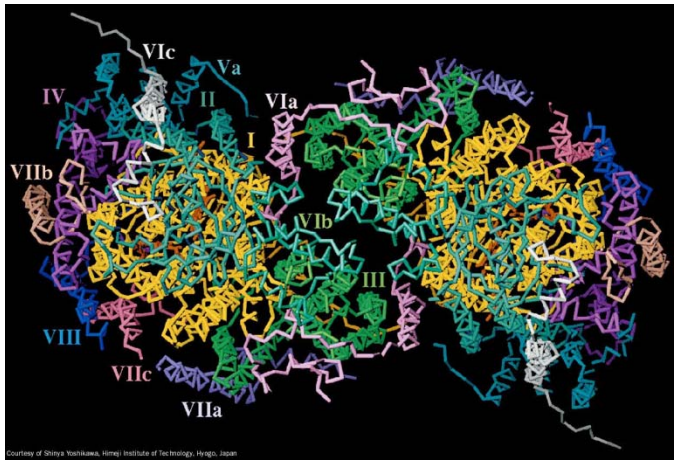
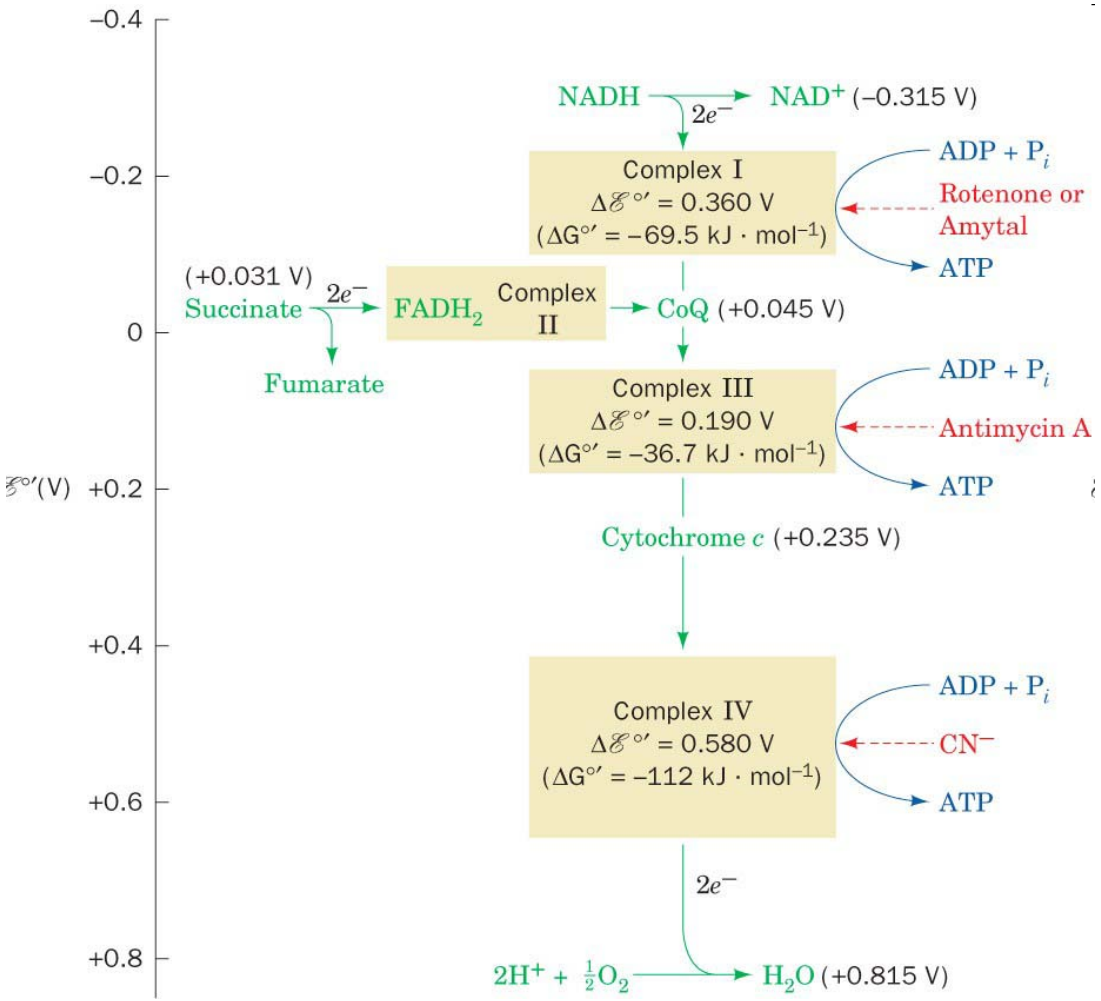
Oxidative Phosphorylation



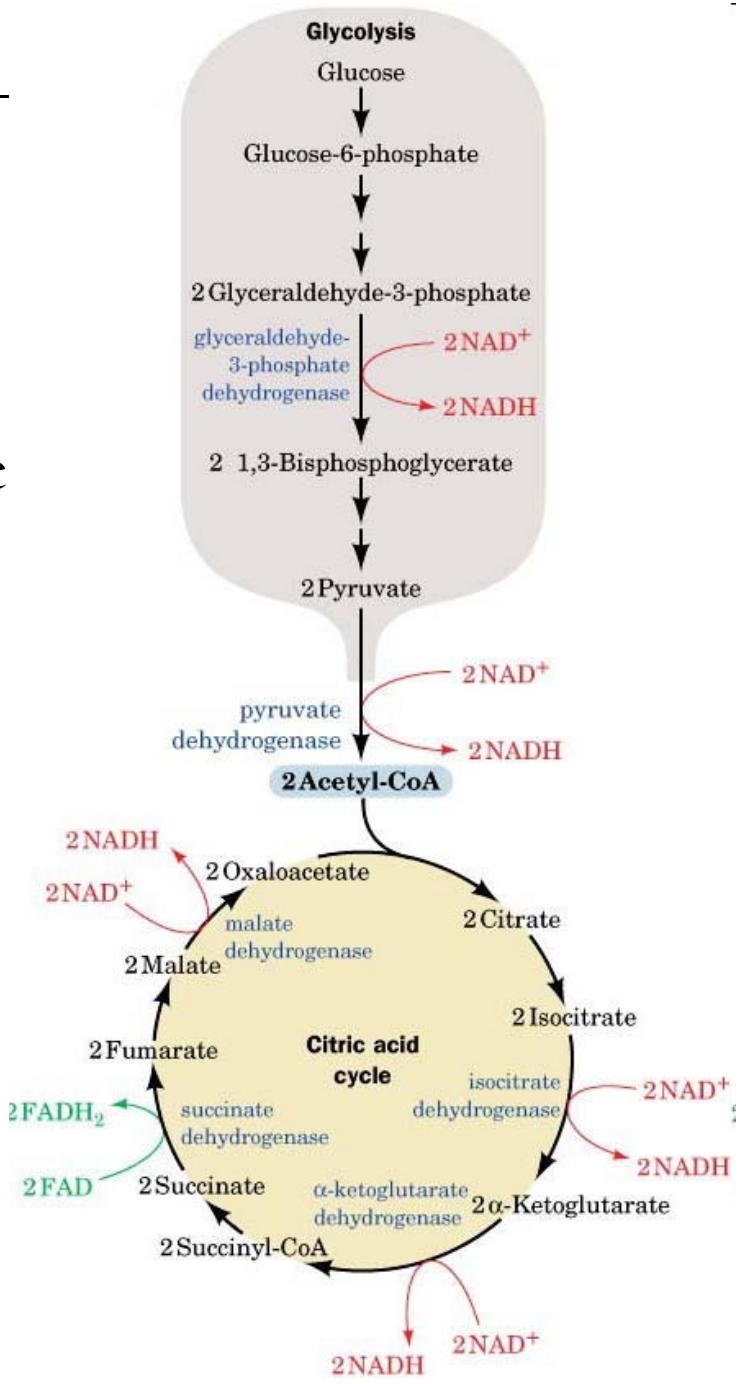




Oxidative Phosphorylation

- In Glycolysis and the citric acid cycle, we've made a lot of reduced cofactors NADH and $FADH_2$

- In oxidative phosphorylation, we use the energy generated by reoxidation of these cofactors to make ATP



Reduction Potential

- Reduction potential E^o is a measure of how much a molecule likes to gain electrons.

- In a reaction $\Delta E^o = E^o_{(acceptor)} - E^o_{(donor)}$

- Thus:

$NAD^+ + H^+ + 2e^- \leftrightarrow NADH$ $\quad E^o = -0.315$ V

$\frac{1}{2}O_2 + 2H^+ + 2e^- \leftrightarrow H_2O$ $\quad E^o = 0.815$ V

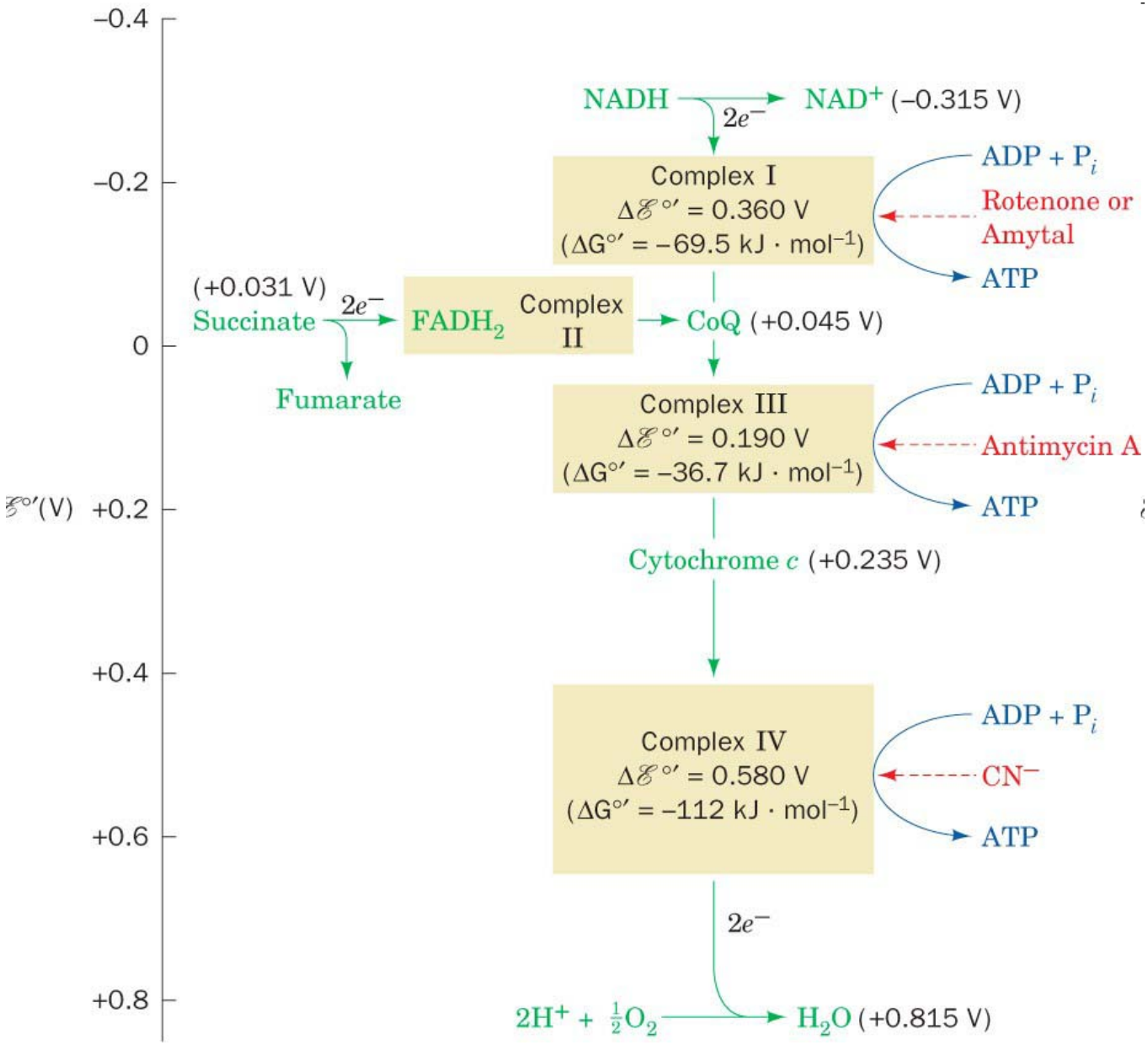
$NADH + H^+ + 2e^- + \frac{1}{2}O_2 \leftrightarrow NAD^+ + H_2O$ $\quad \Delta E^o = 1.130$ V

- Converting to ΔG:

