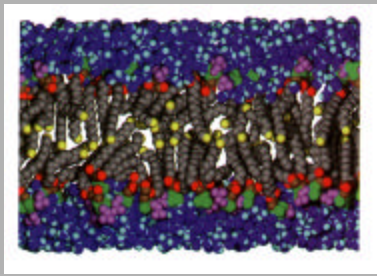
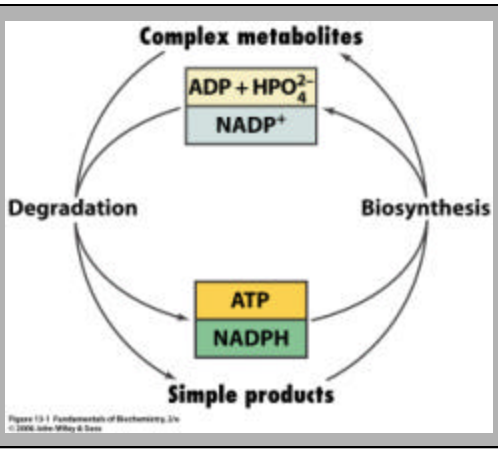
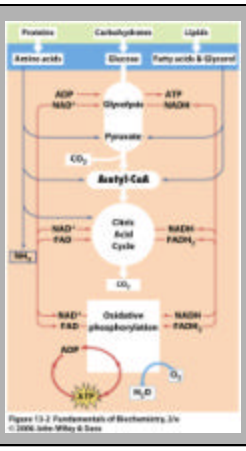
15: Lipids







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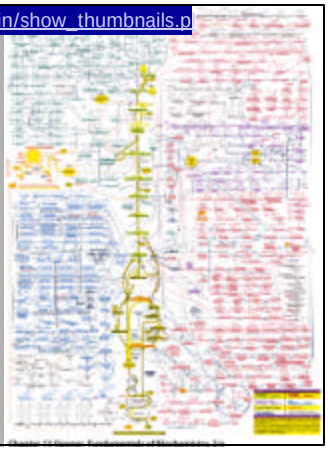
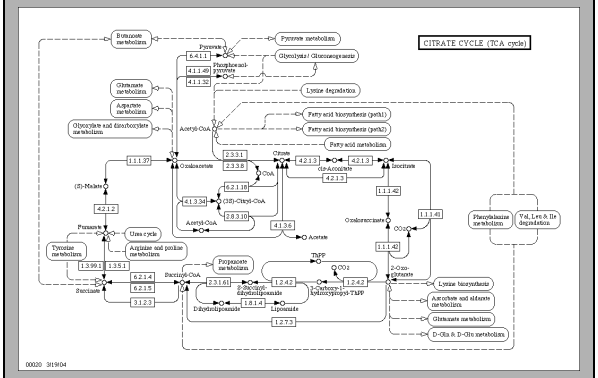
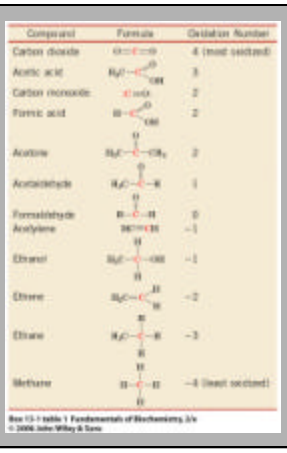
Pathway Diagrams

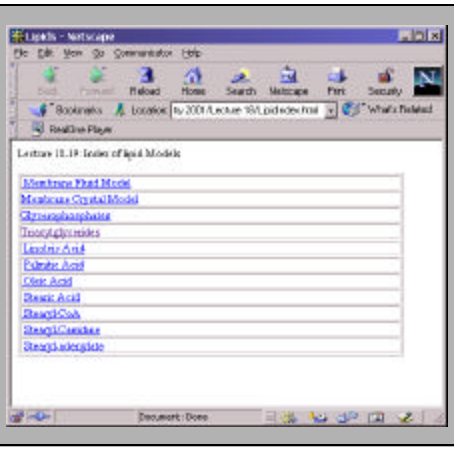






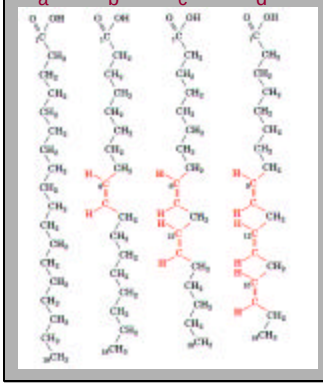
What makes a 'lipid'

