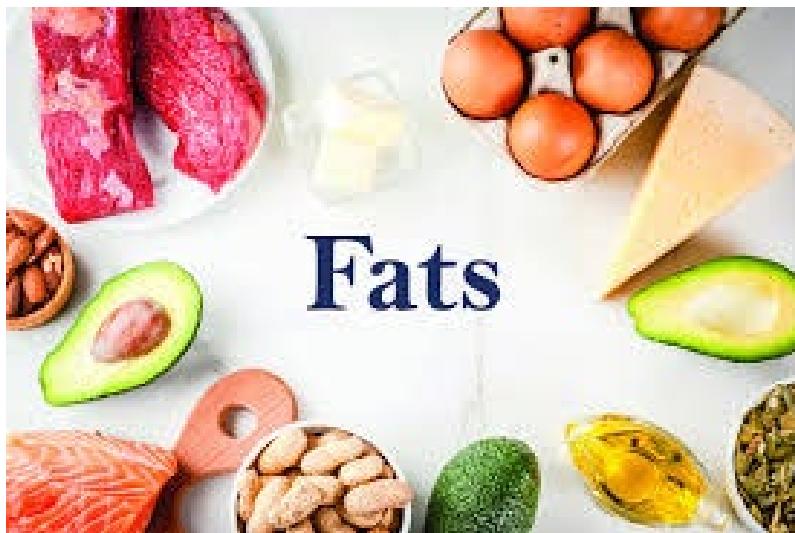


## Lecture 8 – Fatty acid catabolism – Pentose phosphate pathway



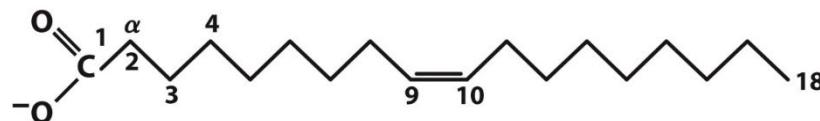
Kwok-On LAI  
Department of Neuroscience

# Learning outcomes

- To describe the digestion, mobilization and storage of lipids
- To explain the catabolic fate of triacylglycerol
- To describe the  $\beta$ -oxidation of fatty acids
- To describe the formation of ketone body and explain the consequences of its over-production in diabetes
- Describe pentose pathway, its importance and relation to disease

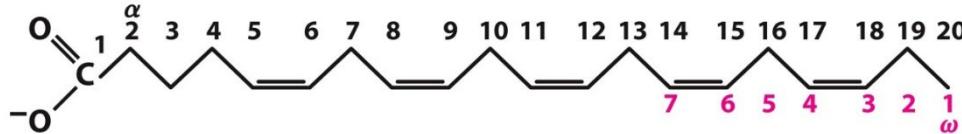
# Basics about fatty acids

- Fatty acids are carboxylic acids with hydrocarbon chains ranging from 4 to 36 carbons long; can contain some or no double bonds (unsaturated or saturated fatty acids)
- Naming convention 1: carboxyl group as “1” then the next carbon as “ $\alpha$ ”; chain length and number of double bonds separated by a colon; double bond is indicated by  $\Delta$  followed by a superscripted number the position indication lower-numbered carbon



(a) 18:1( $\Delta^9$ ) *cis*-9-Octadecenoic acid

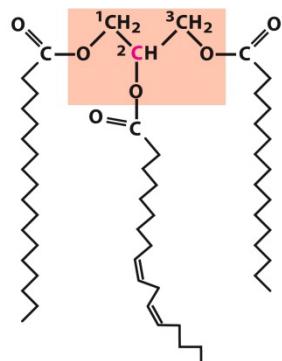
- Naming convention 2: For polyunsaturated fatty acids, the last carbon is assigned as “ $\omega$ ” and the double bond are indicated relative to the  $\omega$  carbon



(b) 20:5( $\Delta^{5,8,11,14,17}$ ) Eicosapentaenoic acid (EPA),  
an omega-3 fatty acid