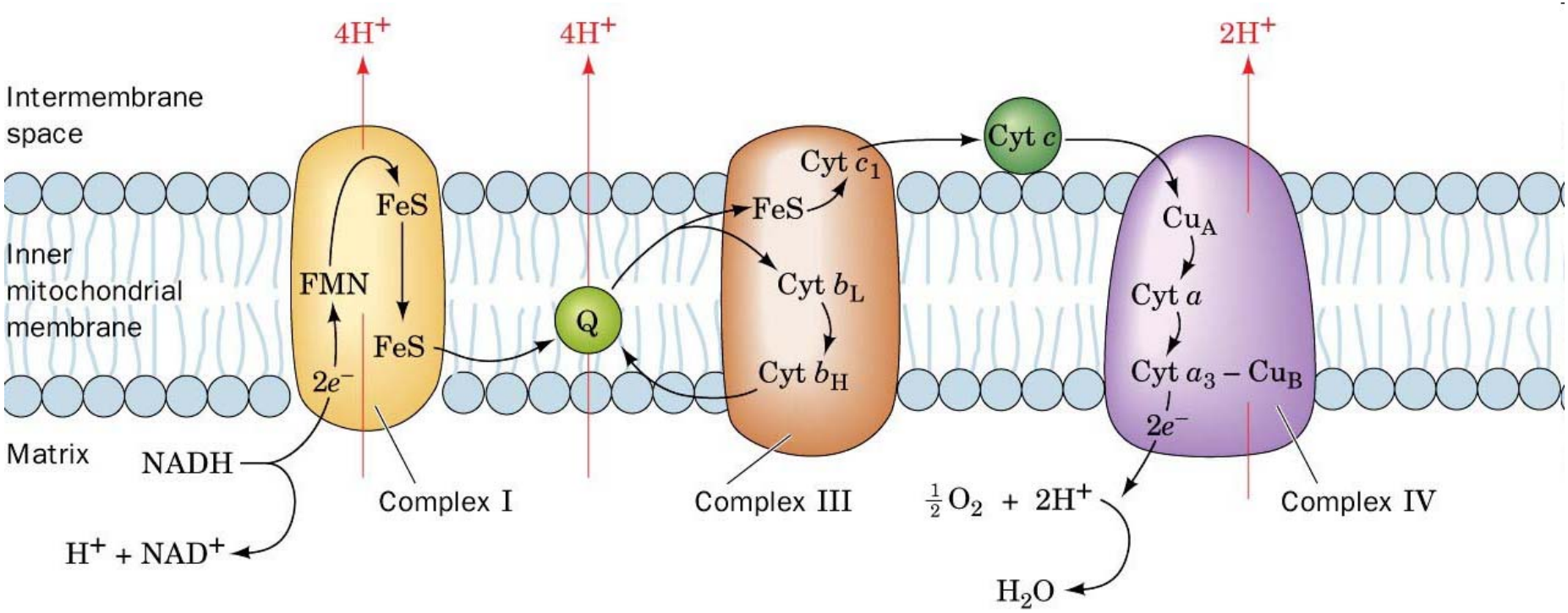
$$\Delta G = -nF(\Delta E^o)$$

(n: # e^-; F: Faraday's const: 96,485 C/mol)

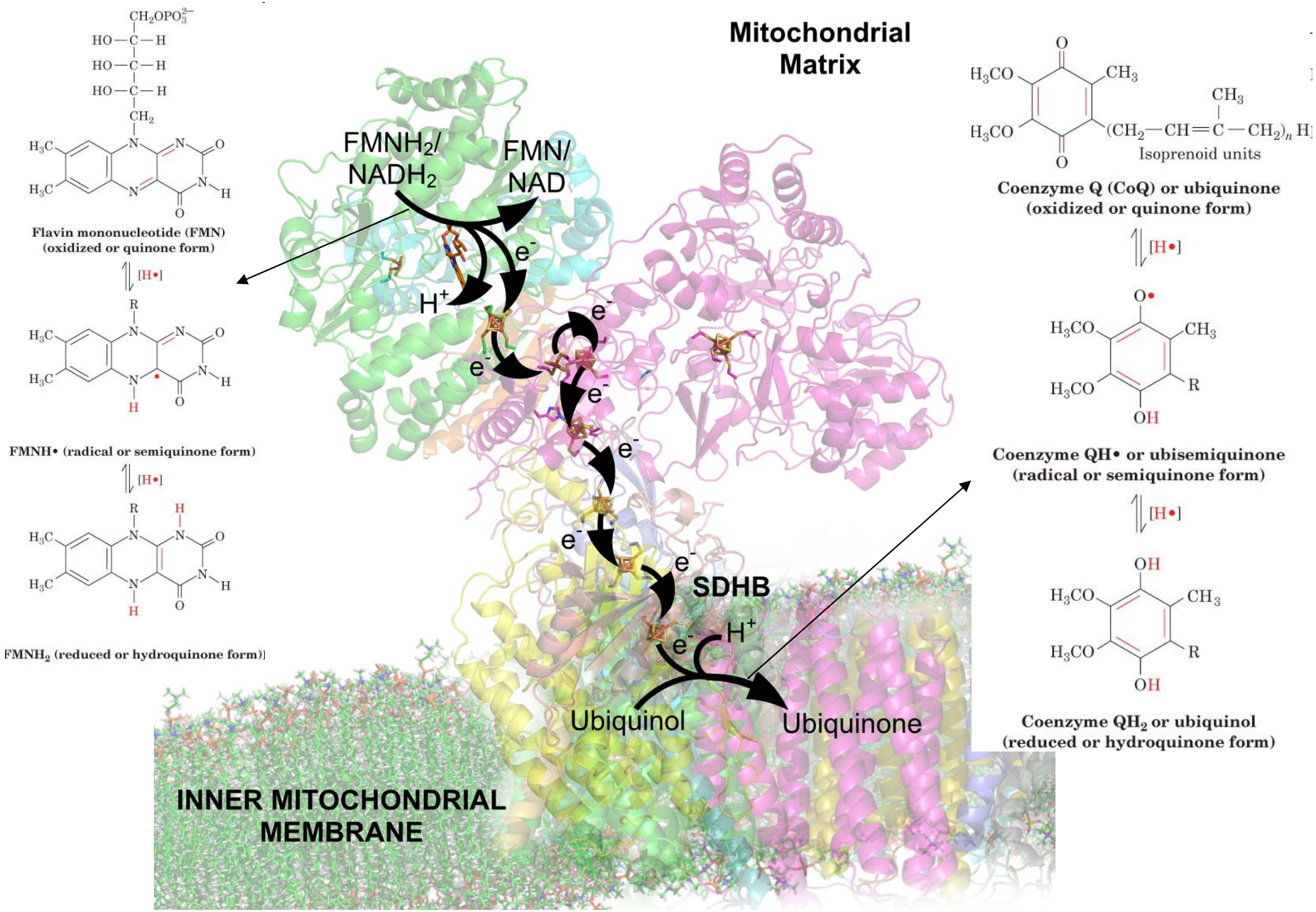
Reduction Potential and Oxidative Phosphorylation



The Complexes: Pumping out protons

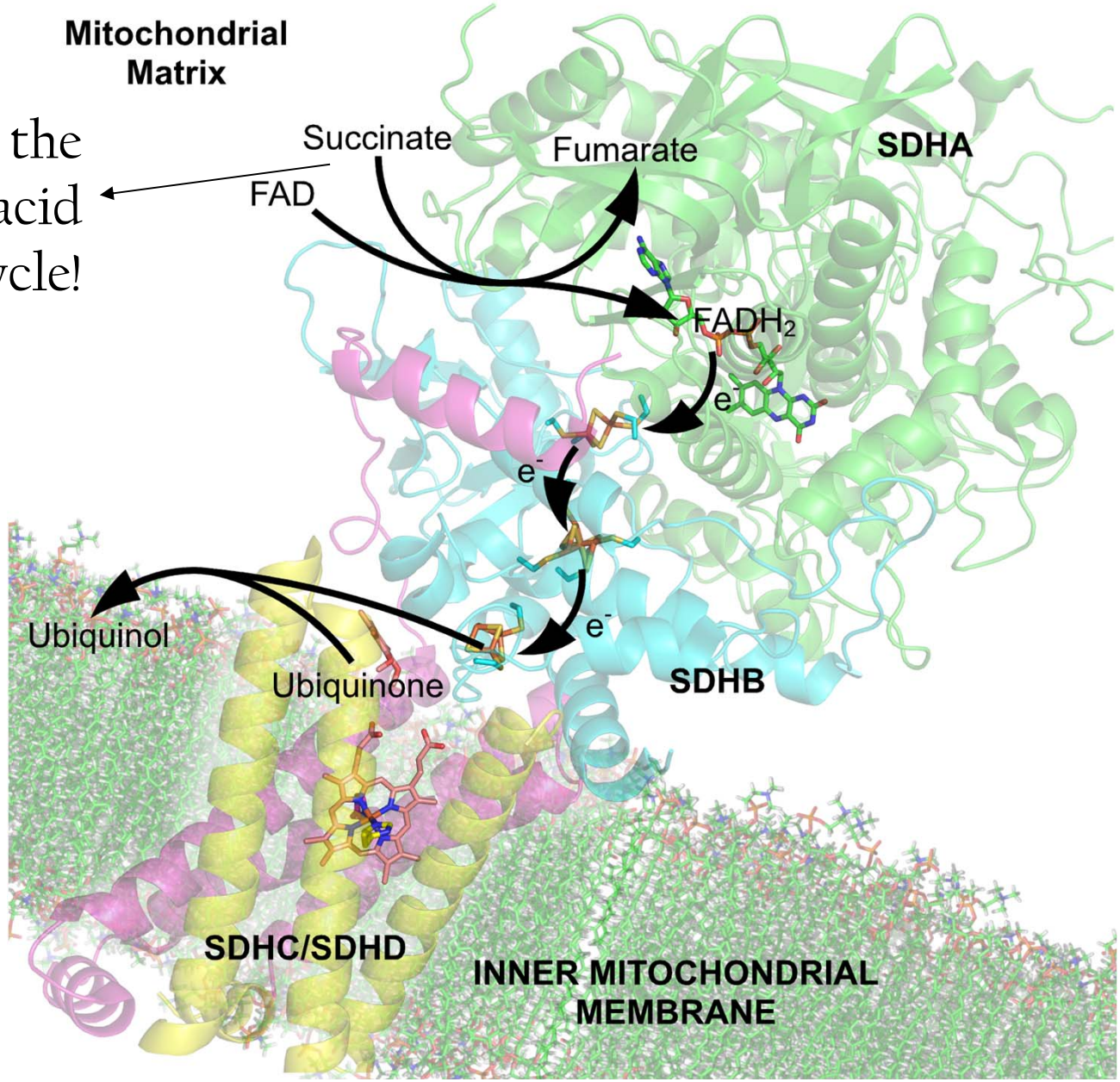


Complex 1: NADH Co-Q Oxidoreductase



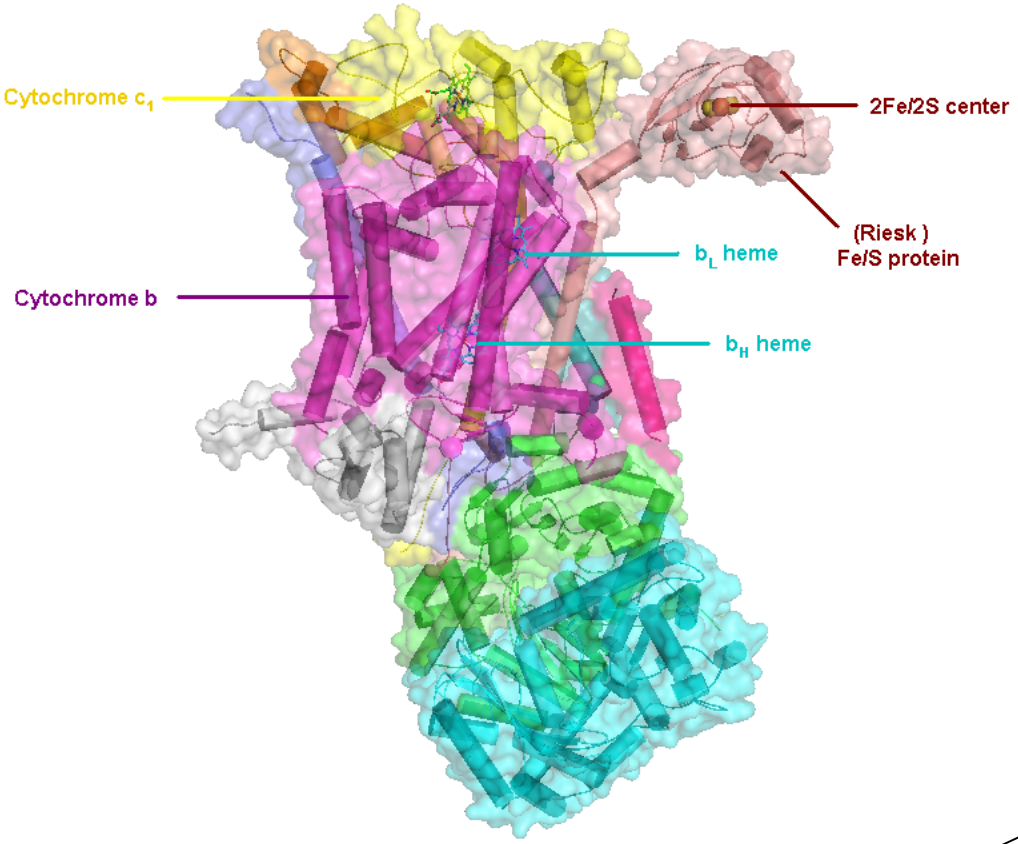
Complex 2: Succinate:Co-Q Oxidoreductase

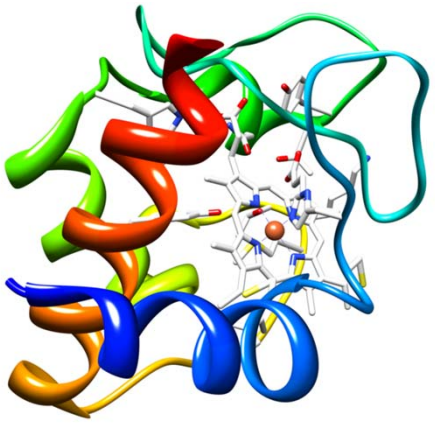
From the citric acid cycle!