- Hydrophobicity
- Functional definition
  - Large structural diversity
  - No oligomerized subunits
- Biological importance
  - Membranes
  - Energy metabolism
  - Intracellular signaling



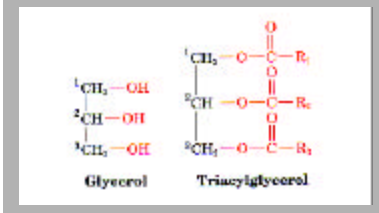
C_{18} Fatty Acids

a b c d



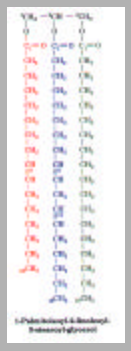
- 18 carbon chains
  - a. stearic acid
  - b. oleic acid
  - c. linoleic acid
  - d. α-linoleic acid
- Δ^9 structure
  - Most unsaturated
  - polyunsaturated

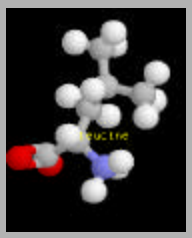
Triacylglycerols



- Fatty acid triesters of glycerol
- Most lipids exist as TAGs
  - Energy metabolism
  - More prevalent than membrane lipids

Hydrophobicity

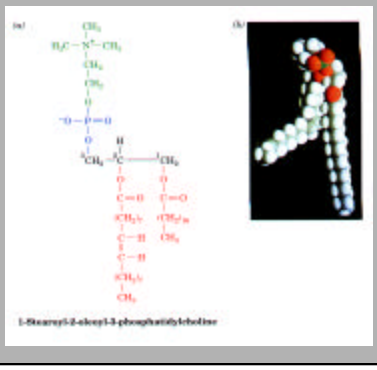




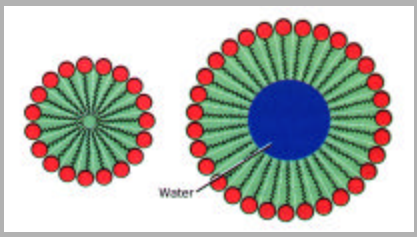
Energy Metabolism

- Lipids are more reduced
- Higher enthalpy of combustion
  - Protein = 24 kJ g^{-1}
  - Carbo = 27 kJ g^{-1}
  - Lipid = 40 kJ g^{-1}
- Lipid stores in humans can provide enough energy to survive starvation for 2-3 months
- Liver glycogen stores are only sufficient for 1d