# The importance of lipid metabolism

- Oxidation of fatty acids to **acetyl-CoA** is a very important energy yielding pathway in many organisms and tissues
- In vertebrates, fatty acids were obtained from food and can also be synthesized in liver
- In mammalian heart and liver, fatty acids provide **up to 80% of energetic needs** under all physiological circumstances
- Fatty acids can become a long-term energy storage source in the form of **triacylglycerol** in adipocytes (fat cells)



1-Stearoyl, 2-linoleoyl, 3-palmitoyl glycerol,  
a mixed triacylglycerol

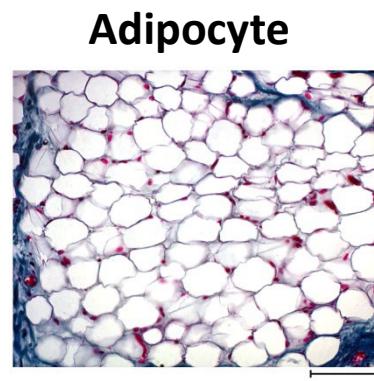
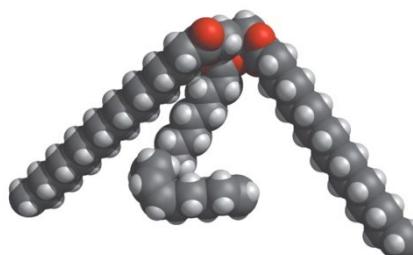


Figure 10-4  
Lipid metabolism  
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# Processing of dietary lipids

