PROF. DR. SHAKIR F. T. ALAARAJI

PH. D. BIOCHEMISTRY

UNIVERSITY OF ANBAR

COLLEGE OF EDUCATION FOR PURE SCIENCES

CHEMISTRY DEPARTMENT

Synthesis of Triglycerides

The **major building block** for the synthesis of triacylglycerols, in tissues *other* than adipose tissue, is **glycerol-3-phosphate**.

What about adipose tissue?

Adipocytes lack ***glycerol kinase***, therefore, the 3C **dihydroxyacetone phosphate**, produced during **glycolysis**, is the precursor for triacylglycerol synthesis in adipose tissue.

This means that adipocytes must have **glucose** to ***oxidize*** in order to store fatty acids in the form of triacylglycerols.

Lipogenesis = Fatty acid *synthesis*

occurs primarily in the cytoplasm
of these tissues:

- Liver
- Adipose (fat)
- Central Nervous System
- Lactating mammary gland

Remember:

Glucagon and epinephrine
inhibit fatty acid synthesis,
and insulin stimulates it

Fatty Acid Synthesis and Oxidation Compared:

Pathway for fatty acid synthesis is in cytoplasm.

FA oxidation occurs in mitochondria.

Lipogenesis involves *oxidation* of NADPH.

F.A. spiral involves *reduction* of FADH+ & NAD+.

Lipogenesis uses a multi-enzyme complex called *fatty acid synthase*.

Fatty acid degradation uses individual enzymes, not necessarily physically associated.

Lipogenesis intermediates are carried by ACP (acyl carrier protein)

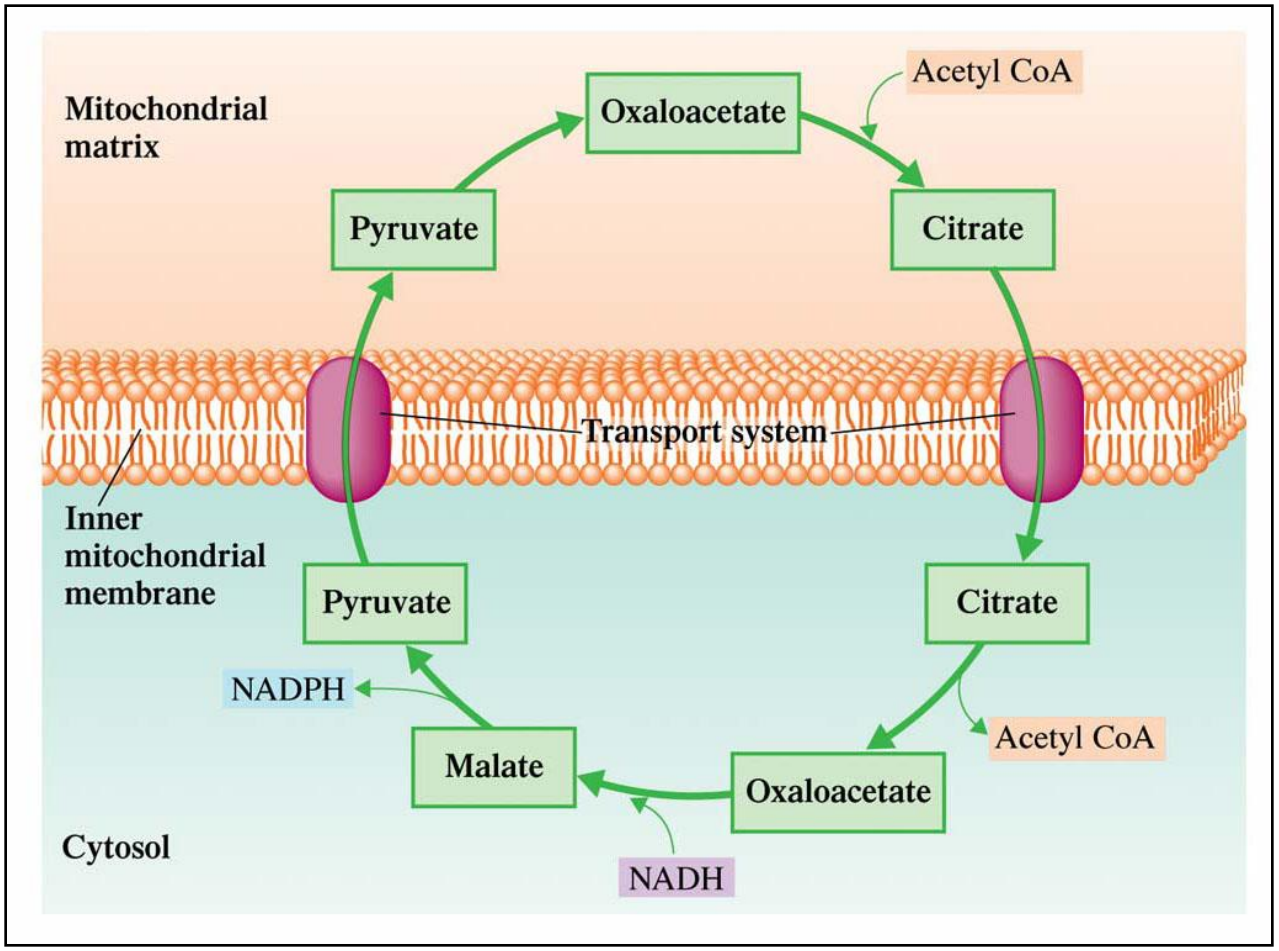
CoA is the carrier for intermediates formed in the fatty acid spiral

The essential chemistry of the two processes are basically reversals of each other.
Both oxidation and synthesis of fats use activated 2 C intermediate: **acetyl-CoA**.