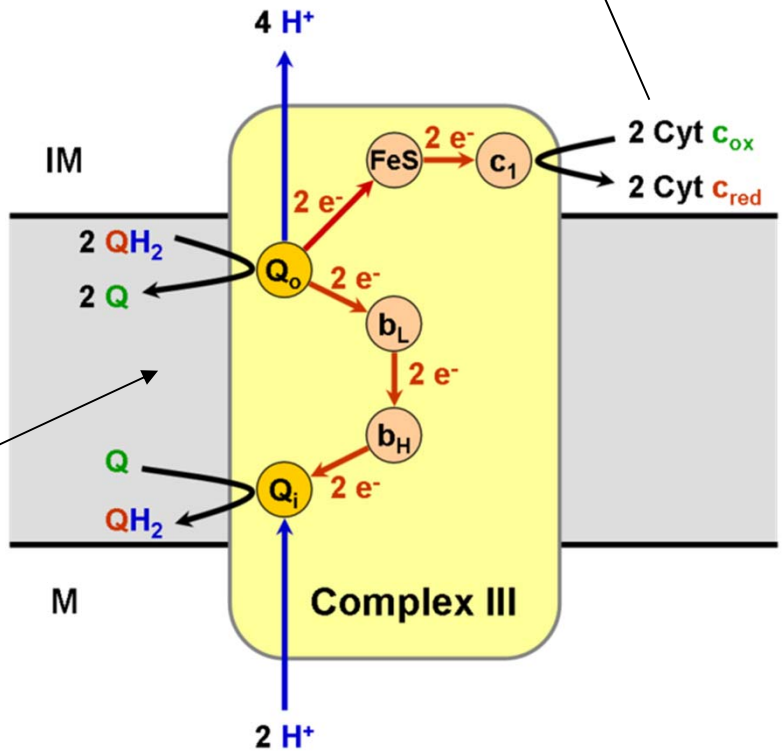


Purpose: To regenerate ubiquinol

Complex 3: Co-Q:Cytochrome c oxidoreductase

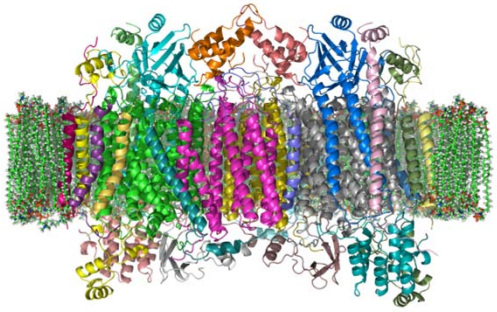




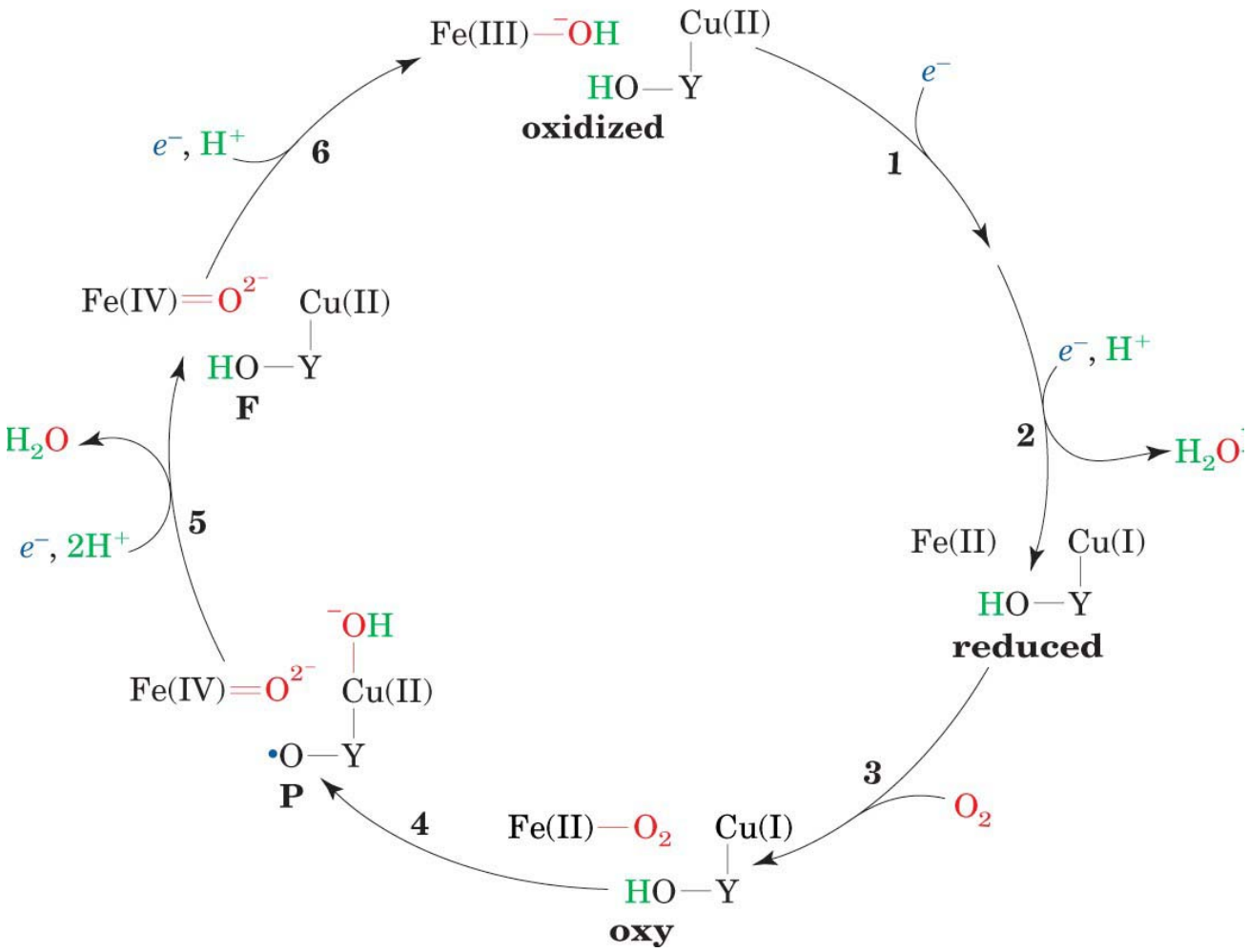


The Q-cycle

Complex IV: Cytochrome C oxidase (COX)

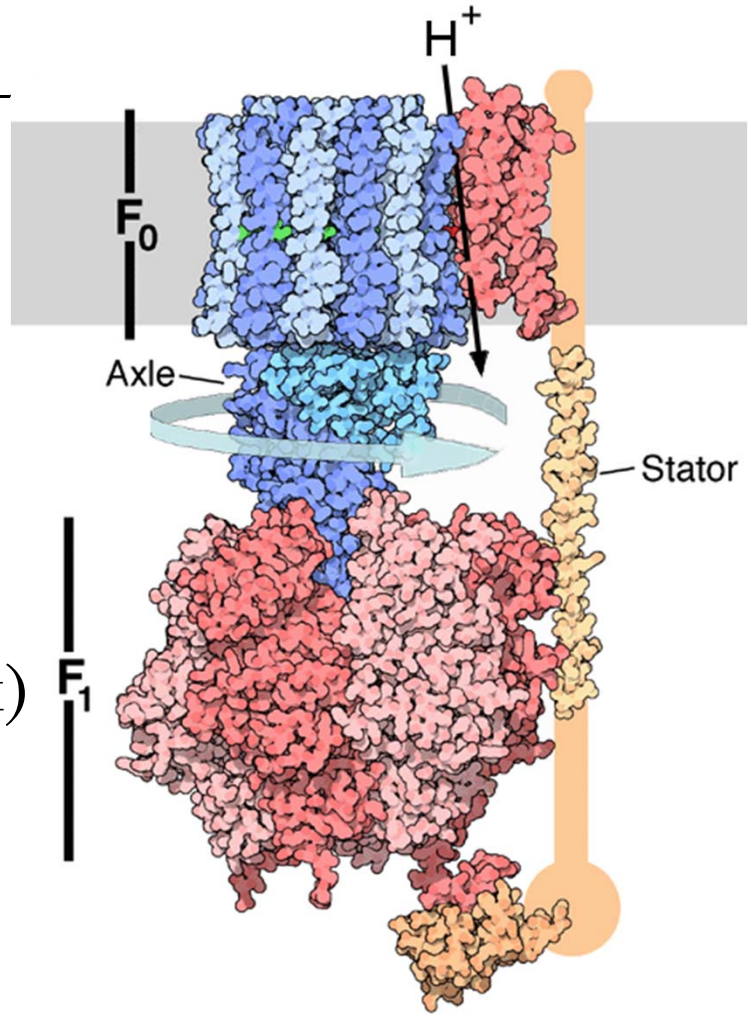


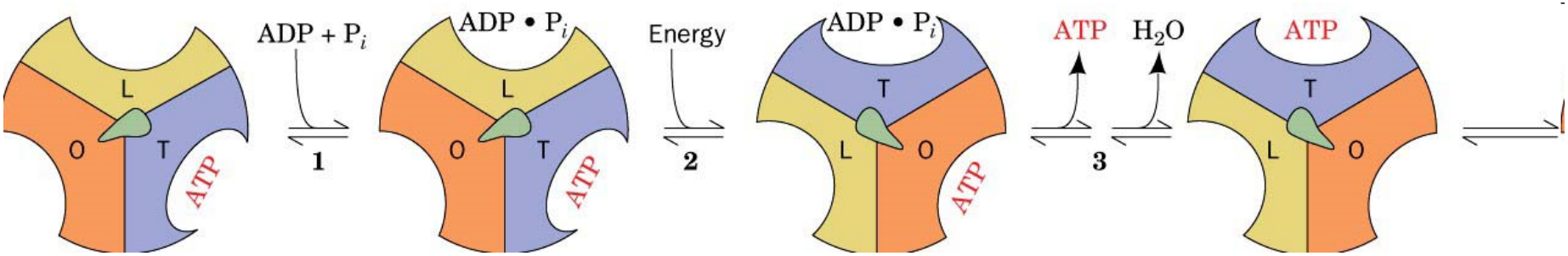
4 Fe^{2+}-cytochrome *c* + 8 H^+_{in} + O_2 →
4 Fe^{3+}-cytochrome *c* + 2 H_2O + 4 H^+_{out}



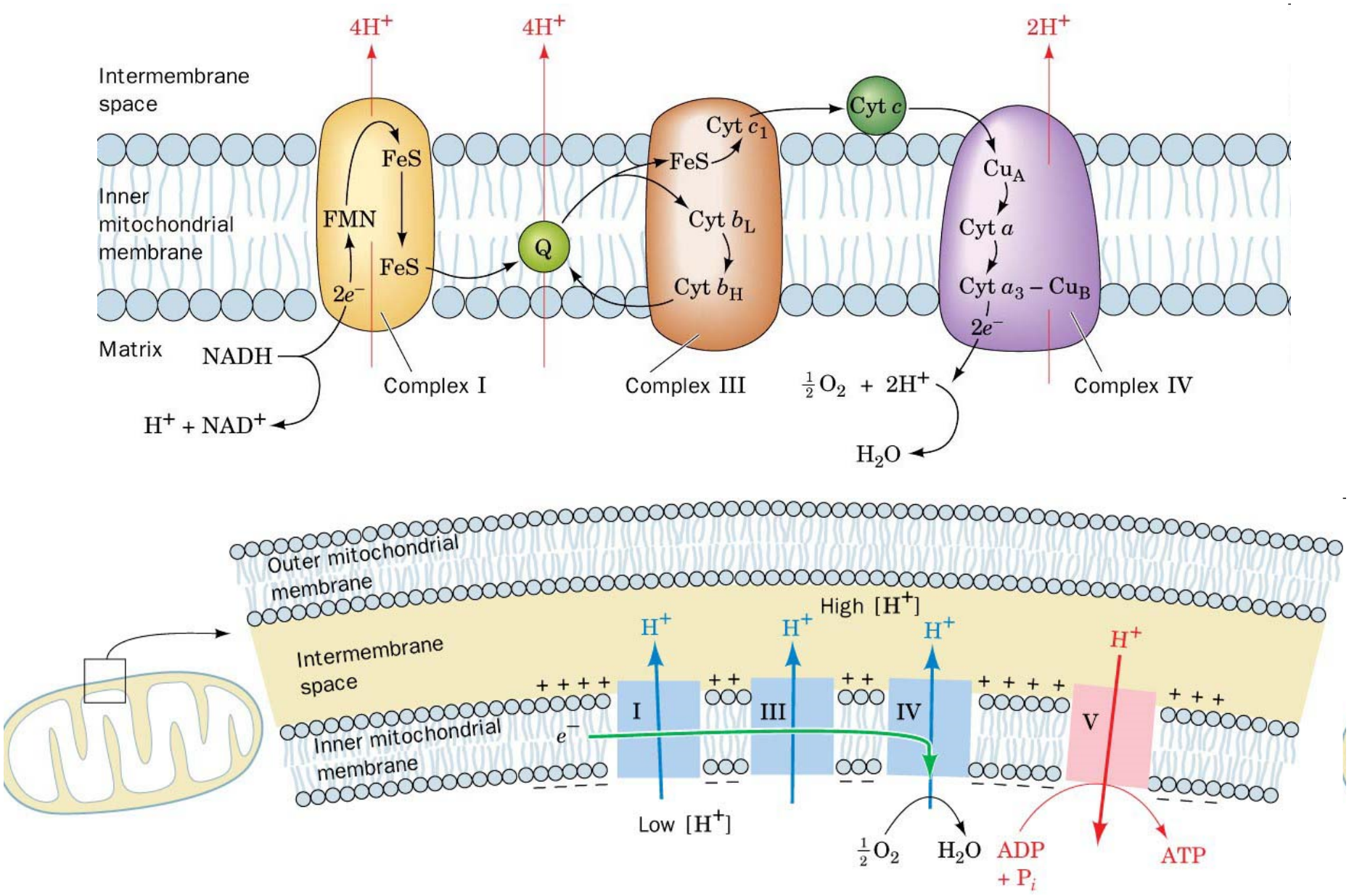
Complex V: ATP synthase

- This large complex uses the proton gradient to drive the phosphorylation of ADP.





