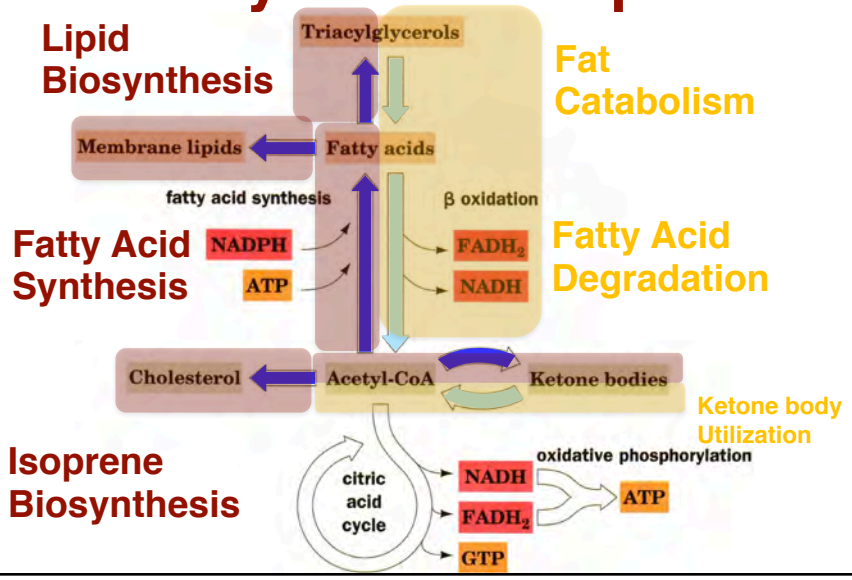
# ANABOLISM II: Biosynthesis of Fatty Acids & Lipids




# ANABOLISM II: Biosynthesis of Fatty Acids & Lipids

1. Biosynthesis of fatty acids
2. Regulation of fatty acid degradation and synthesis
3. Assembly of fatty acids into triacylglycerol and phospholipids

Exam 4 ↑

4. Metabolism of isoprenes

Exam 5 ↓

   a. Ketone bodies and Isoprene biosynthesis
   b. Isoprene polymerization
      i. Cholesterol
      ii. Steroids & other molecules
      iii. Regulation
      iv. Role of cholesterol in human disease

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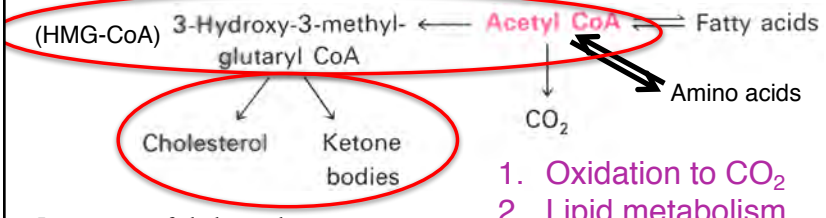
# Cholesterol and Steroid Biosynthesis

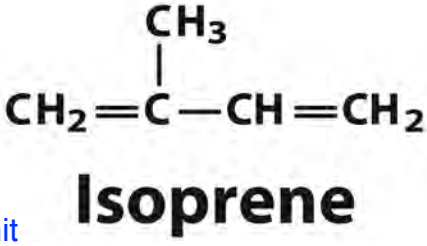
## Fates of Acetyl CoA




1. Oxidation to $CO_2$
2. Lipid metabolism
3. Amino acid metabolism

Importance of cholesterol:
Dr. Kornberg:
**Lecture 04.05.17 (12:02-17:12) 5 min**

- Nearly all the remaining lipids have a chemical relationship, and their biosynthesis are built on the 5-carbon isoprene unit