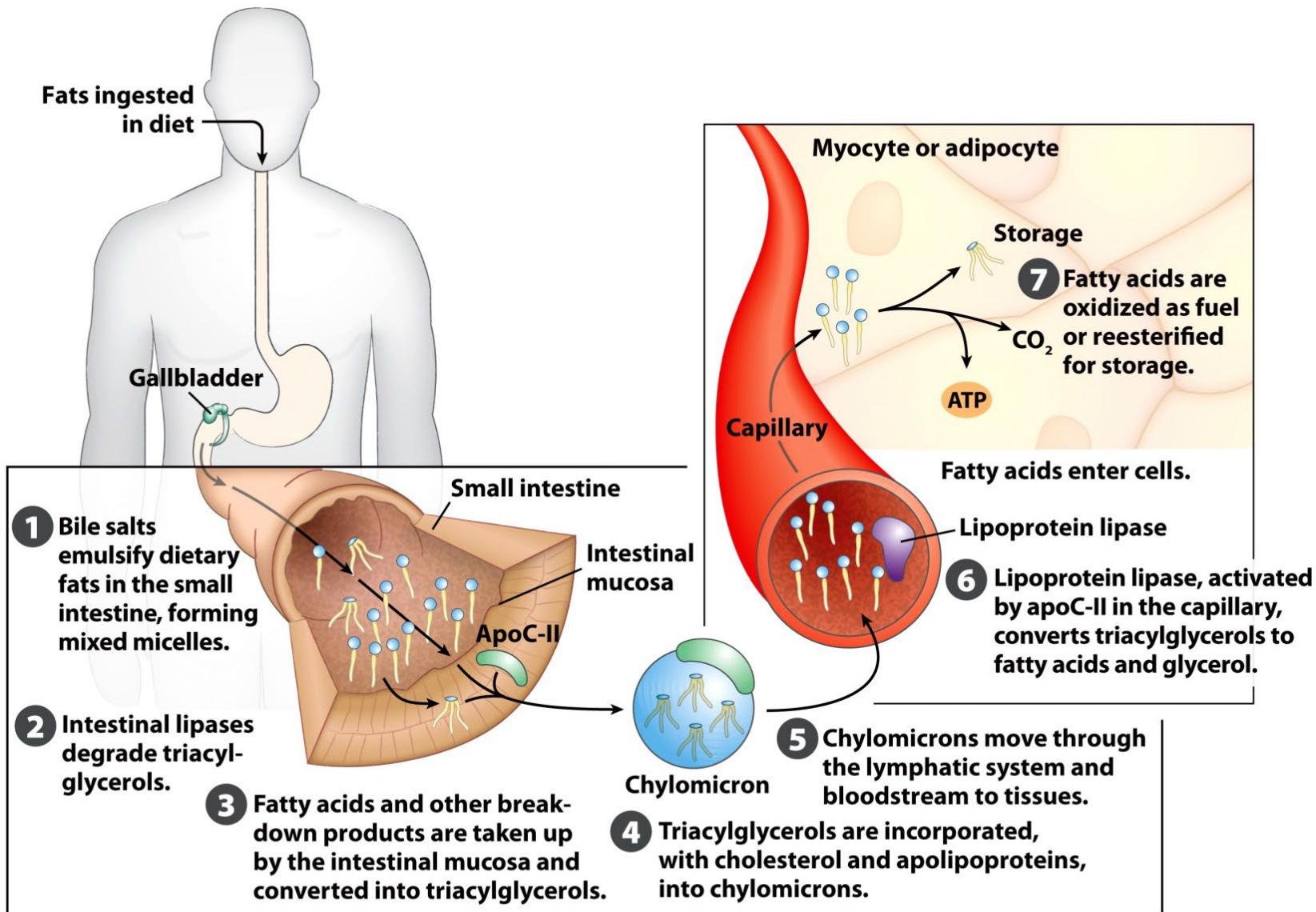


Figure 17-1

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- Bile (acids) salts: A form of cholesterol; synthesized in the liver, secreted by gallbladder into the small intestine. Amphipathic and serves as “biological detergent”

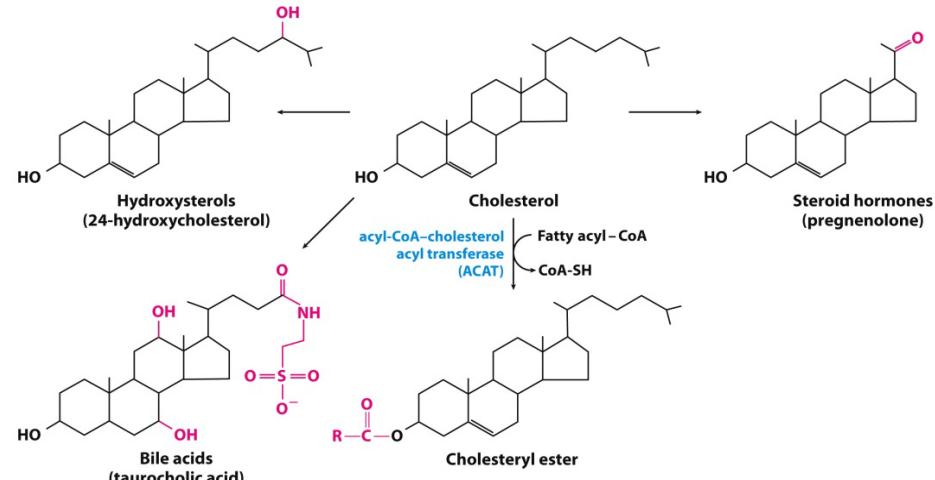


Figure 21-38  
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- Apolipoproteins: lipid binding proteins in blood, responsible for the transport of triacylglycerols, phospholipids, cholesterol between organs
- Chylomicrons: triacylglycerols packaged with dietary cholesterol and specific lipoproteins; diameter ranges from 100 to 500 nm