Acetyl-CoA in **fat synthesis** temporarily bound to enzyme complex as **malonyl-CoA.**

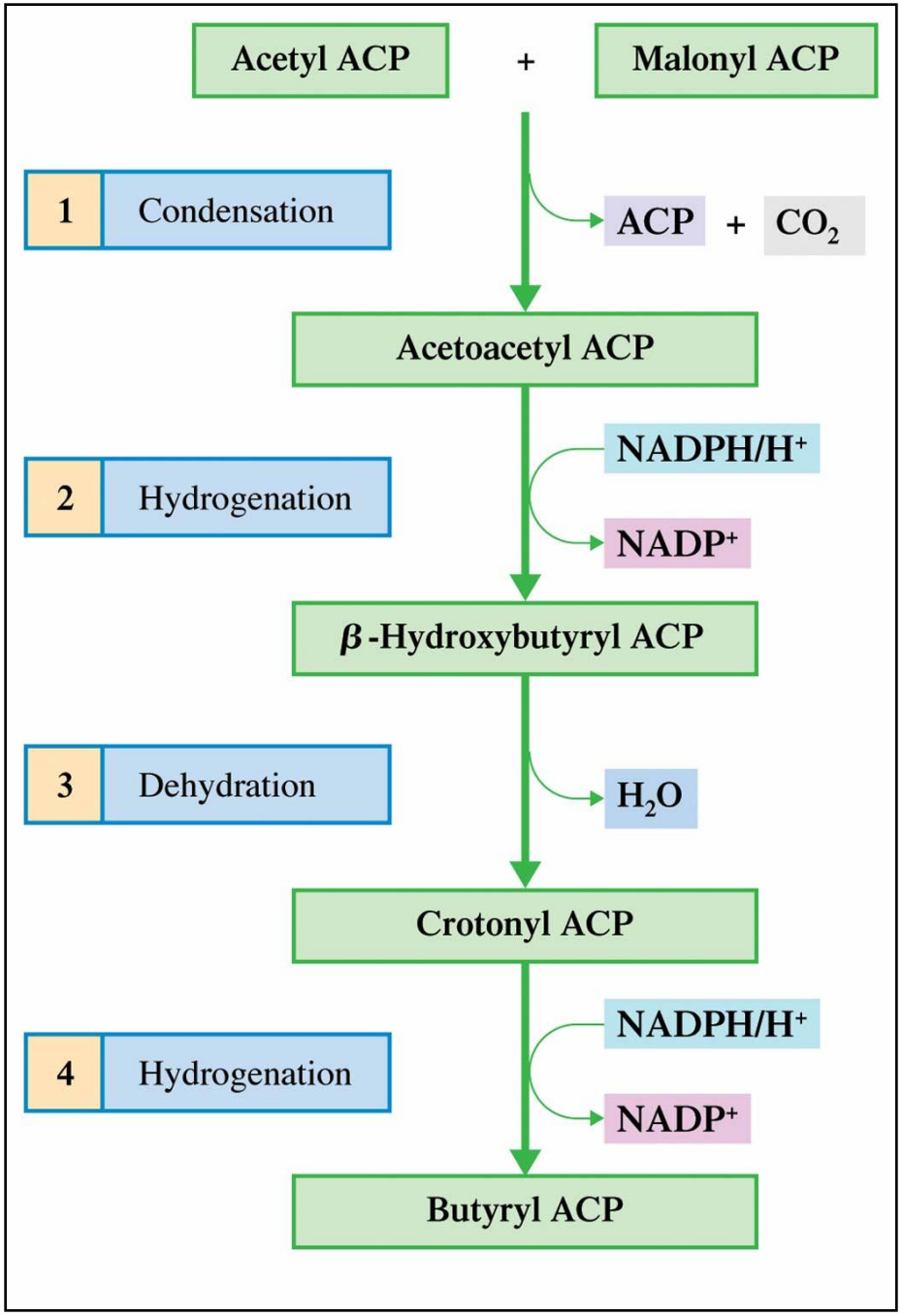
The synthesis of malonyl-CoA is
the 1st step of fatty acid synthesis

The citrate–malate–pyruvate shuttle system for transferring **acetyl CoA** from mitochondrion to cytosol.



Provides **Acetyl CoA** to **cytosol** for biosynthesis of fatty acids

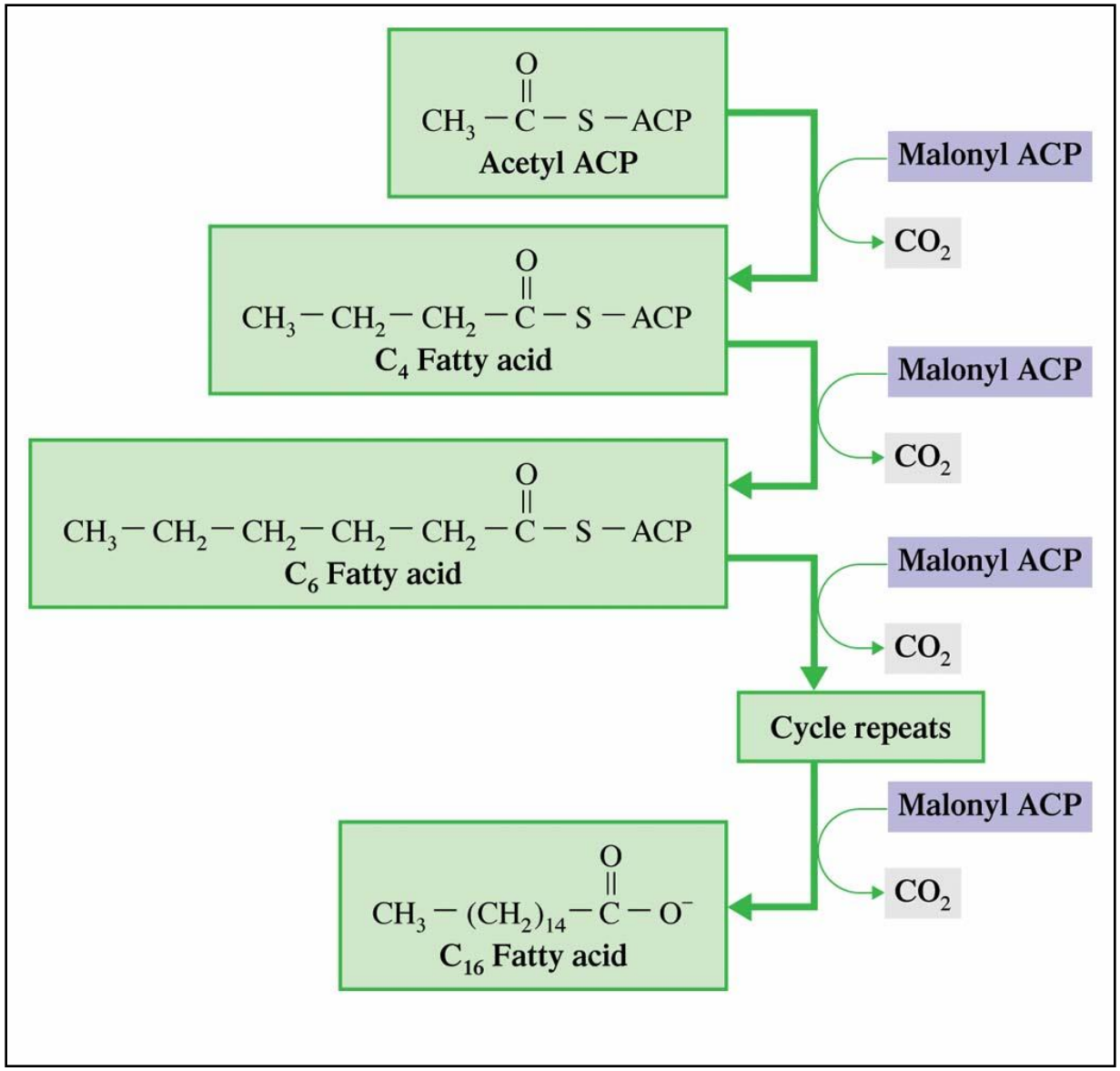
In the **first cycle** of the fatty acid biosynthetic pathway, **acetyl ACP** is converted to **butyryl ACP.**