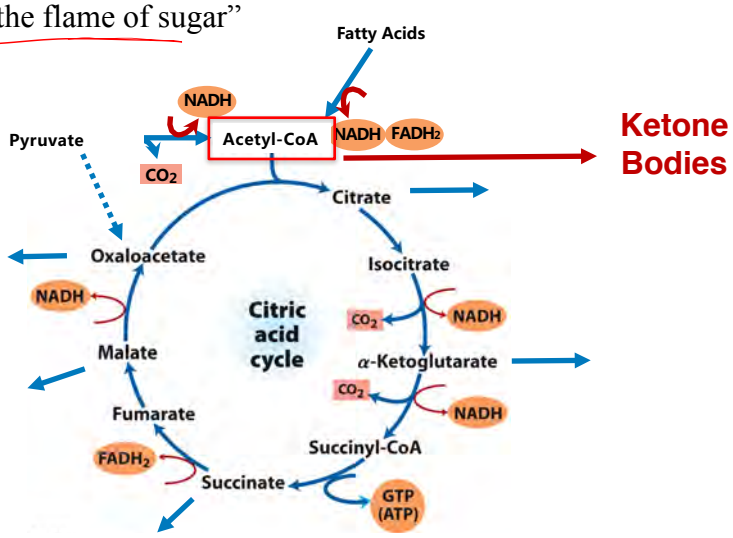



**Isoprene**

1912-2000
Nobel Prize 1964

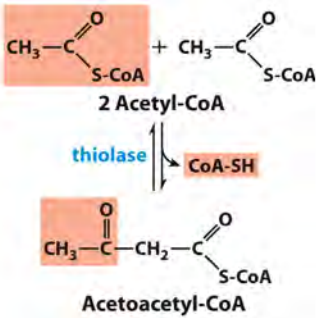
# Cholesterol and Steroid Biosynthesis

"Fat burns in the flame of sugar"




# Cholesterol and Steroid Biosynthesis

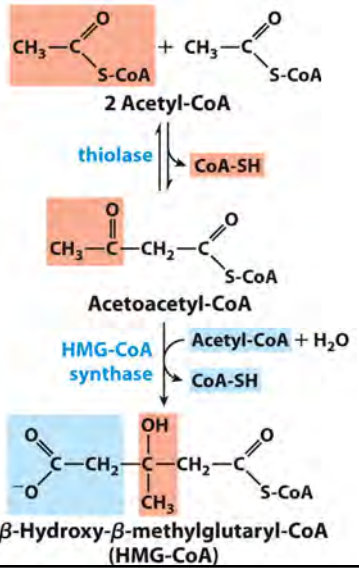
## Ketone Body Biosynthesis




- The first step is reverse of the last step in the $\beta$ oxidation: thiolase reaction joins two acetate units.
- A third acetyl-CoA is incorporated in the second step.
- Together, two CoASH are freed from three acetyl-CoA.
- In the liver, this synthesis occurs regardless of excess acetyl-CoA
- HMG-CoA is a metabolic junction

# Cholesterol and Steroid Biosynthesis

## Ketone Body Biosynthesis

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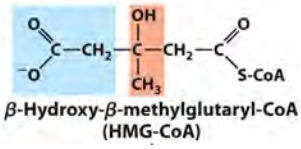
# Cholesterol and Steroid Biosynthesis

## Ketone Body Biosynthesis

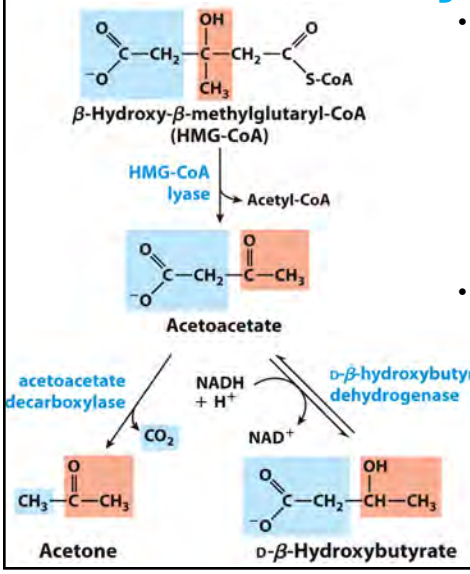



- In order to traffic to other tissues, CoA must be removed. This is done by removing as acetyl-CoA leaving Acetoacetate. This along with Acetone and $\beta$-hydroxybutyrate can then travel through the blood to other tissues for energy (catabolism).
  - In the mitochondria
- Acetone is removed as a gas and exhaled (although some species or tissues can metabolize acetone), but acetoacetate and $\beta$-hydroxybutyrate can traffic to the heart, kidney, muscle, and adapted brain for use in energy production.