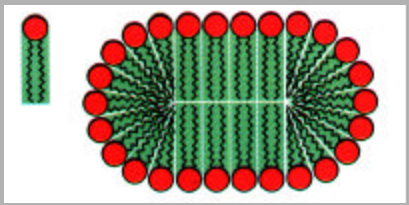
Glycerophospholipids



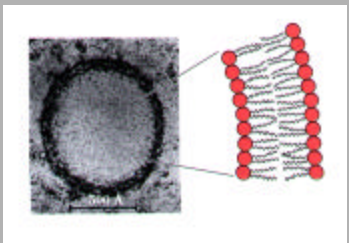
Single Micelle layer



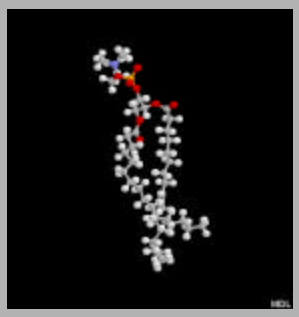
Alignment of bilayer tails



Bilayer structures

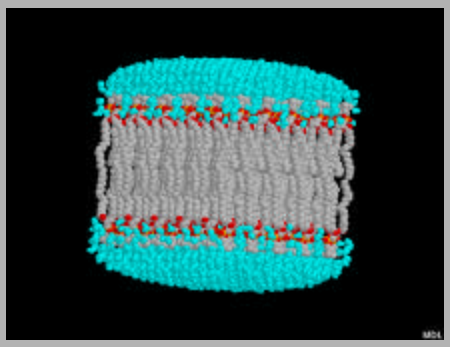


Phospholipids

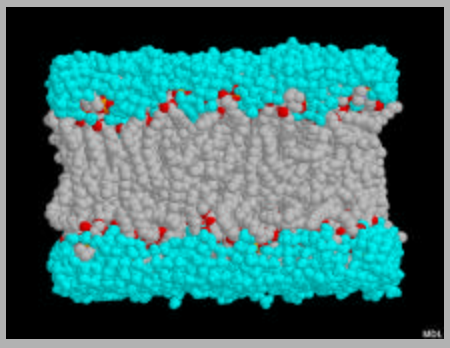


- model file: glycerophospholipid.pdb

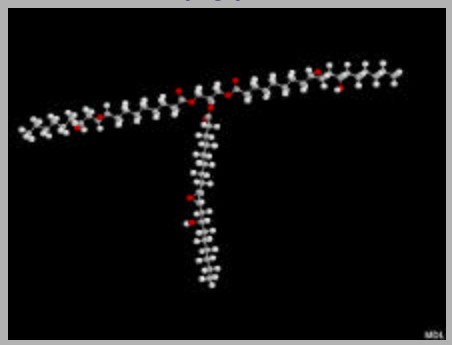
Membranes: crystal



Membranes: fluid



Triacylglycerides



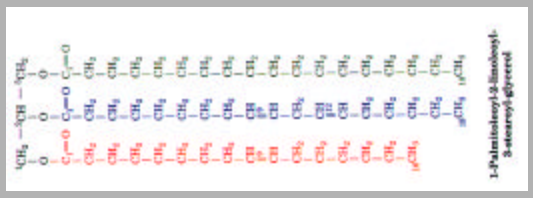
- 9,10-epoxy-12-hydroxyoctadecanoic acid-glycerotriester
- File: TAG.pdb

Lipid Droplets

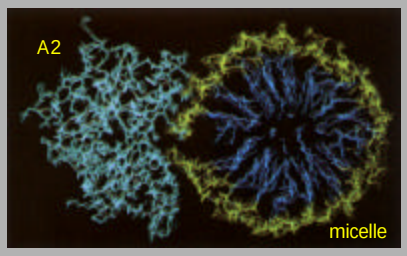
- TAGs do not form an organized structure

Fatty Acid Oxidation

- 1. Lipase mediated hydrolysis of glycerol esters



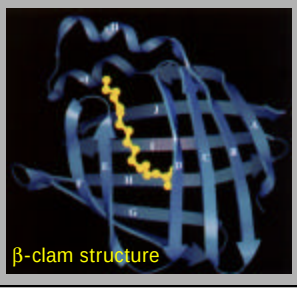
Phospholipase A2



- Interfacial activation
- Conformational change opens hydrophobic core

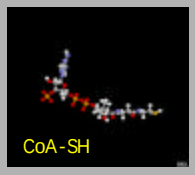
Fatty acid binding proteins

- 2. Transport and handling
- Protein BP:
  - Increase FA aqueous solubility
  - Protect cellular components from detergent effects



Activation

- 3. Fatty Acids chemically modified
  - Signal structure
  - Hydrophilic 'handle'
- Structural Modification:
  - FA + CoA-SH + ATP → FA-CoA + AMP + Pi



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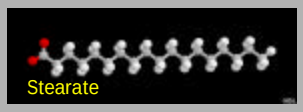
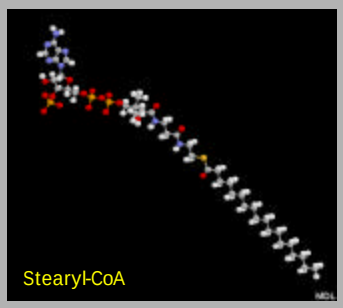


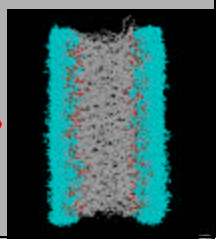
Fatty-acyl-CoA



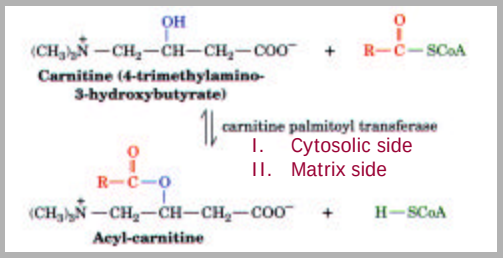
- File: stearyl_coA.pdb

OK. Ready to go . . .