The sequence of cycles needed to produce a **C_{16} fatty acid** from **acetyl ACP**.

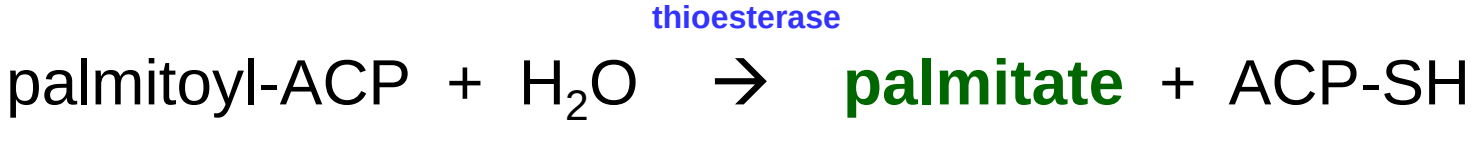
Malonyl ACP adds **2 carbons** at each cycle.

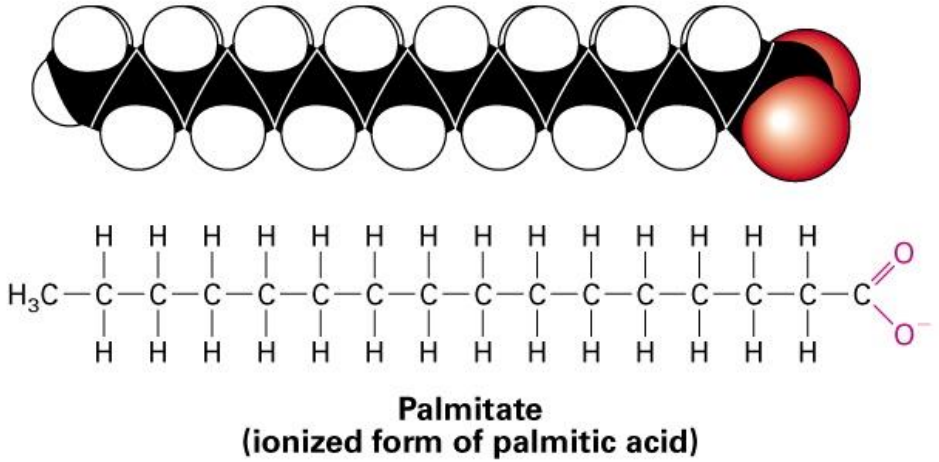
Each loop represents one cycle.



The acyl group is now ready to condense with a new malonyl group to **repeat the process**.

When fatty acyl group becomes **16 carbons** long, a **thioesterase** hydrolyzes it, forming free **palmitate**:





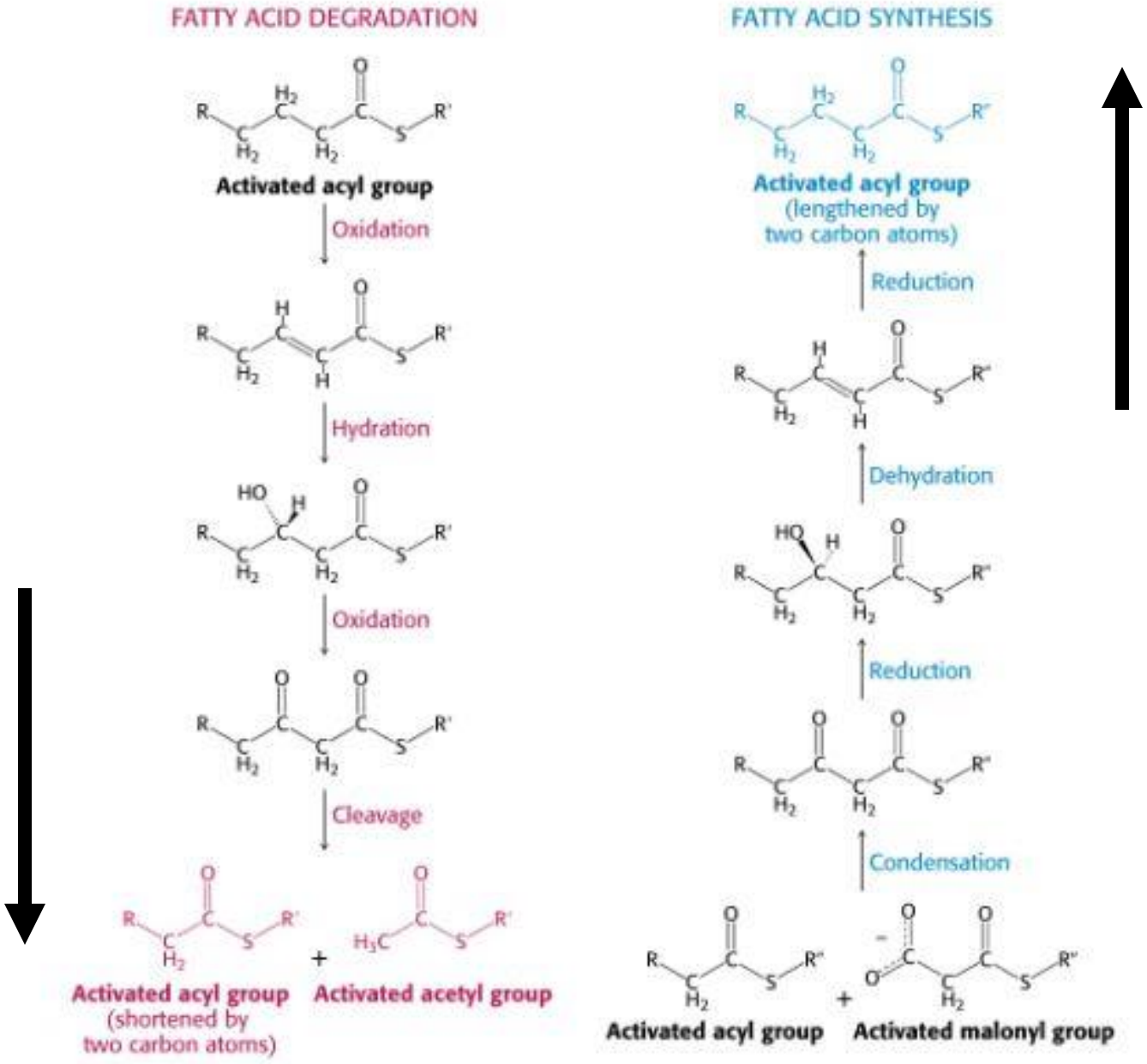
Palmitate
(ionized form of palmitic acid)

Palmitate is then released from the enzyme by a ***thioesterase*** reaction and can then undergo

separate elongation

and/or **unsaturation**

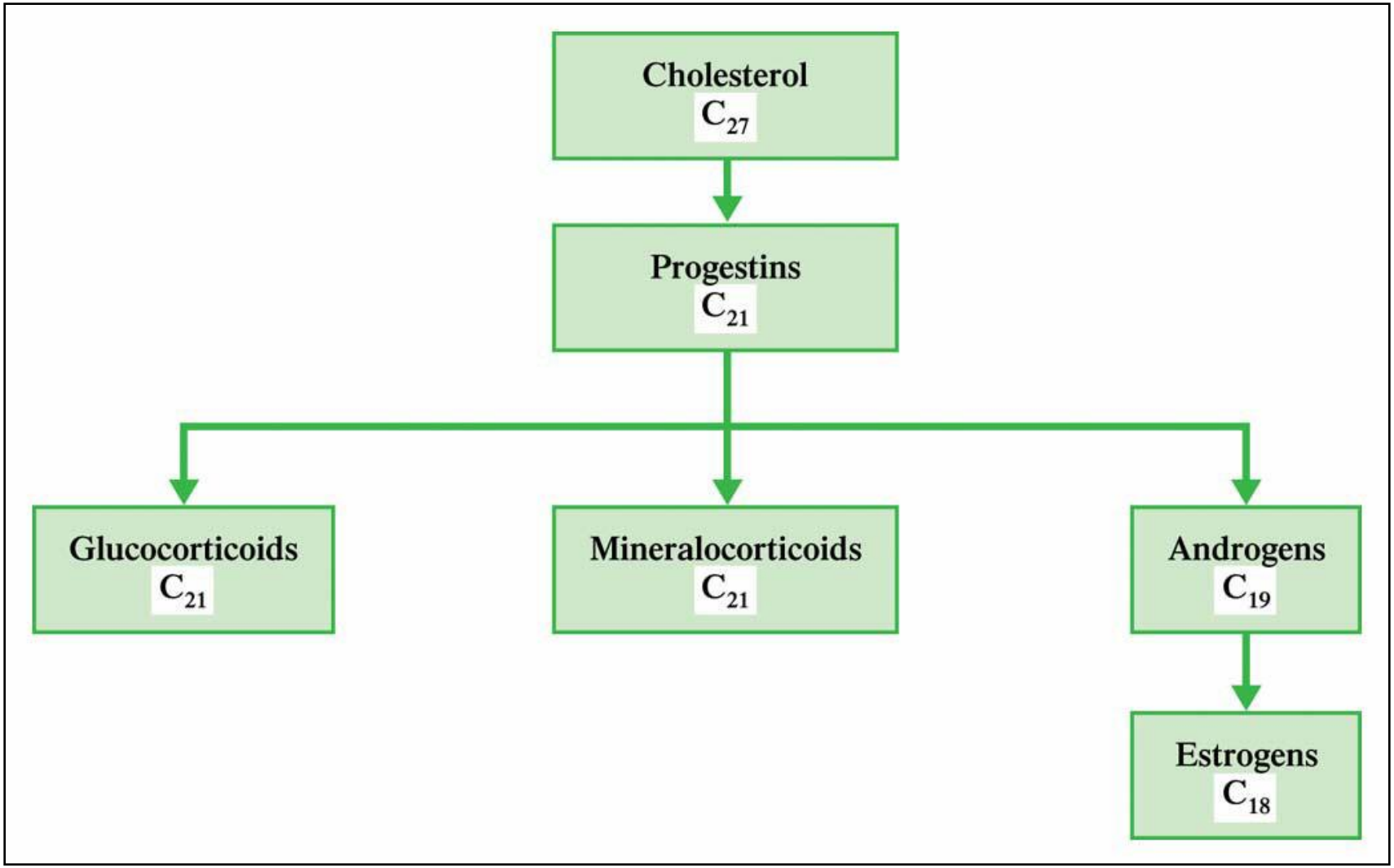
to yield other fatty acid molecules.