HMG-CoA & ketone bodies:
Dr. Kornberg:
**Lecture 03.01.17 (27:34-32:16) 4.5 min**

# Cholesterol and Steroid Biosynthesis

## Ketone Body Biosynthesis

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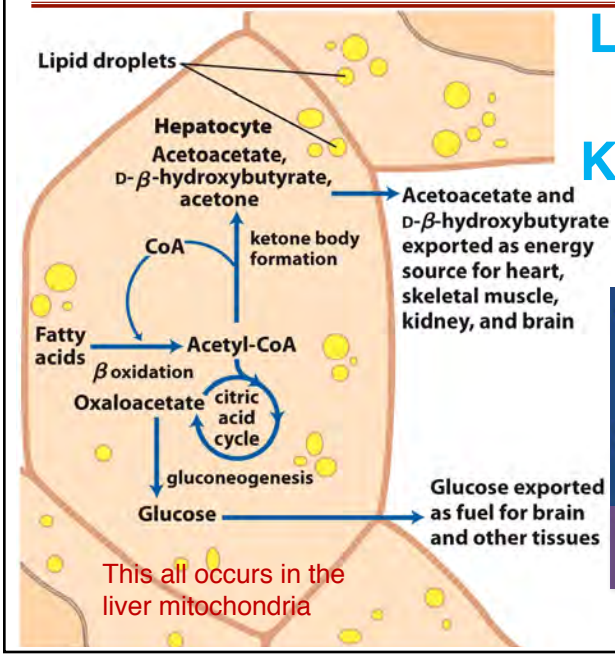
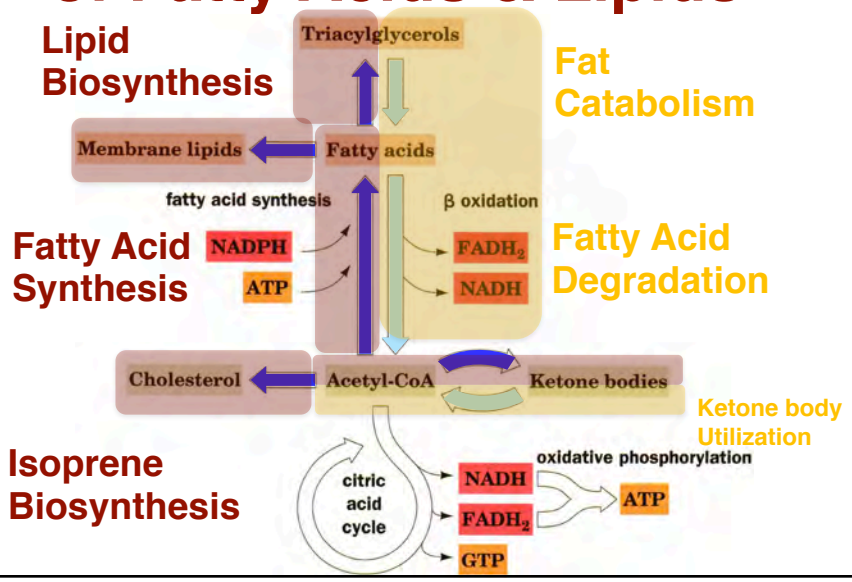
# Cholesterol and Steroid Biosynthesis

## Liver as a fuel source: Ketone Bodies & Glucose




- HMG CoA is present in both cytosol and mitochondria of liver
- Mitochondrial-ketogenesis
- Cytosolic – cholesterol synthesis