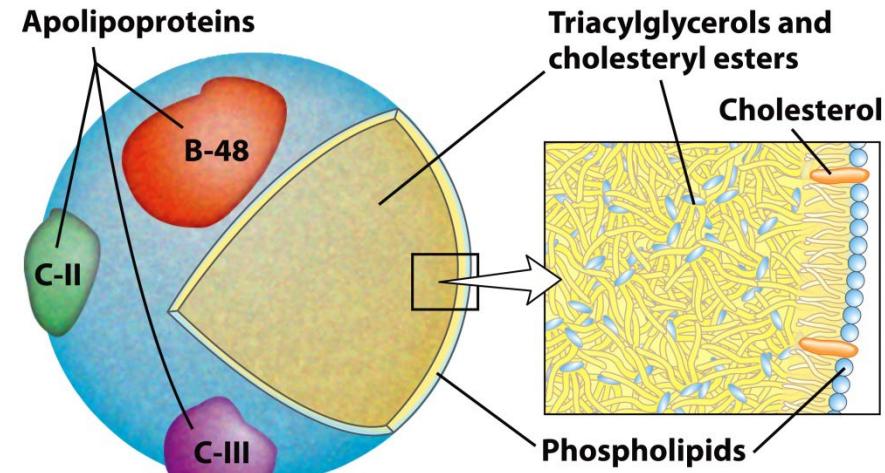
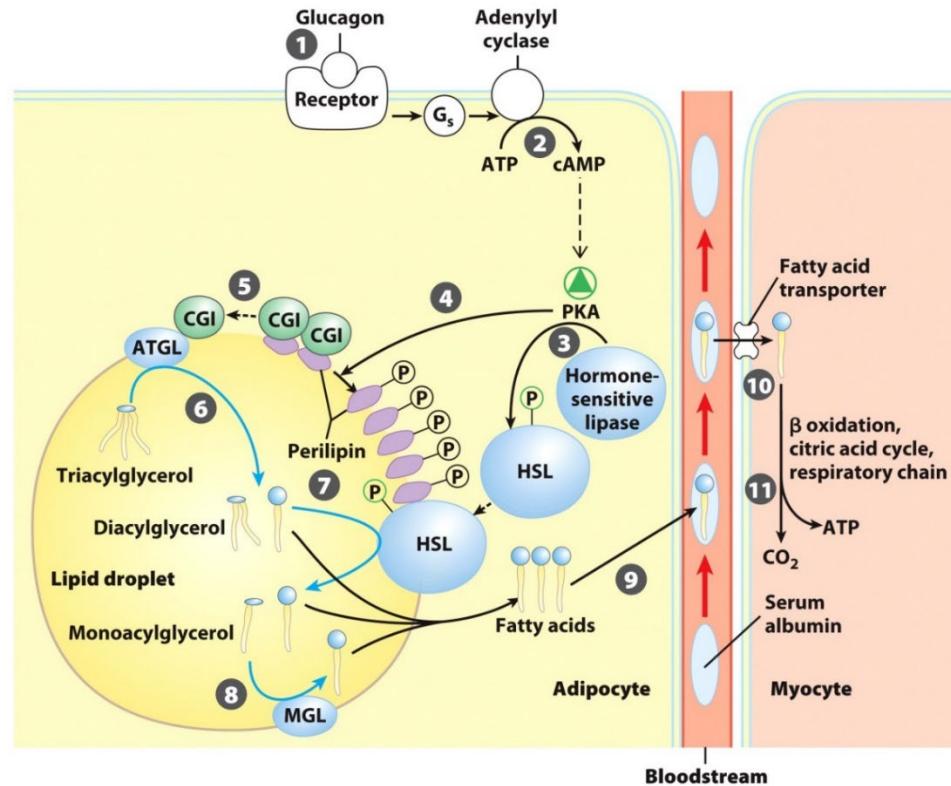


Figure 17-2  
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# Mobilization of triacylglycerol stored in adipose tissue

- Low level of blood glucose triggers the release of glucagon, which causes a signal transduction cascade involving a GPCR
- Activation of lipases, including adipocyte triacylglycerol lipase (ATGL, from tri- to di-glycerol), hormone-sensitive lipase (HSL, from di- to mono-glycerol) and monoacylglycerol lipase (MGL, remove glycerol)
- Single chain fatty acids are transported in blood after bound to the protein albumin; fatty acids are then taken up by myocytes