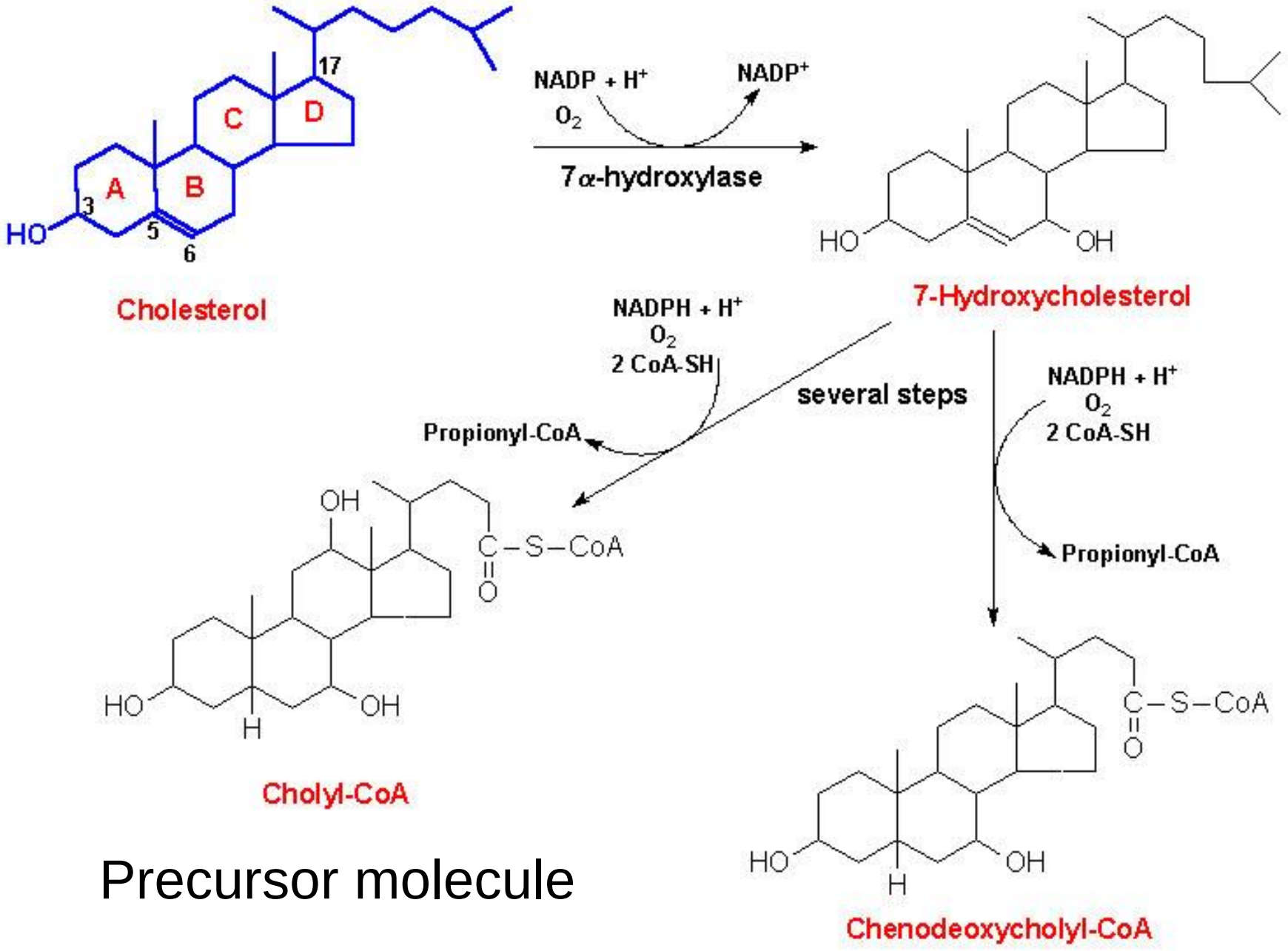

FATTY ACID DEGRADATION
Activated acyl group
Oxidation
Hydration
Oxidation
Cleavage
Activated acyl group
(shortened by
two carbon atoms)
Activated acetyl group
FATTY ACID SYNTHESIS
Activated acyl group
(lengthened by
two carbon atoms)
Reduction
Dehydration
Reduction
Condensation
Activated acyl group
Activated malonyl group

Cholesterol synthesis:

- Cholesterol used in every cell membrane
- Precursor for:
    - Bile salts
    - Vitamin D
    - Adrenal hormones:
        - Glucocorticoids
        - Mineralocorticoids
    - Sex hormones:
        - Estrogens (female)
        - Progestins (pregnancy)
        - Androgens (male)

Biosynthetic relationships among steroid hormones.