- The fatty acid in the cytoplasm has been activated . . . . .
- Fatty acid oxidation occurs in the mitochondria to maximize the energy yield from the electron transfer reactions
- Just one small detail . . . . .

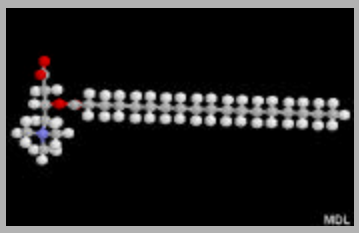


Another modification



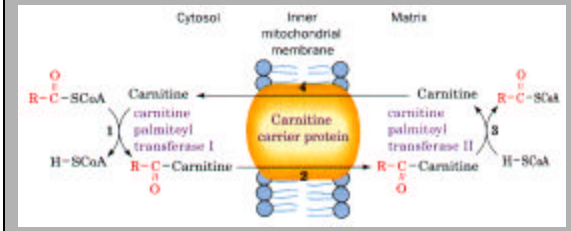
- Transesterification reaction has an equilibrium constant close to 1.0

Acyl-carnitine derivative



- Stearyl-carnitine

Carnitine Transporter

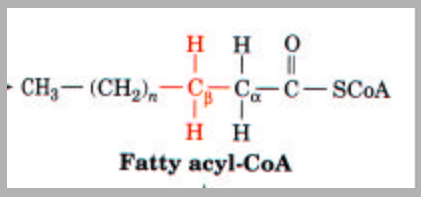


- The fatty-acyl-CoA structure is then regenerated on the matrix side
- CoA is not transported . . . .why?

Fatty Acid Oxidation

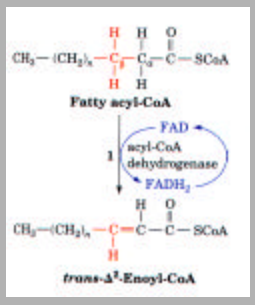
- 1. Lipase mediated hydrolysis of glycerol esters
- Translocation
- Activation
- Mitochondrial uptake (carnitine transporter)

Fatty Acid β-Oxidation

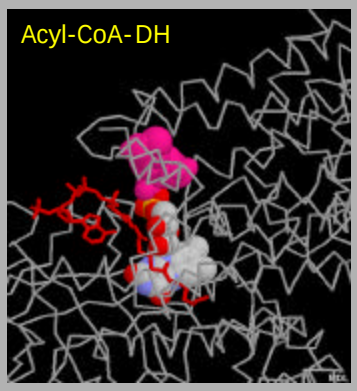


- Step 1. Acyl-CoA Dehydrogenase:
  - α,β trans double bond
  - Flavoenzyme = FAD accepts e-