# Summary of lipid transport pathways

## Uptake of lipids by dietary pathway

All kinds of lipid

Intestinal lipases

Fatty acids

Uptake and conversion in  
intestinal epithelial cells

Triacylglycerol

## Small intestine

Adipocyte

Triacylglycerol

Lipases  
ATGL, HSL, MGL

Fatty acids

Mobilization of stored lipids

Blood lipoprotein  
lipase

Fatty acids

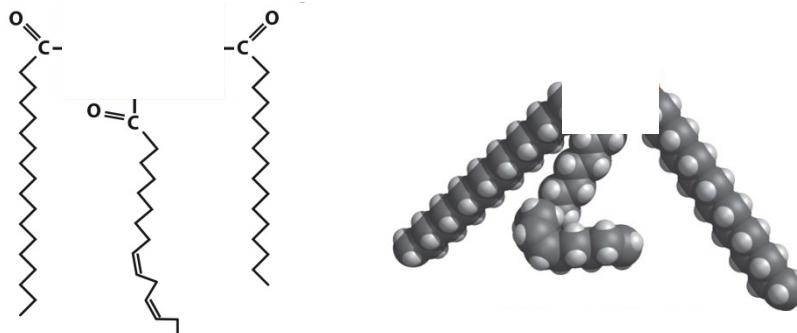
Bloodstream

Oxidation

Myocyte (muscle cell)