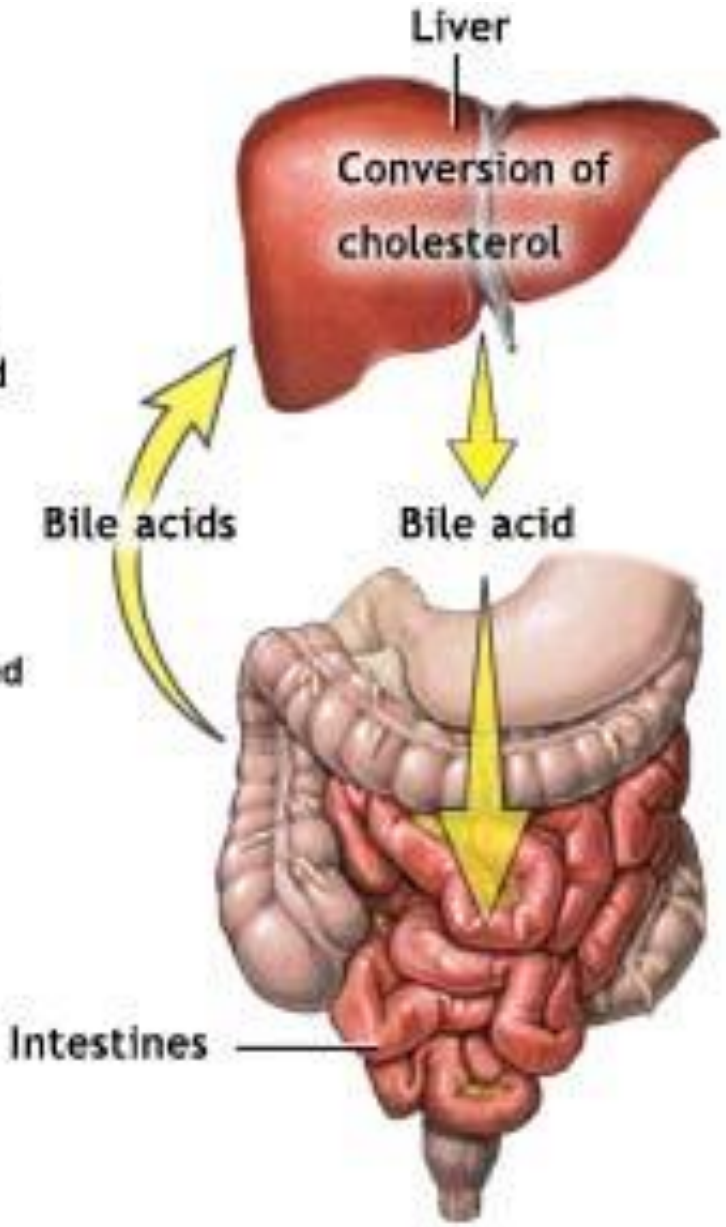




Precursor molecule

- Cholesterol has 27 carbons
- Synthesis takes 15 Acetyl CoA molecules
- 27 separate enzymatic steps
- Occurs in the **liver**, makes 1.5 to 2.0 g / day
- Average diet takes in 0.3 g cholesterol / day

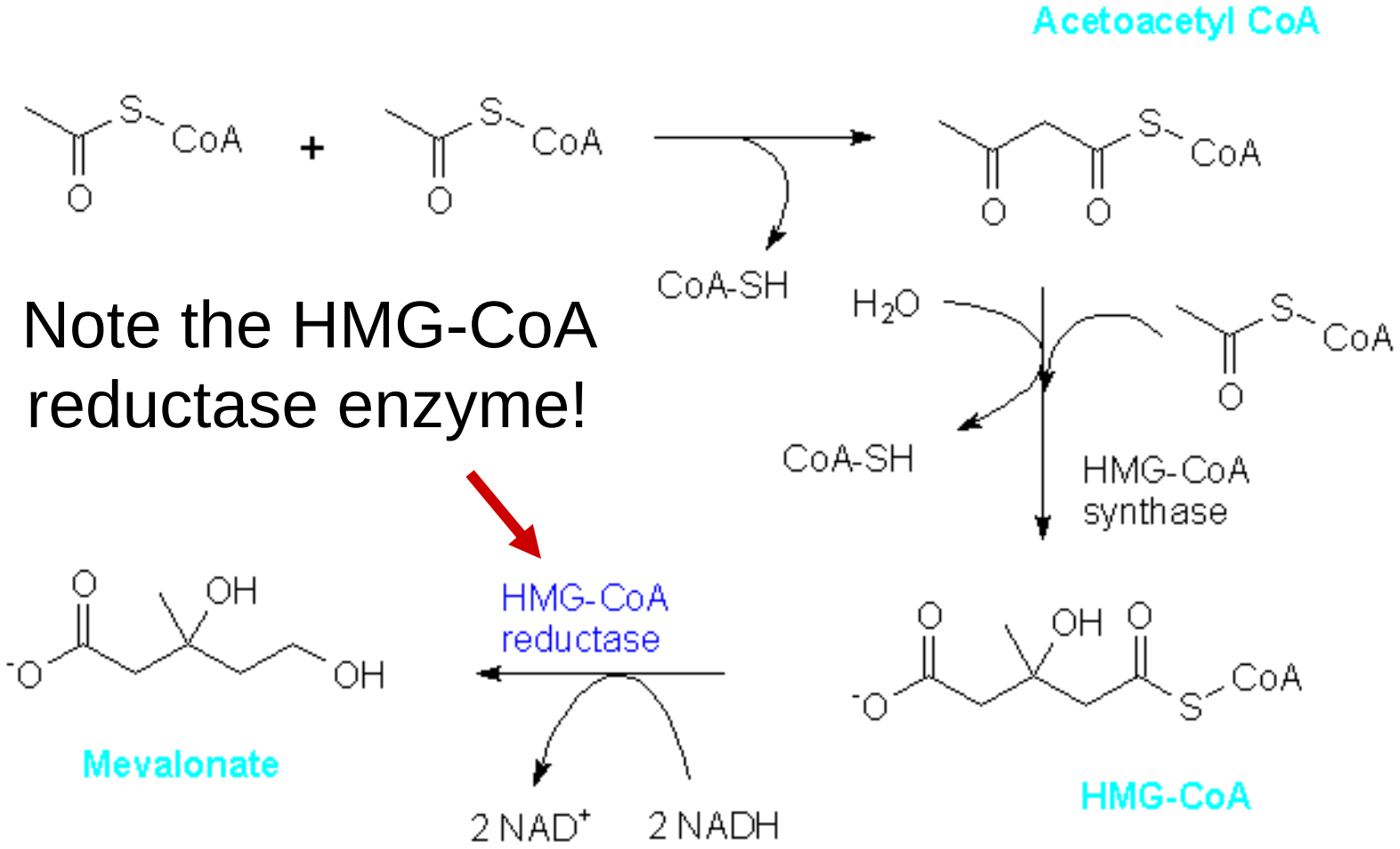
- Liver normally converts cholesterol into bile acid
- Bile acids move into intestines
- Most bile acid is returned to liver
- Result = Higher blood cholesterol levels



Blood cholesterol levels

A.D.A.M.

Biosynthesis of cholesterol begins with 3 **acetyl CoA** molecules forming a 6 C **mevalonate** molecule

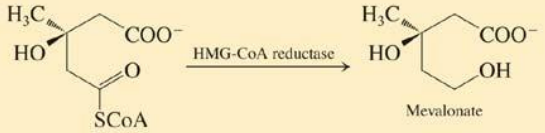


CHEMICAL CONNECTIONS

Statins: Drugs That Lower Plasma Levels of Cholesterol

Over half of all deaths in the United States are directly or indirectly related to heart disease, in particular to atherosclerosis. Atherosclerosis results from the buildup of plaque (fatty acid deposits) on the inner walls of arteries. Cholesterol, obtained from low-density-lipoproteins (LDL) that circulate in blood plasma, is also a major component of plaque.