Summing up Oxidative Phosphorylation



Control of Oxidative Phosphorylation

- Oxidative phosphorylation is a target for many highly effective poisons, but is only weakly controlled metabolically.

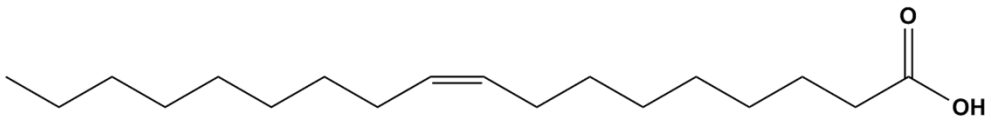
- It is possible to 'uncouple' oxidative phosphorylation by making the inner mitchondrial membrane permeable (dinitrophenol and fatty acids in brown fat).

- Generally, control boils down to the strength of the matrix/ intermembrane space proton gradient. If it's too high, oxidative phosphorylation backs up at Complex I.

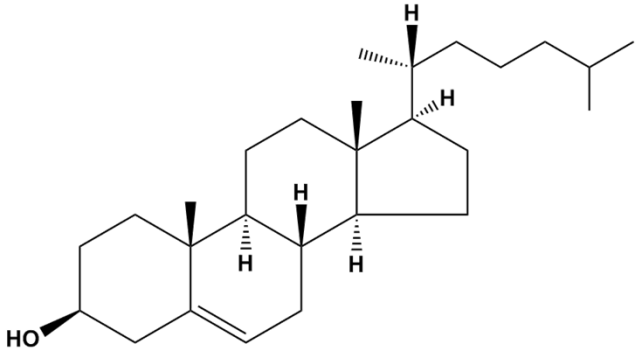
- Otherwise, control is via the presence or absence of NADH and/or ADP (acceptor control).

Lipid Metabolism

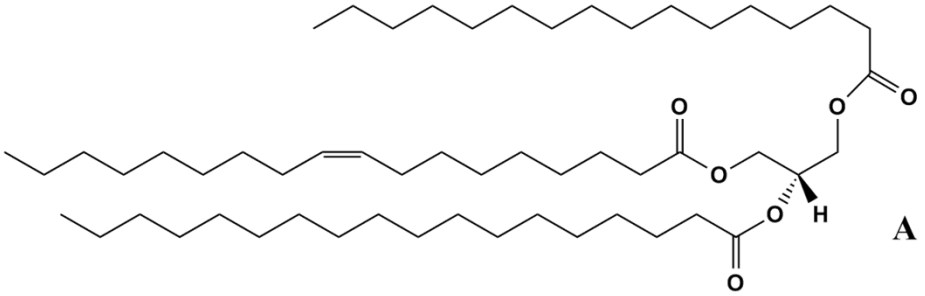
- Lipids are loosely defined: Fat soluble (lipophilic) molecules



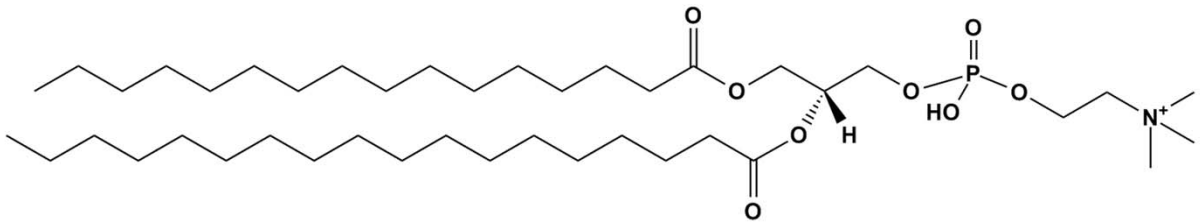
A free fatty acid



Cholesterol



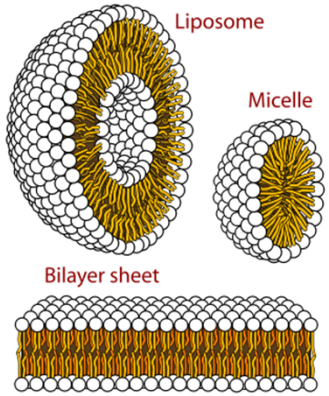
A triglyceride



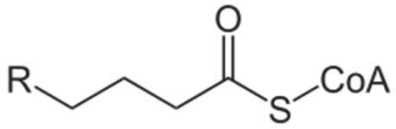
A phospholipid

Biological Roles of Lipids

- Lipids can do all kinds of stuff:
  - Membranes (phospholipids)

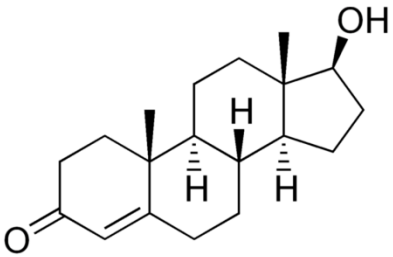


  - Energy Storage and Metabolism



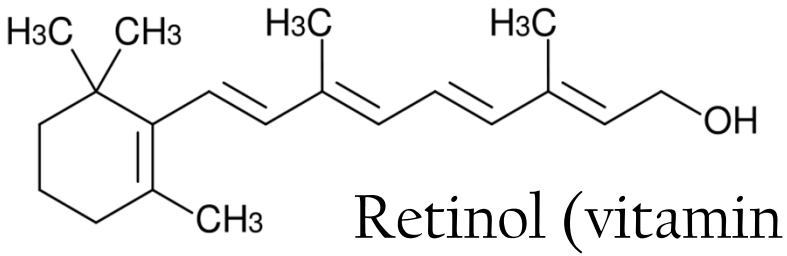
Acyl-CoA

  - Signaling



testosterone

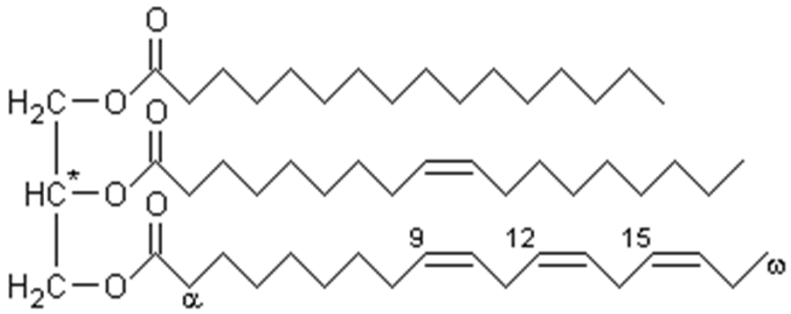
  - Vitamins, intermediates



Retinol (vitamin A)

Lipids and Energy Storage

- The primary long term energy storage molecules of the body are Triacylglycerols, e.g.



- Good for energy storage because:
  - Carbons are in lower oxidation states
  - Triacyclycerols exclude water (higher energy/weight)

Constituent	ΔH(kJ · g^{-1} dry weight)
Carbohydrate	16
Fat	37
Protein	17

Source: Newsholme, E.A. and Leech, A.R., *Biochemistry for the Medical Sciences,* p. 16, Wiley (1983).

Triacylglycerols to Fatty Acids

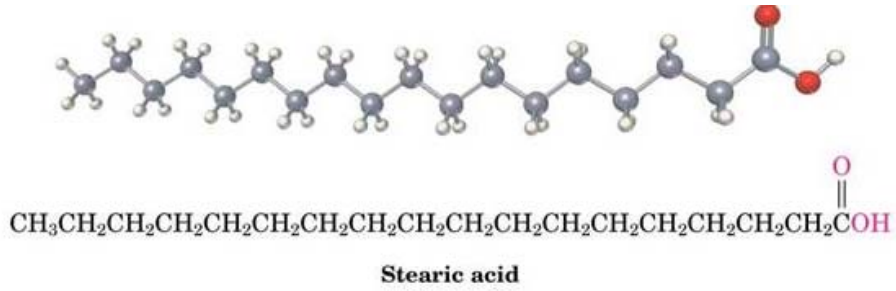
- Breakdown of triacylglycerols to liberate fatty acids is by lipase enzymes, mostly in the pancreas

- Attacks C_1 and C_3 to form sequentially a 1,2-diacylglycerol and a 2-acylglycerol

- Mechanism is like chymotrypsin: Activated Serine nucleophilic attack on a carbonyl carbon with oxianion hole stabilization of the tetrahedral intermediate and the transition state

Fatty Acids

- Once we've got our fatty acids:

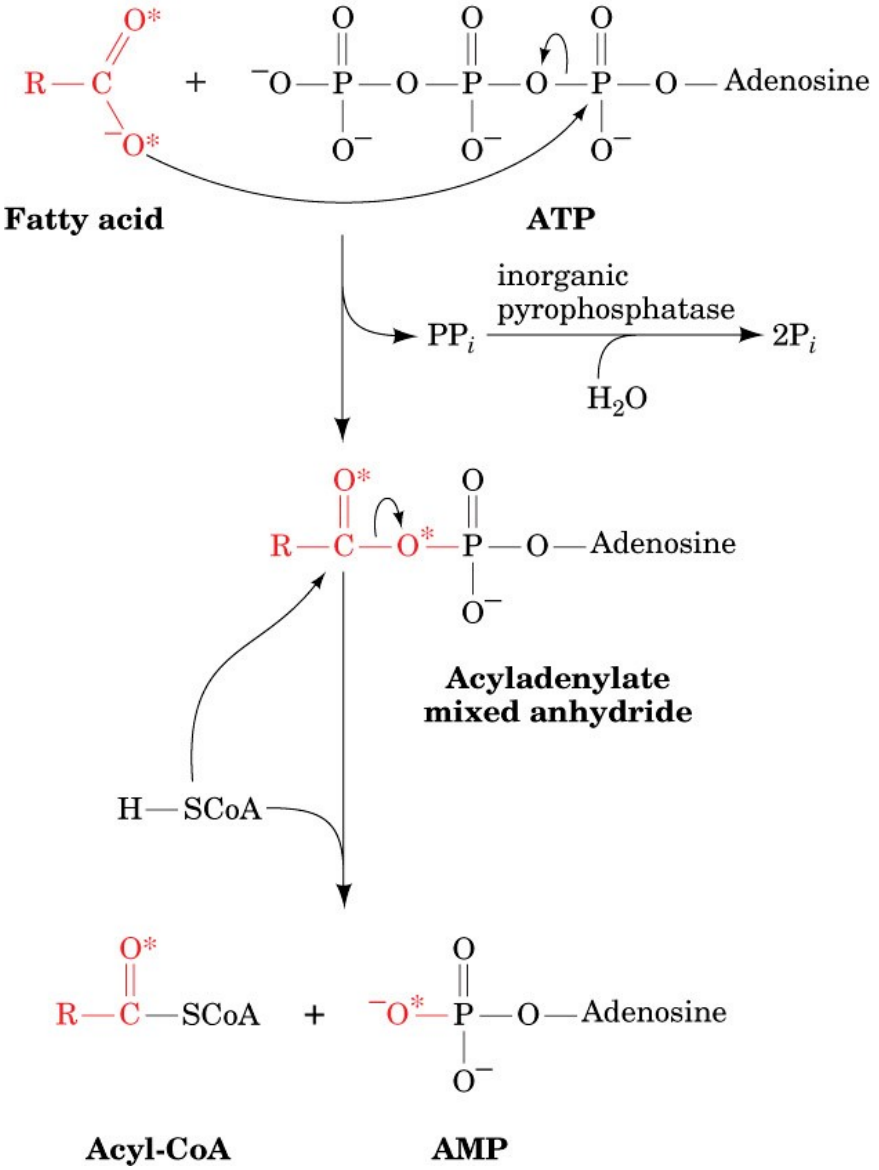


- We've gotta activate them!