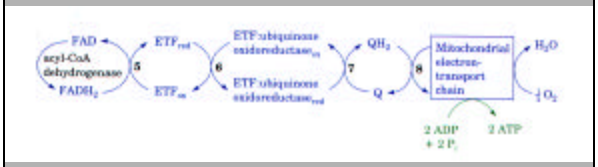
Acyl-CoA Dehydrogenase



- Mitochondria contain three aCoA-DH optimized for handling different length FAs

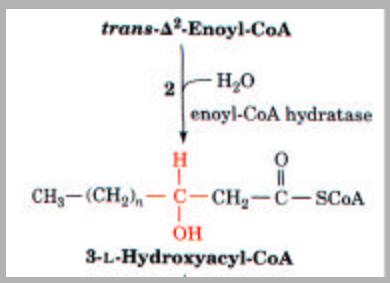


Mitochondrial Electron Transfer



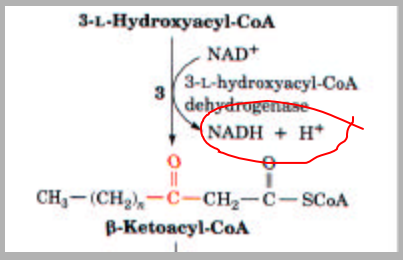
- Net: 2 ATP per reaction step

β-Oxidation: step 2



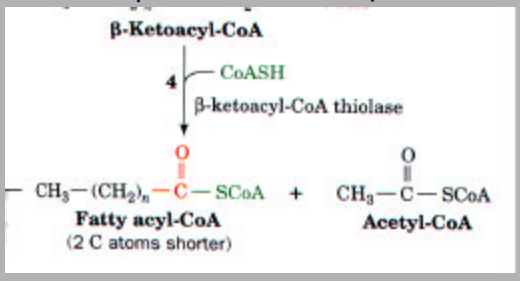
- Hydrate the double bond on C_β

β-Oxidation: step 3



- Re-hydrate the double bond on C_β
- Net: 1 NADH/H+

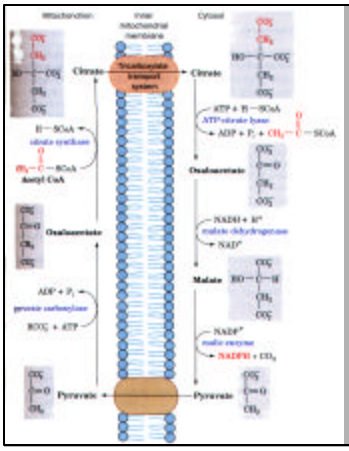
β-Oxidation: step 4



- Thiolysis at C_β
- FA-CoA, but 2 C shorter
- Net production of 1 ACoA

Energy Metabolism

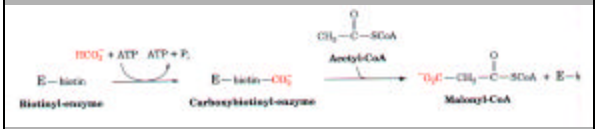
- Each round of β-oxidation produces:
  - 1 FADH2
  - 1 NADH
  - 1 Acetyl-CoA
    - TCA cycle = 3 NADH + 1 FADH2 + 1 GTP
- For palmitic acid (C16):
  - What is the total ATP yield?
- How many β-ox cycles?
- What is the total NADH yield?
- What is the total FADH2 yield?
- What is the total GTP yield?
- What is the total ATP equivalent yield?
- Now subtract the 2 ATP used for fa-CoA formation.



Biosynthesis

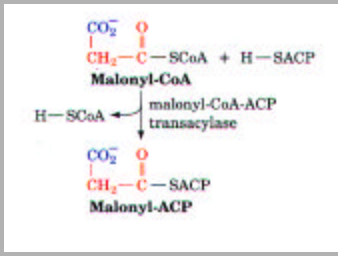
- Building blocks
- ACOA synthesis
- Exchange

Modification of ACOA



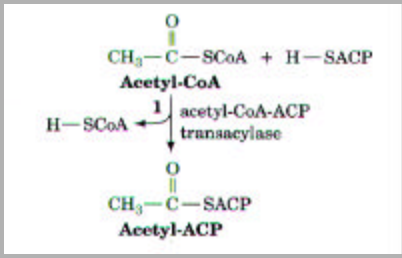
- Carboxylation of ACOA to malonyl-CoA
  - First reaction commitment
  - Rate controlling step
- CO_2 fixation into a carbon chain

Activation of Malonyl-CoA



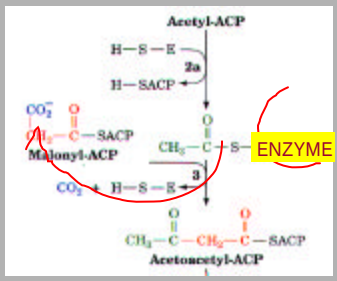
- Acyl-carrier protein (ACP) anchors synthesis

Activation of ACOA



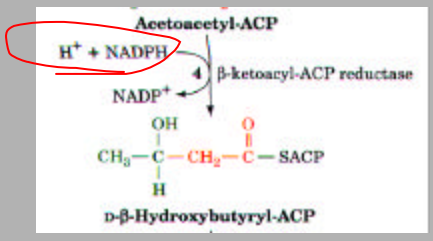
- ACP is the handle
- Recognized by "Fatty Acid Synthase"

Condensation reaction

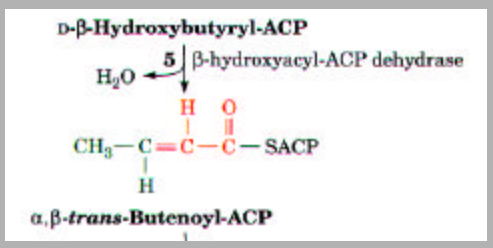


- Double carbonyl structure (β-keto group)
- Acetyl-ACP group is only used to start synthesis