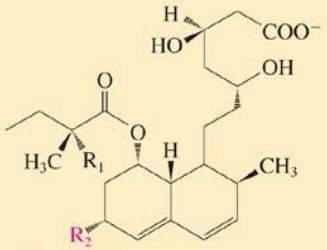
Because most of the cholesterol in the human body is synthesized in the liver, from acetyl CoA, much research has focused on finding ways to inhibit its biosynthesis. The rate-determining step in cholesterol biosynthesis involves the conversion of 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) to mevalonate, a process catalyzed by the enzyme HMG-CoA reductase.



3-Hydroxy-3-methylglutaryl-CoA (HMG-CoA)

Mevalonate

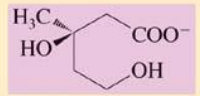
In 1976, as the result of screening more than 8000 strains of microorganisms, a compound now called *mevastatin*—a potent inhibitor of HMG-CoA reductase—was isolated from culture broths of a fungus. Soon thereafter, a second, more active compound called *lovastatin* was isolated.



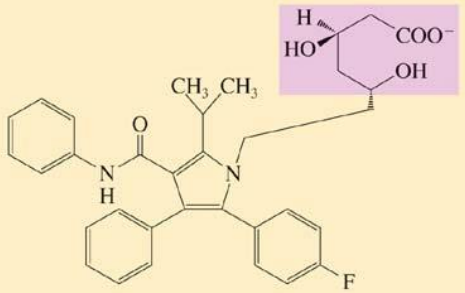
$R_1 = R_2 = H$, mevastatin
$R_1 = H, R_2 = CH_3$, lovastatin (Mevacor)
$R_1 = R_2 = CH_3$, simvastatin (Zocor)

These "statins" are very effective in lowering plasma concentrations of LDL by functioning as competitive inhibitors of HMG-CoA reductase.

After years of testing, the statins are now available as prescription drugs for lowering blood cholesterol levels. Clinical studies indicate that use of these drugs lowers the incidence of heart disease in individuals with mildly elevated blood cholesterol levels. A later-generation statin, with a ring structure distinctly different from that of earlier statins—atorvastatin (Lipitor)—became the most prescribed medication in the United States in the year 2000. Note the structural resemblance between part of the structure of Lipitor and that of mevalonate.



Mevalonate



Atorvastatin (Lipitor)

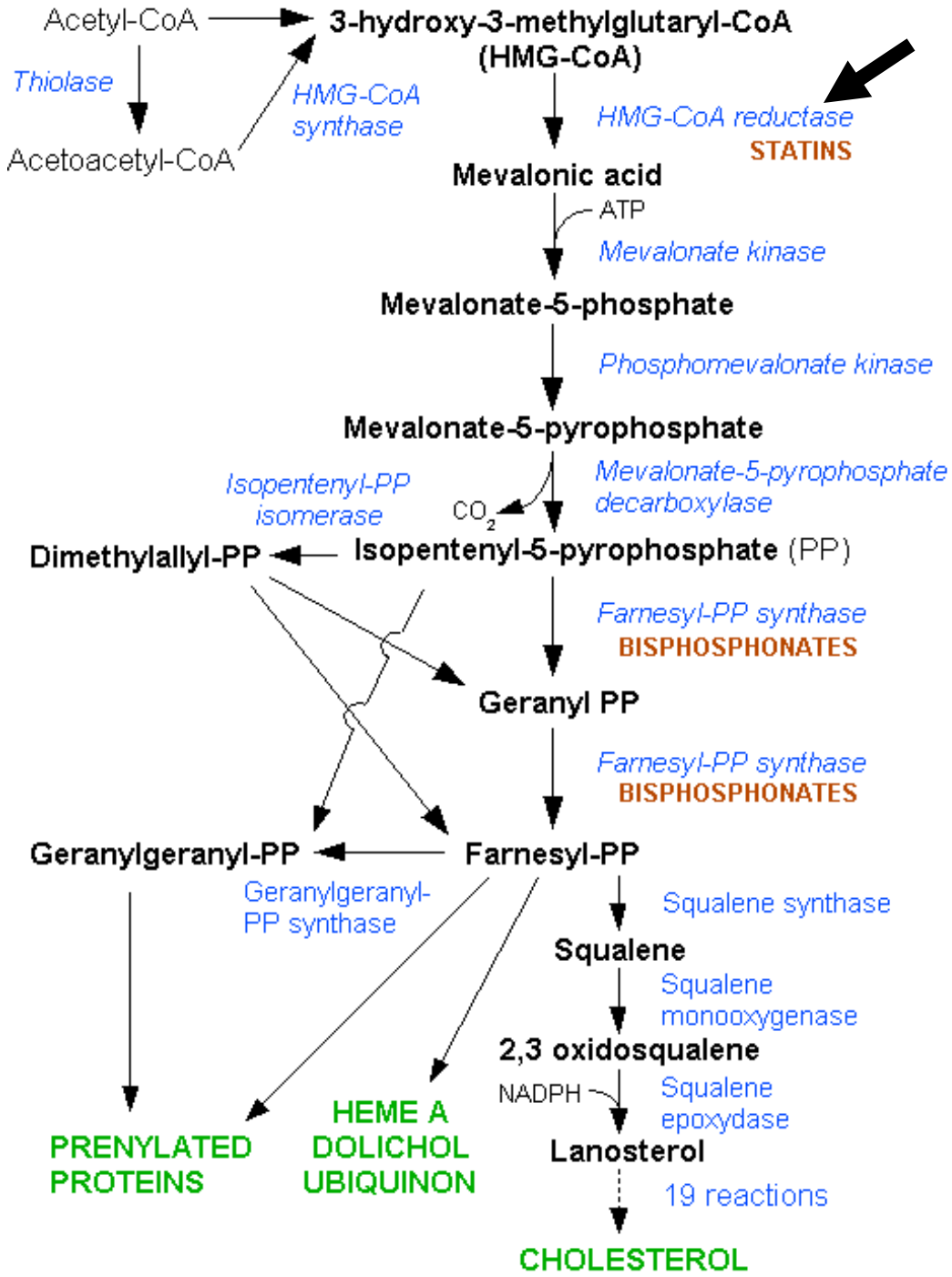
Recent research studies have unexpectedly shown that the cholesterol-lowering statins have two added benefits.