- Acyl-coA Synthetase does it

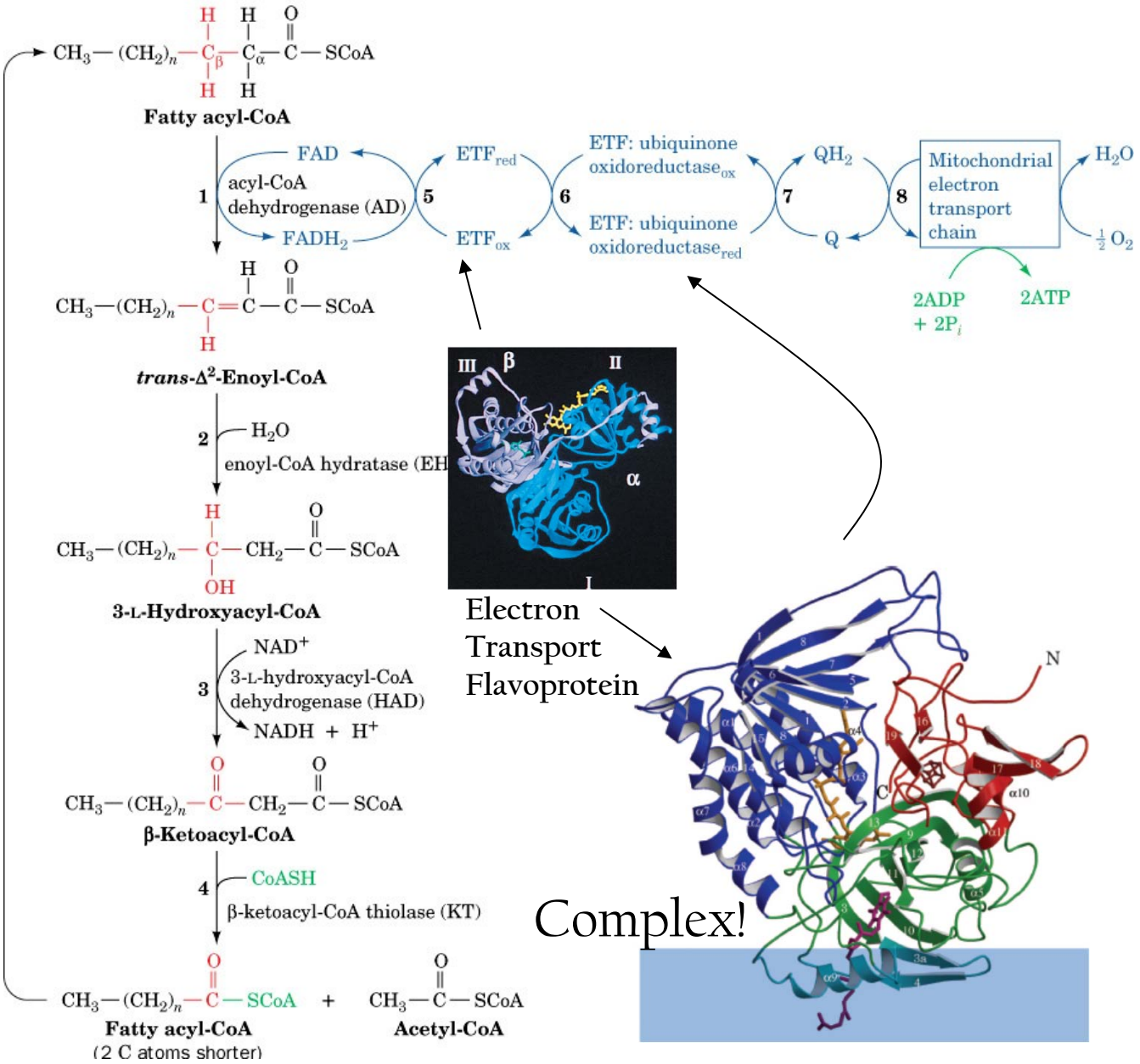
- Fatty acid → Acyl-CoA is ***endergonic***

- Hydrolysis of pyrophosphate is ***exergonic***



β-Oxidation of Acyl-CoA

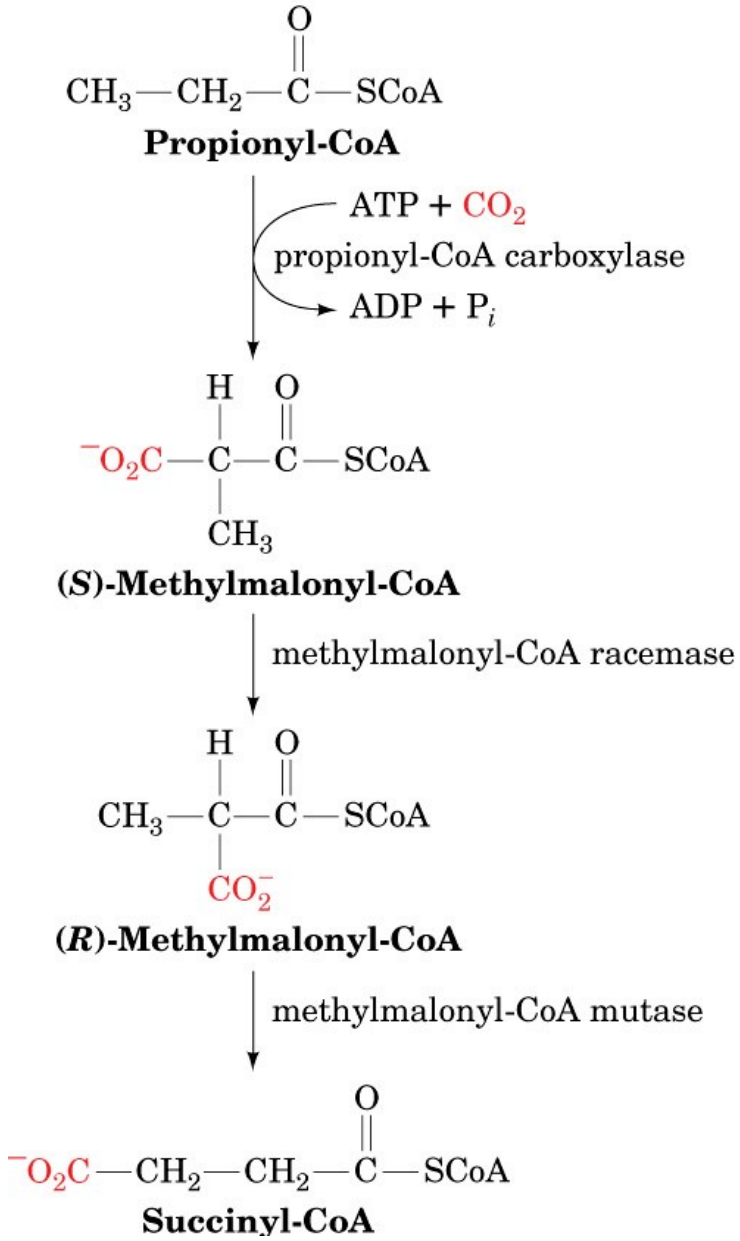
- We can feed both the citric acid cycle and oxidative phosphorylation with fatty acids:



Troubles With 'Different' Fatty Acids

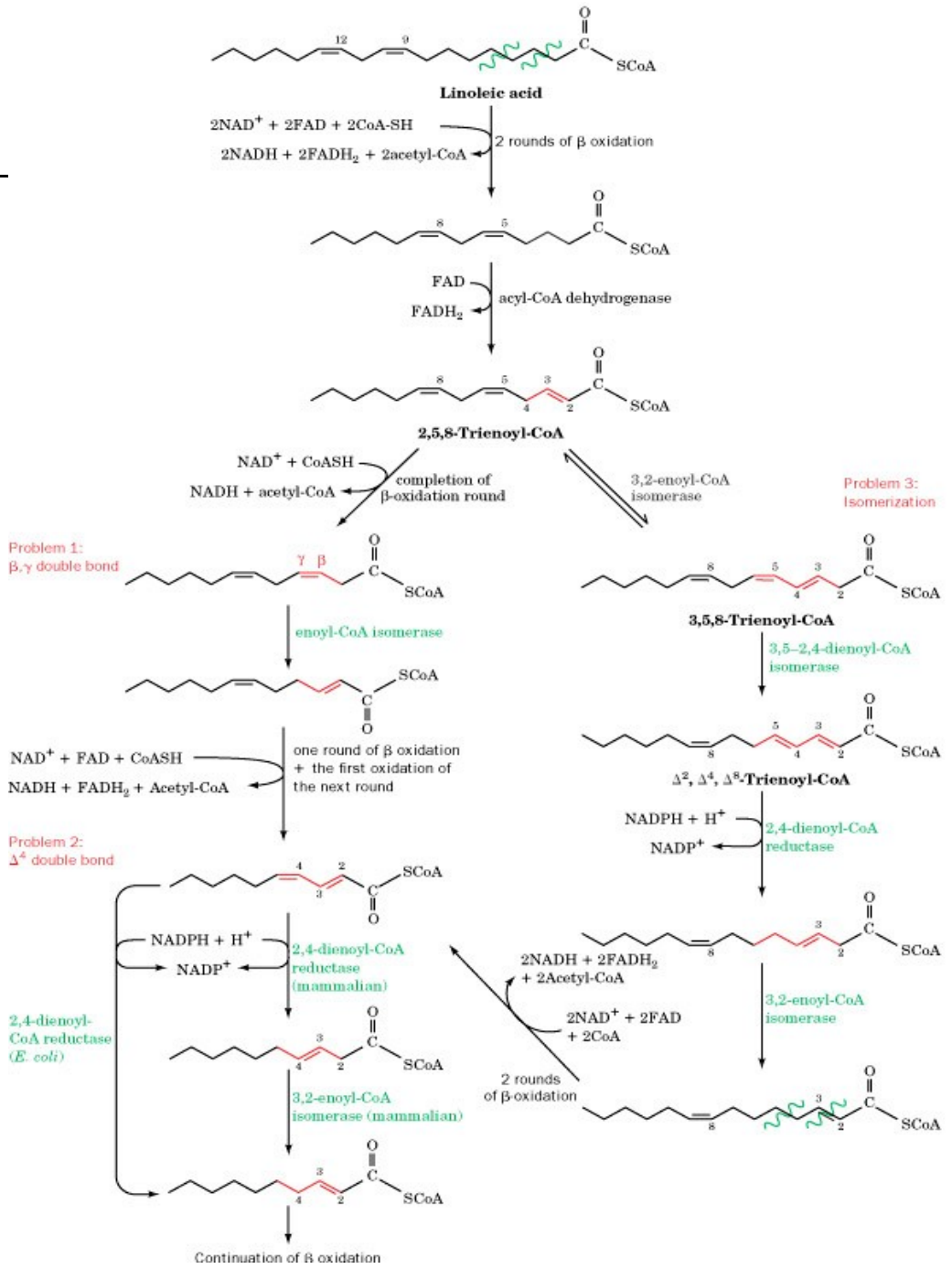
- Most fatty acids are even numbered chains, but if they're odd numbered, then we end up with propionyl-CoA instead of Acetyl-CoA

- This problem is solved by conversion to succinyl-CoA, which we can also feed into the citric acid cycle