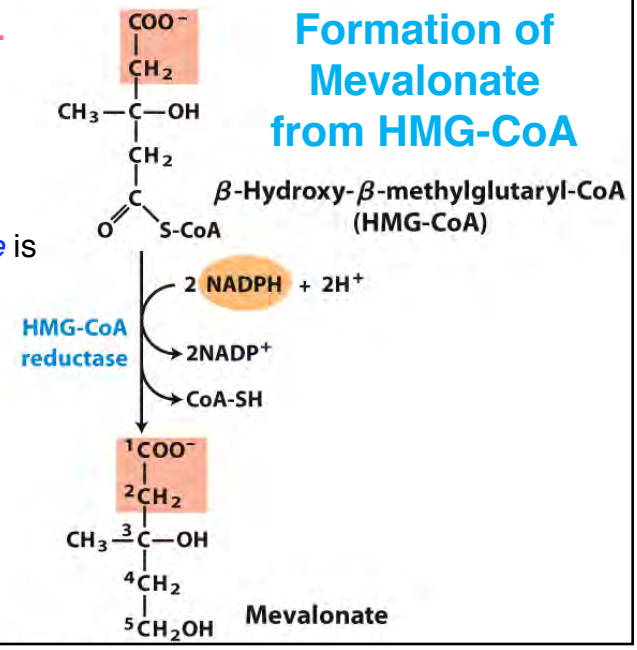
# ANABOLISM II: Biosynthesis of Fatty Acids & Lipids




# Cholesterol and Steroid Biosynthesis

## IN THE CYTOSOL

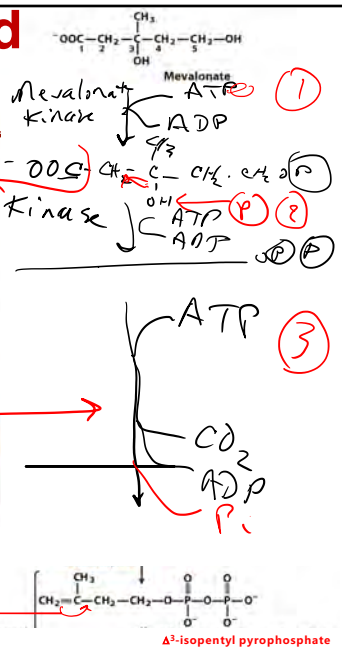
- HMG-CoA (from 3 acetyl-CoAs) is reduced to form mevalonate.
- *HMG-CoA reductase* is a common target of cholesterol-lowering drugs; called Statins



# Cholesterol and Steroid Biosynthesis

## Mevalonate to Activated Isoprenes

- Two phosphates are transferred stepwise from ATP to mevalonate.
- A third phosphate from ATP is added at the hydroxyl, followed by decarboxylation and elimination catalyzed by pyrophospho-mevalonate decarboxylase creates a diphosphorylated 5-C product; *$\Delta^3$-isopentyl pyrophosphate (IPP)* **(isoprene)**.
- Isomerization to a second isoprene *dimethylallylpyrophosphate (DMAPP)* gives two activated isoprene compounds that act as precursors for all of the other lipids in this class

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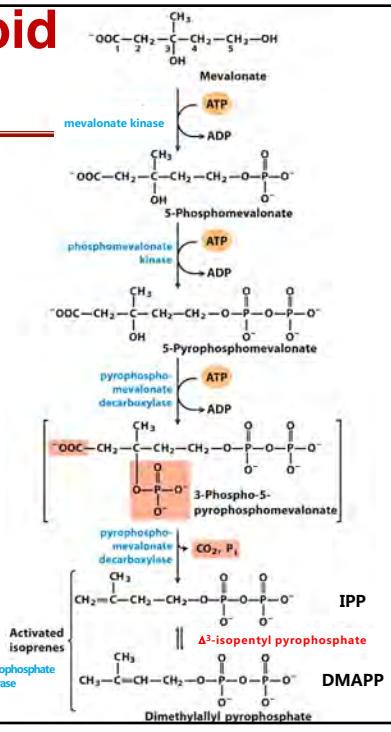
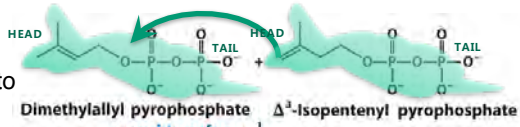


# Cholesterol and Steroid Biosynthesis

## Joining Isoprenes

- The two isoprenes join head to tail, displacing one set of diphosphates, forming 10-carbon geranyl pyrophosphate (GPP).




prenyl transferase (head-to-tail condensation) → $PP_i$ (geranyl-pyrophosphate synthase)