Laboratory studies with animals indicate that statins prompt growth cells to build new bone, replacing bone that has been leached away by osteoporosis ("brittle-bone disease"). A retrospective study of osteoporosis patients who also took statins shows evidence that their bones became more dense than did bones of osteoporosis patients who did not take the drugs.

Statins have also been shown to function as anti-inflammatory agents that counteract the effects of a common virus, cytomegalovirus, which is now believed to contribute to the development of coronary heart disease. Researchers believe that by age 65, more than 70% of all people have been exposed to this virus. The virus, along with other infecting agents in blood, may actually trigger the inflammation mechanism for heart disease.

Statins: cholesterol lowering Drugs

May also help with osteoporosis and as anti-inflammatory for virus that affects heart



cholesterol lowering drugs

Most are **competitive inhibitors** for particular enzymes:

e.g.

HMG-CoA reductase

Exercise and Carbohydrate & Lipid metabolism

Humans burn more fat than carbs (2:1) in resting state.

Beginning exercise: sudden need for energy.
Glycogen much faster to release glucose-6-phosphate for fuel. 1st few minutes = 80% fuel from glycogen.

Fats 1st broken down to F.A.s, then attach to protein carriers & carried to muscles via bloodstream; then released and undergo energy producing reactions.

Low intensity workout eventually
cuts over to burning **fat**.
High intensity relies more on **glucose**.

Relationship between Lipid and Carbohydrate Metabolism

Acetyl CoA is the link between
lipid and carbohydrate metabolic pathways.

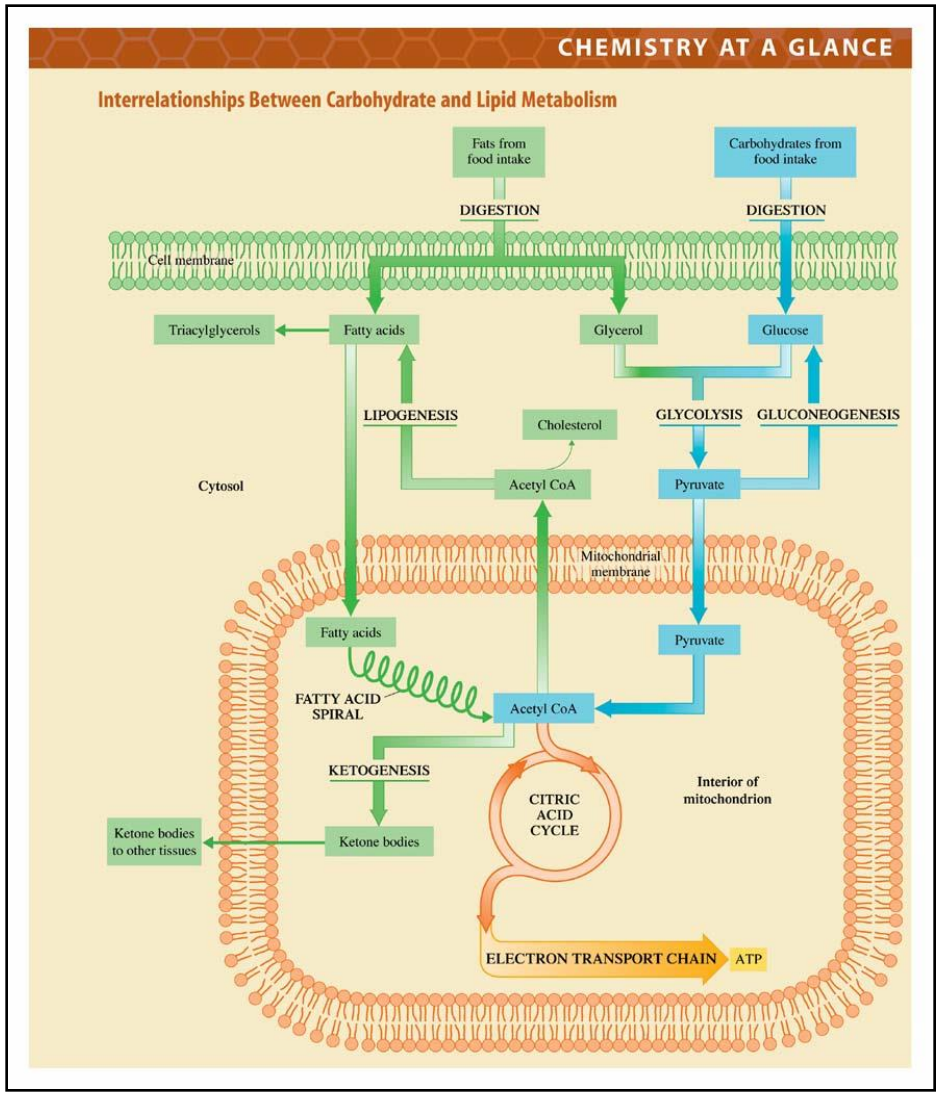
Glucose, Glycerol, & Fatty acids
all degrade into **acetyl CoA**

Biosynthesis of
fatty acids, ketone bodies, & cholesterol
all use **acetyl CoA**.

Glucose, Glycerol, & Fatty acids
all supply **acetyl CoA**
to be oxidized in the Krebs cycle.

Ketone bodies form when there is an imbalance
between lipids and carbohydrates:
Inadequate amounts of glucose,
during adequate times of lipid metabolism.

Cholesterol and **Fatty Acid synthesis** occurs
when body is overly rich in **acetyl CoA**,
beyond energy needs for cellular activity.



Review: can you…

- Describe ATP production from F.A. Oxidation
- Define “Ketone Bodies” & explain formation significance
- Compare & contrast Lipogenesis to biosynthesis of Cholesterol
- Compare & contrast relationship between Lipid & Carbohydrate Metabolism
- Discuss effect of exercise on carbohydrate & lipid metabolism
- Discuss cholesterol lowering drugs