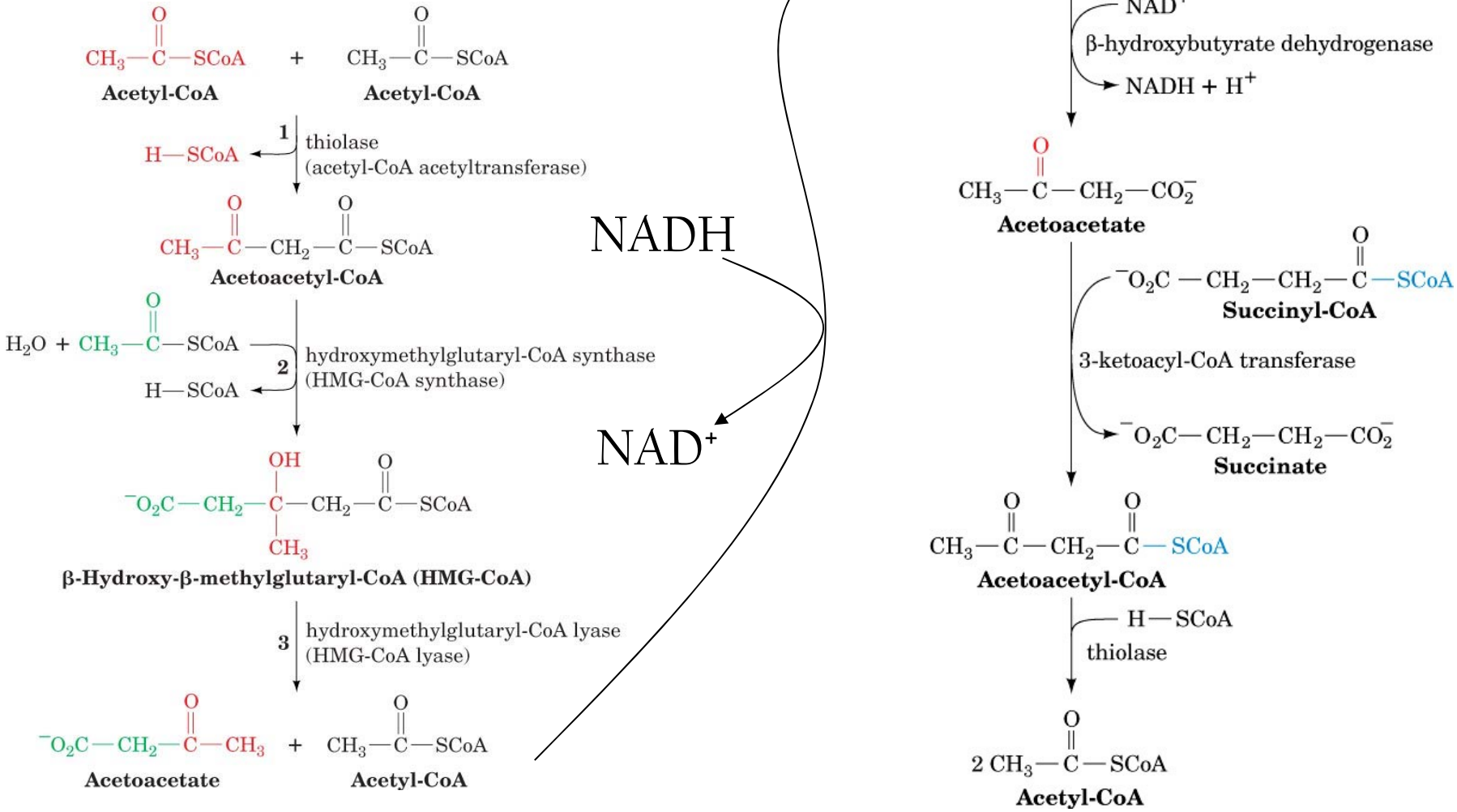
Dealing with Double Bonds

- Cis double bonds can cause us all kinds of headaches



Water Soluble Acetyl-CoA Packaging

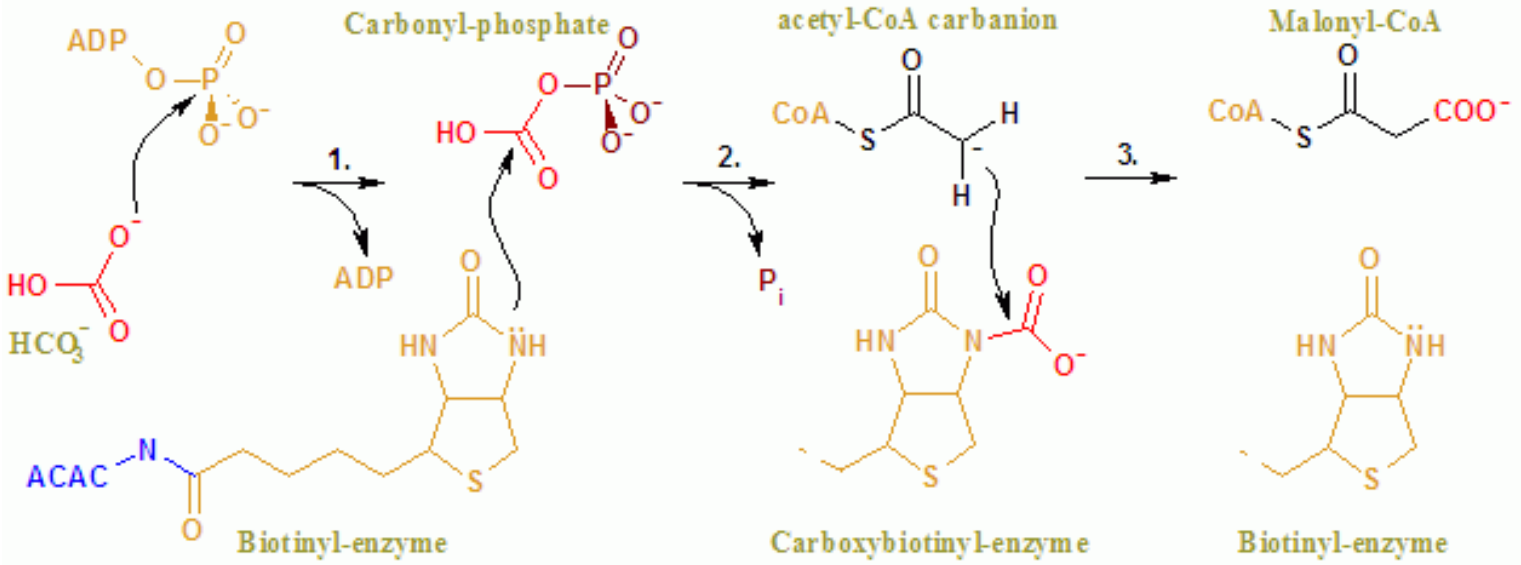
- The liver can supply energy to peripheral tissues via water soluble 'ketone bodies'.



Fatty Acid Synthesis

- So far, we've broken down fatty acids via β-oxidation to get energy. But what if we want to store our Acetyl-CoA?

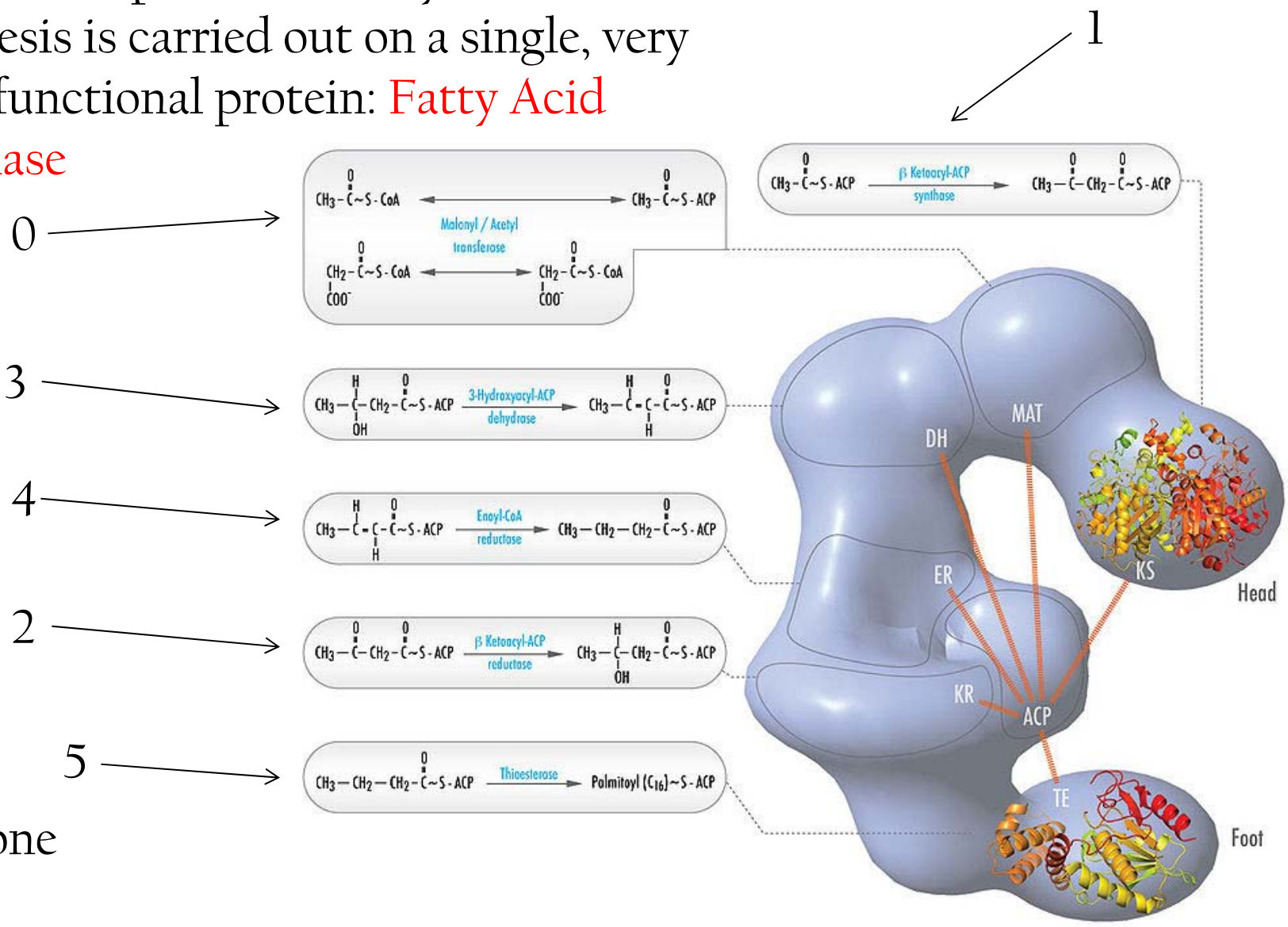
- To start off, we need an acyl-CoA molecule with an activated c-terminus in the form of a carboxylate group: Malonyl-CoA



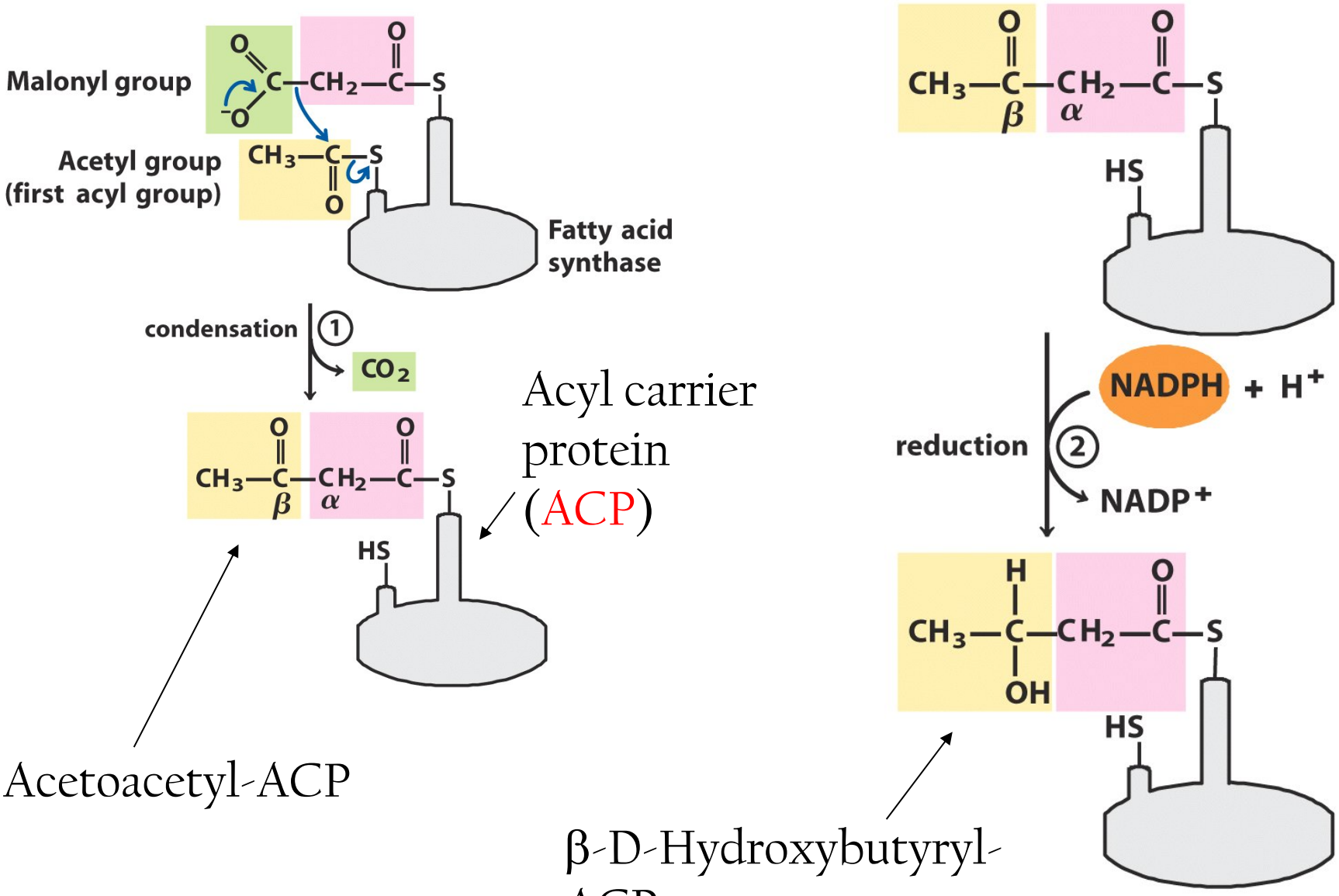
(Acyl-CoA carboxylase)

Fatty Acid Synthesis

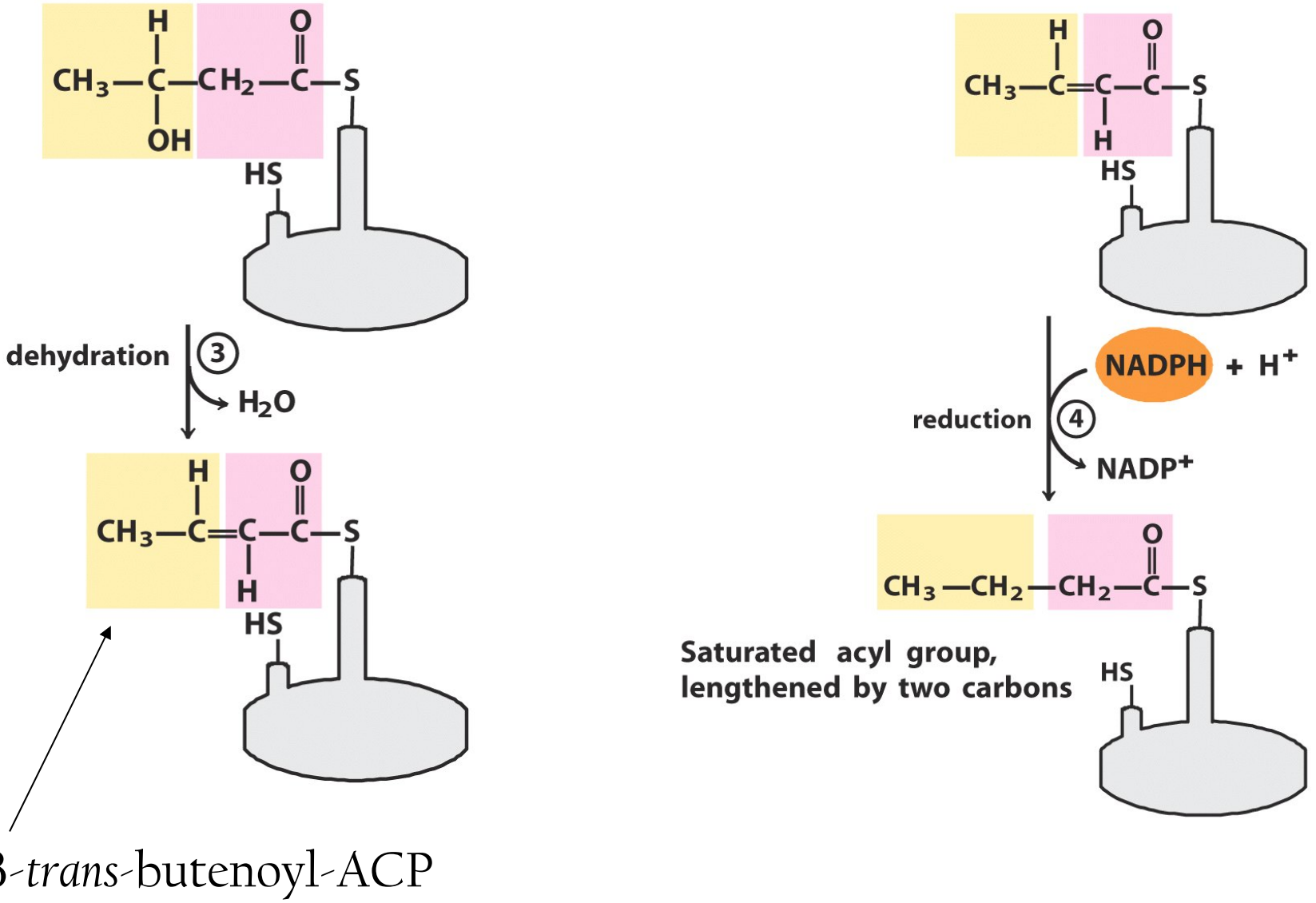
- The entire process of fatty acid synthesis is carried out on a single, very multifunctional protein: Fatty Acid Synthase