β-keto Reduction

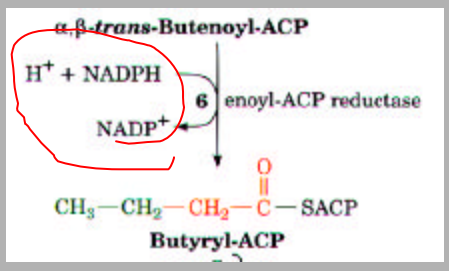


Dehydration



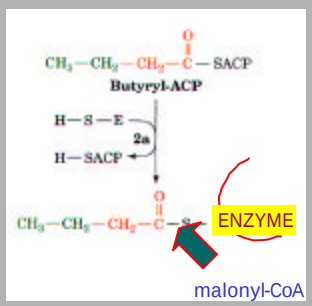
- Formation of α,β trans double bond

Alkene Reduction



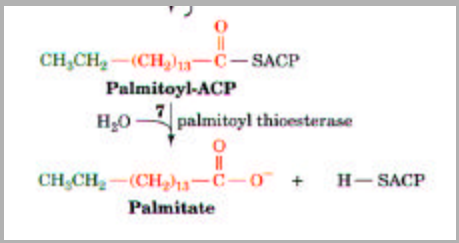
- Formation of α,β alkane
- Next round: add another malonyl-CoA

Next Round



- Fatty acid chain elongation results in the new carbons being added from malonyl-CoA

Final Round

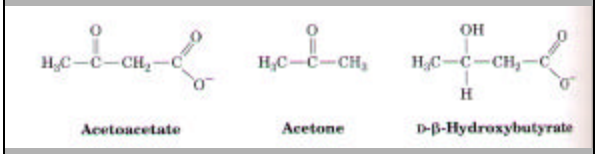


- The carboxyl group ends up on the end where the last carbon group was added
- Pathway for even-C chains . . . . . .
- What is the metabolic cost ?

Comparison of two pathways

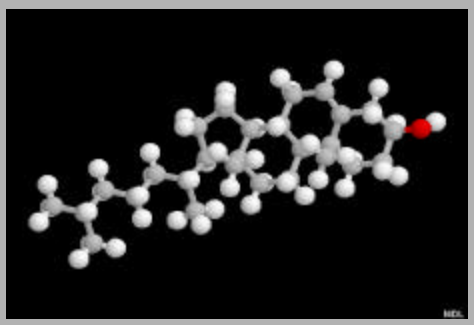
- Same mechanism but different pathways

Other Lipids: Ketone Bodies



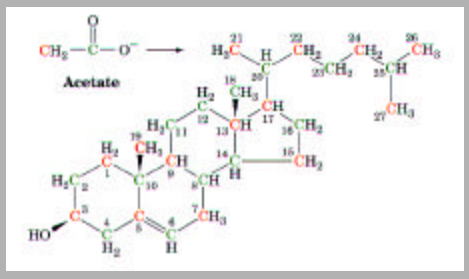
- Acetyl-CoA interconversion
- Diffusable through membranes
- Higher aqueous solubility

Other Lipids: Steroids

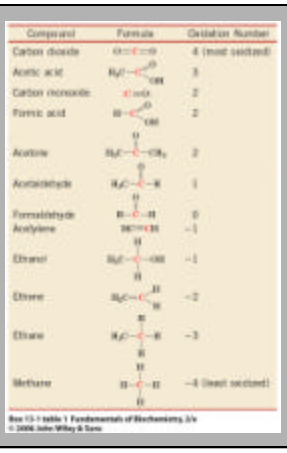


Cholesterol

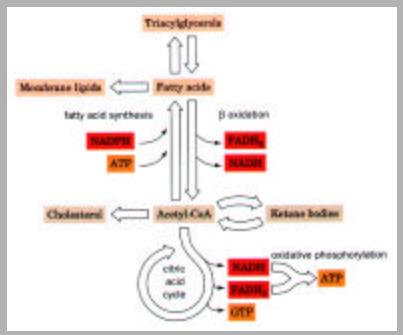
Cholesterol



- All the carbon atoms are derived from acetate
- Complex synthesis from simple building block



Lipid Metabolism



In terms of cellular energy, lipid metabolism is the primary determinant of metabolic organization