Fatty Acid Synthesis, Steps 1 and 2:



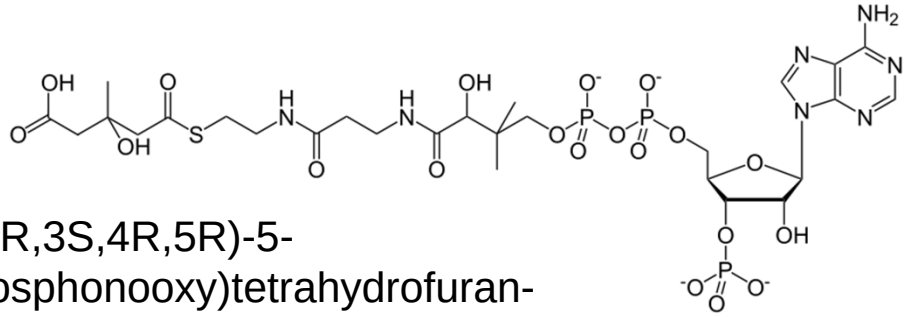
Fatty Acid Synthesis, Steps 3 and 4:



α-β-*trans*-butenoyl-ACP

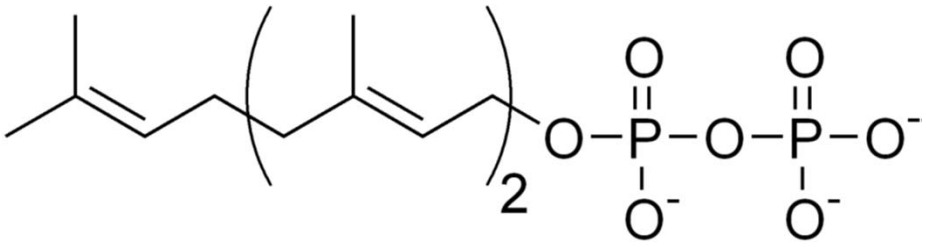
Cholesterol Biosynthesis

- It all starts with HMG-CoA

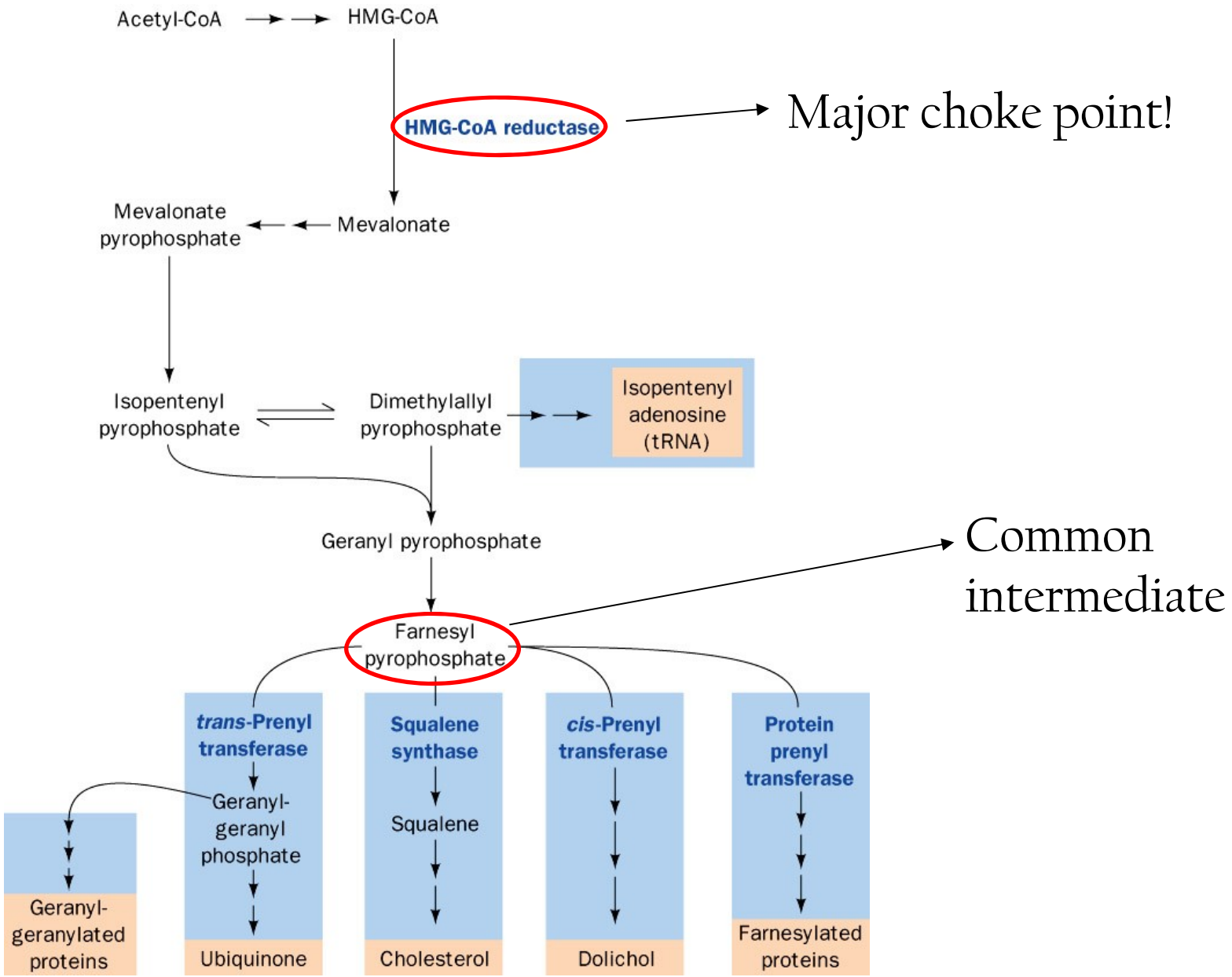


IUPAC name: (9R,21S)-1-[(2R,3S,4R,5R)-5-(6-amino-9H-purin-9-yl)-4-hydroxy- 3-(phosphonooxy)tetrahydrofuran-2-yl]- 3,5,9,21-tetrahydroxy-8,8,21-trimethyl- 10,14,19-trioxo-2,4,6-trioxa-18-thia- 11,15-diaza-3,5-diphosphatricosan-23- oic acid 3,5-dioxide

- The end goal of the 'first stage' of cholesterol (isoprenoid) synthesis gets us to Farnesyl pyrophosphate:

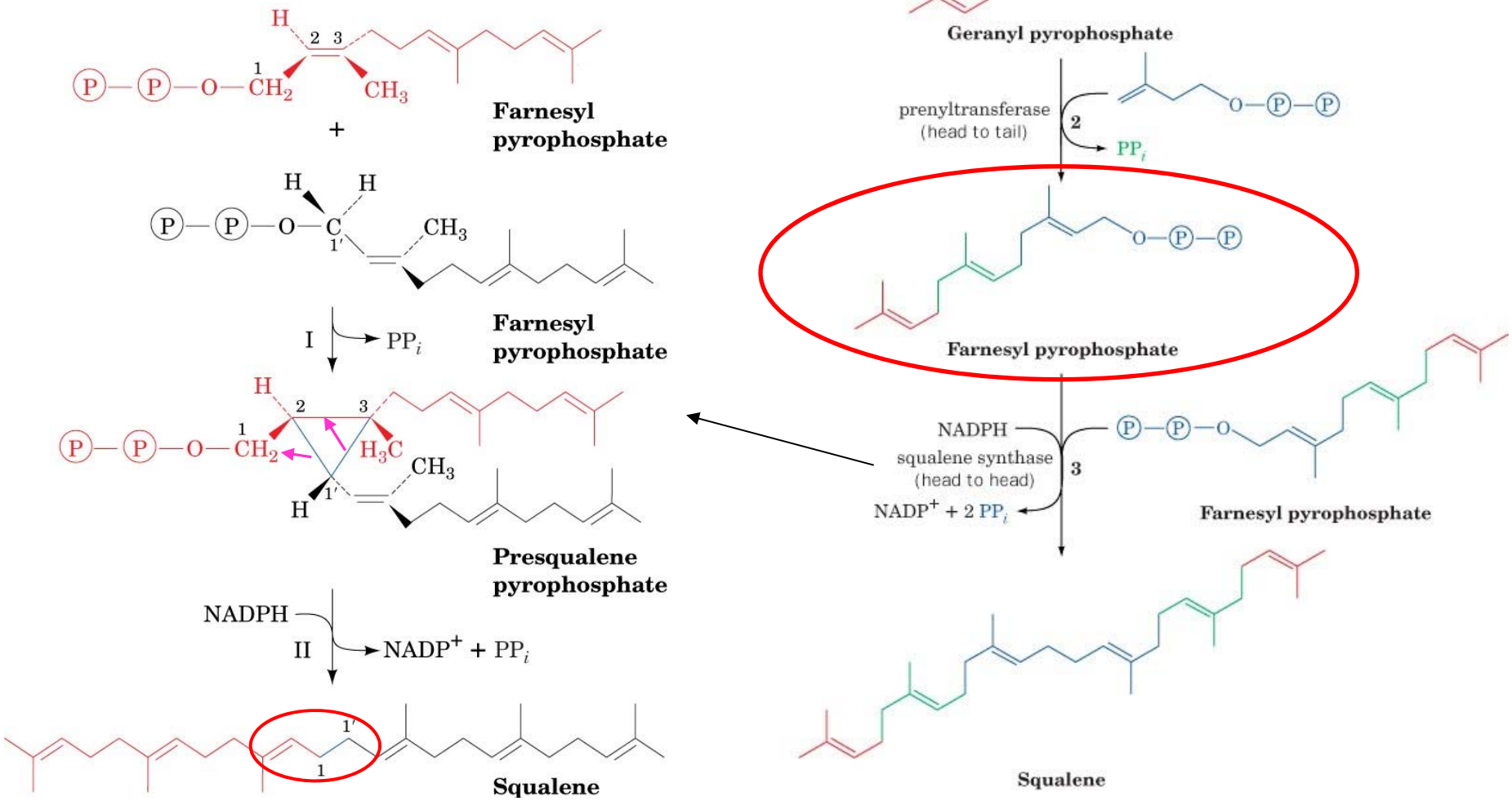


Overview of Isoprenoid Synthesis



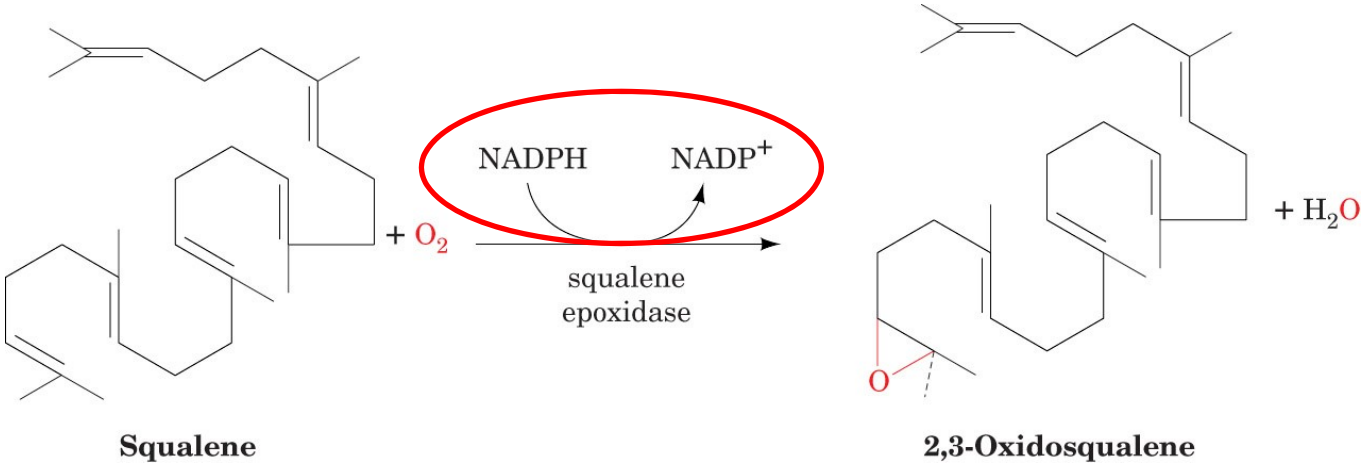
Cholesterol Biosynthesis

- If we're making cholesterol (or a derivative) the next step is to make Squalene



Cholesterol Biosynthesis

- Next step: Oxidize Squalene



- This will allow us to initiate a super-cool cyclation reaction

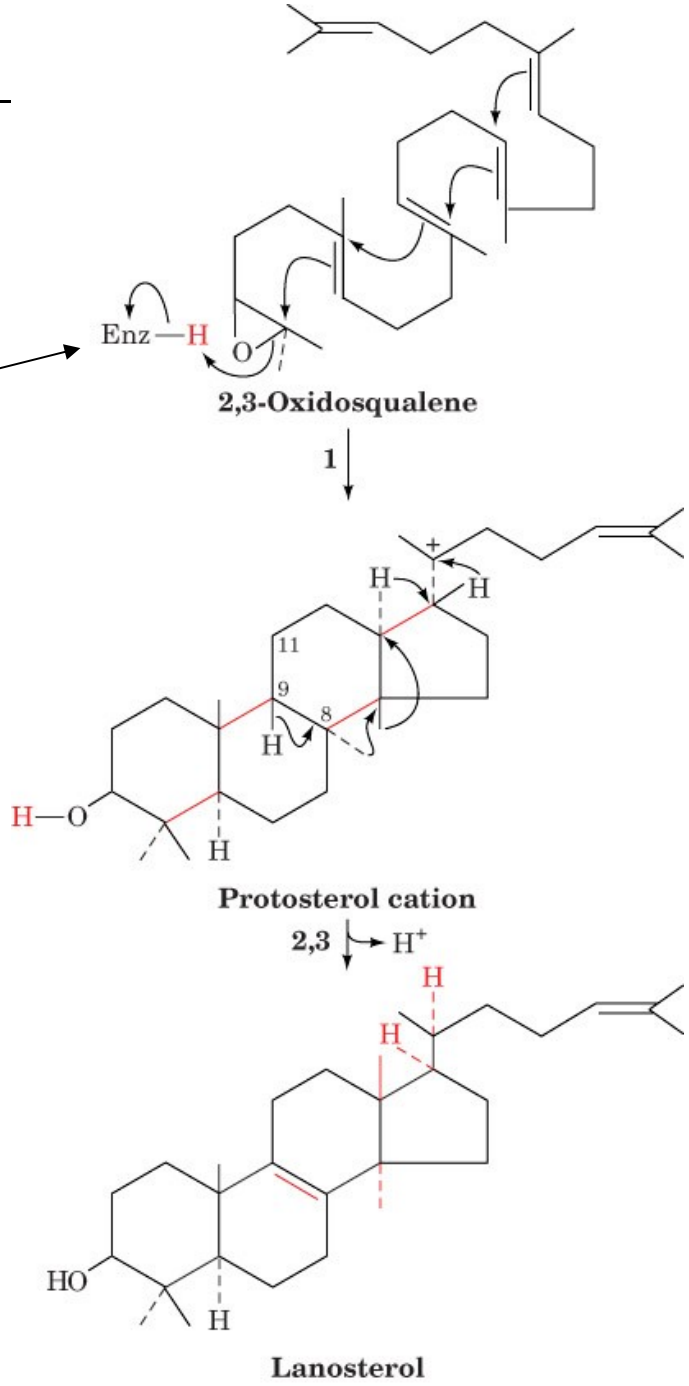
Cholesterol Biosynthesis

- Super-cool cyclation:

- The process is initiated by protonation of the oxidosqualene epoxide oxygen.

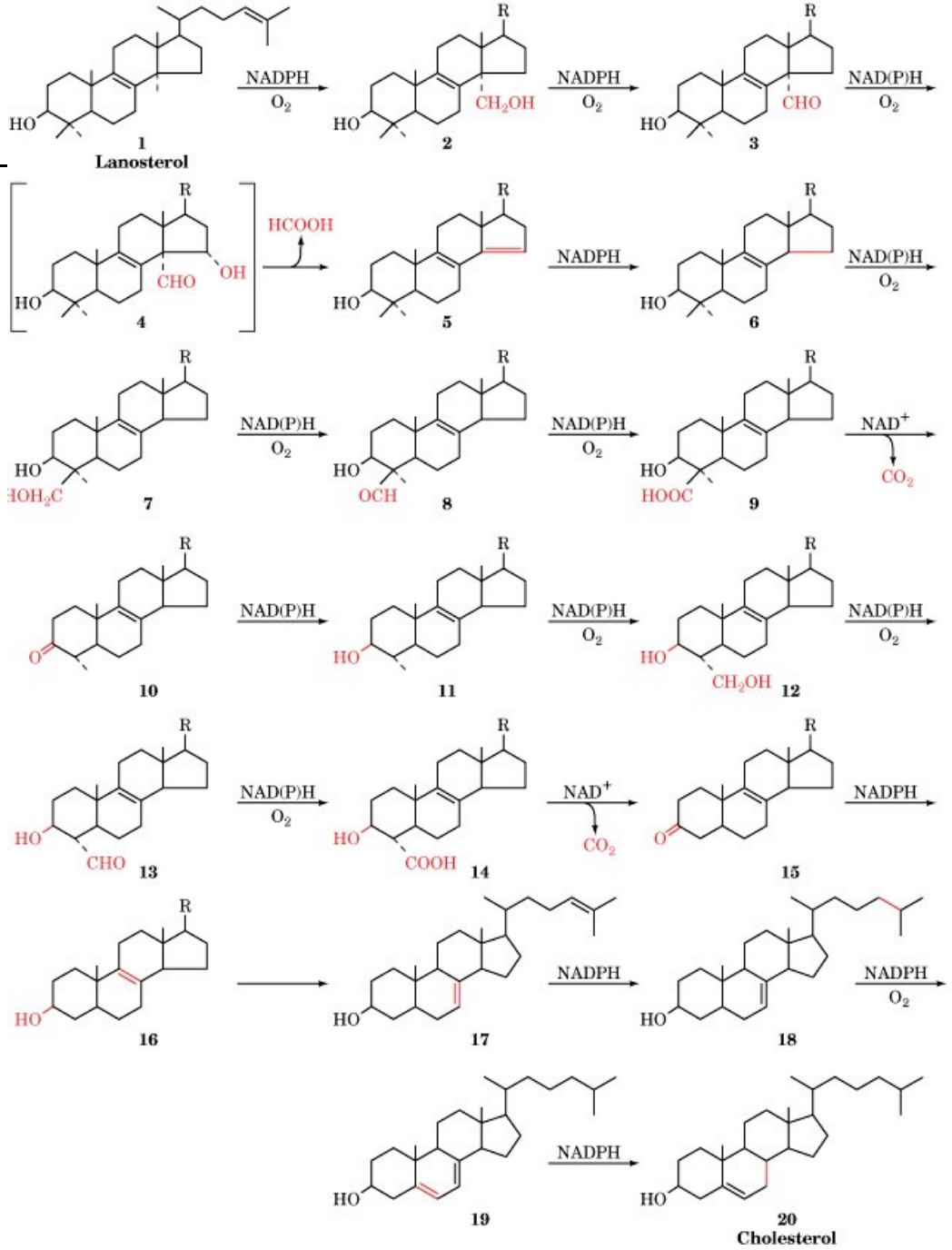
- Now we have the 6,6,6,5 ring system associated with most steroids.

- But we still have a long way to go!!



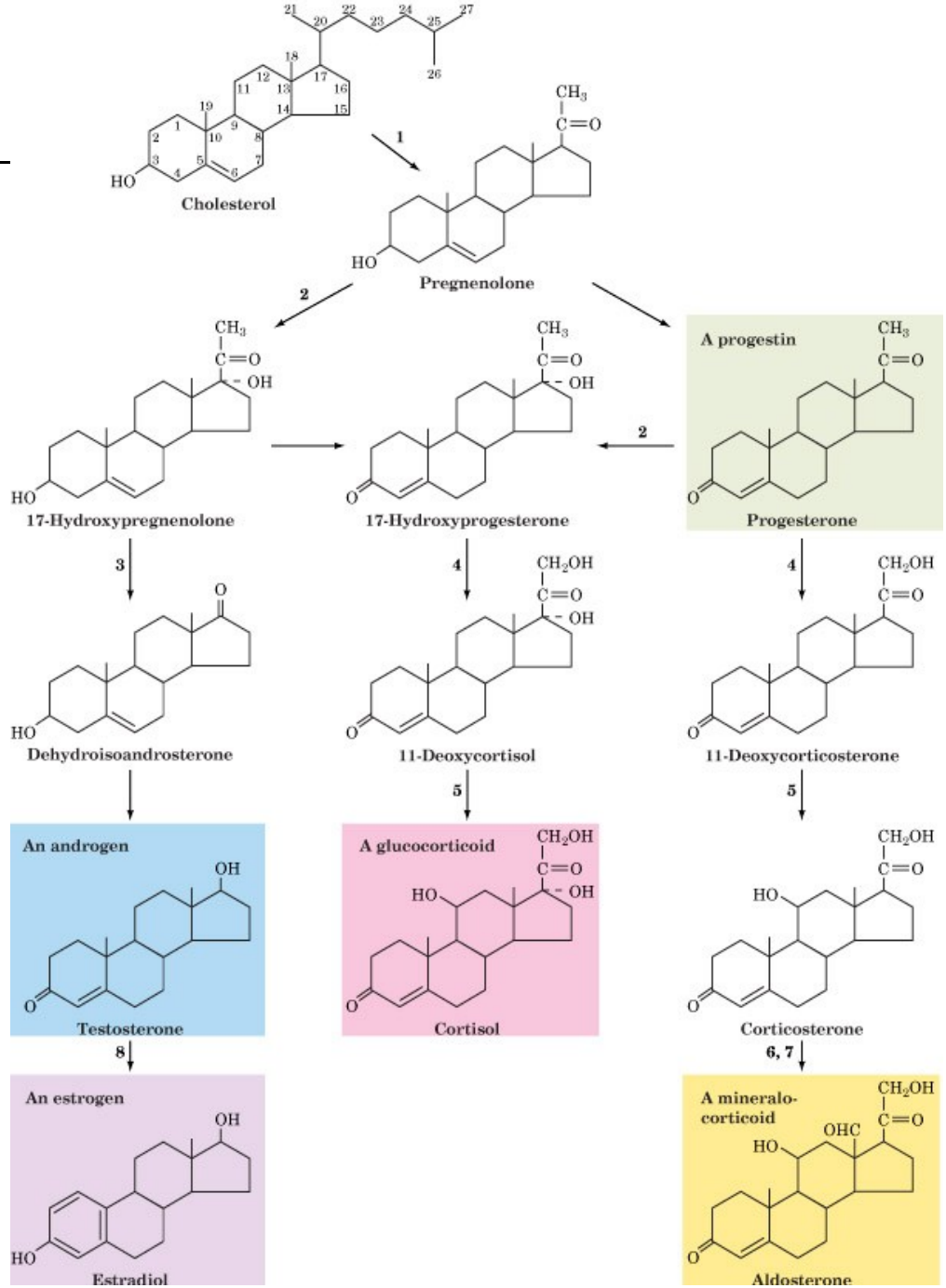
Cholesterol Biosynthesis

- It's a long trip from lanosterol to cholesterol



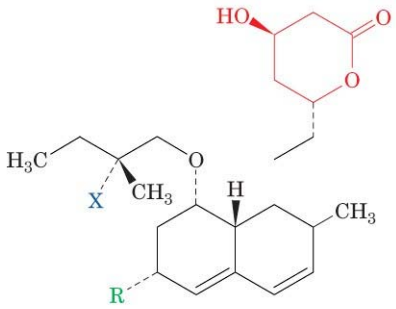
Cholesterol As a Precursor

- Cholesterol can be converted to many hormone signalling molecules including:
  - Progestins (female reproductive)
  - Androgens/Estrogens
  - Corticoids (general metabolism)

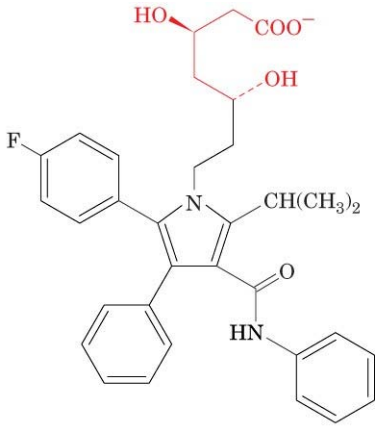


Statins: It's All About Timing

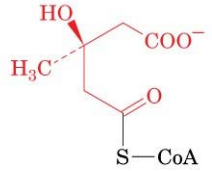
- Statins, like lipotor, zocor *etc*. are competitive HMG-CoA reductase inhibitors



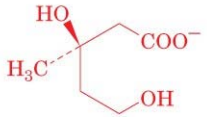
X = H R = CH_3 **Lovastatin (Mevacor)**
X = H R = OH **Pravastatin (Pravachol)**
X = CH_3 R = CH_3 **Simvastatin (Zocor)**



Atorvastatin (Lipitor)



HMG-CoA



Mevalonate

- These inhibitors cause a sudden decrease in cholesterol concentration

- Cells respond by making more HMG-CoA reductase and low density lipoprotein (LDL) receptor

- Increased expression of HMG-CoA returns cholesterol levels to normal, but the extra LDL receptor causes above normal removal of LDL from the blood-stream!