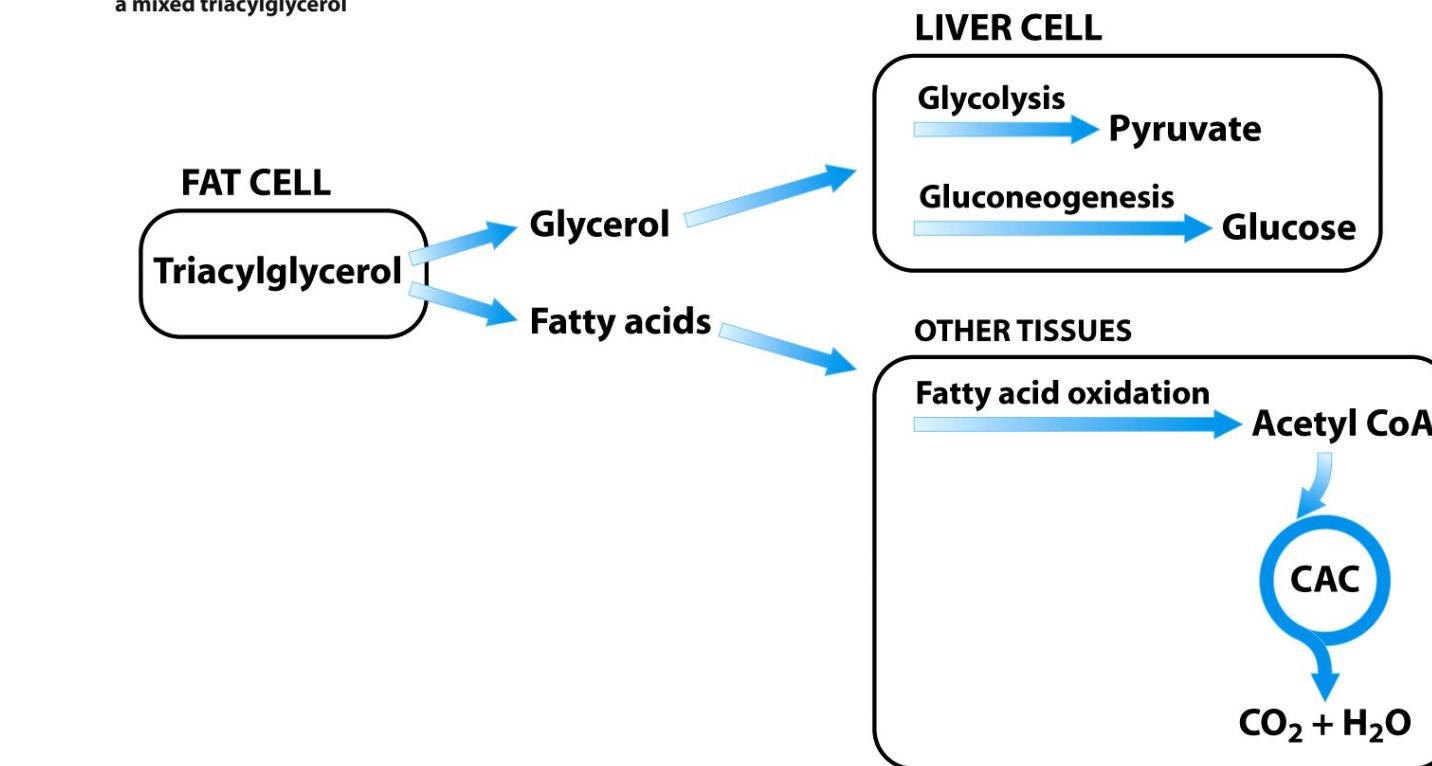
Fatty acids

# The catalytic fate of triacylglycerol



1-Stearoyl, 2-linoleoyl, 3-palmitoyl glycerol,  
a mixed triacylglycerol

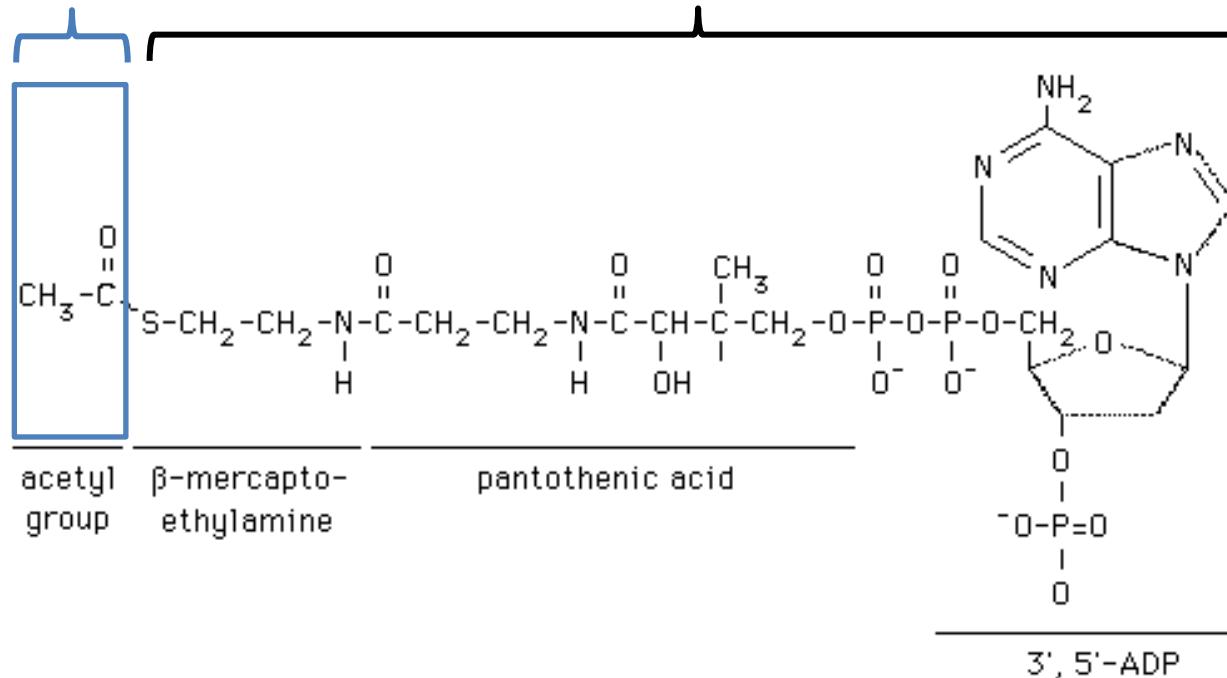
Problem 1: catabolize the glycerol



# Acetyl-CoA

Acetyl

Coenzyme A

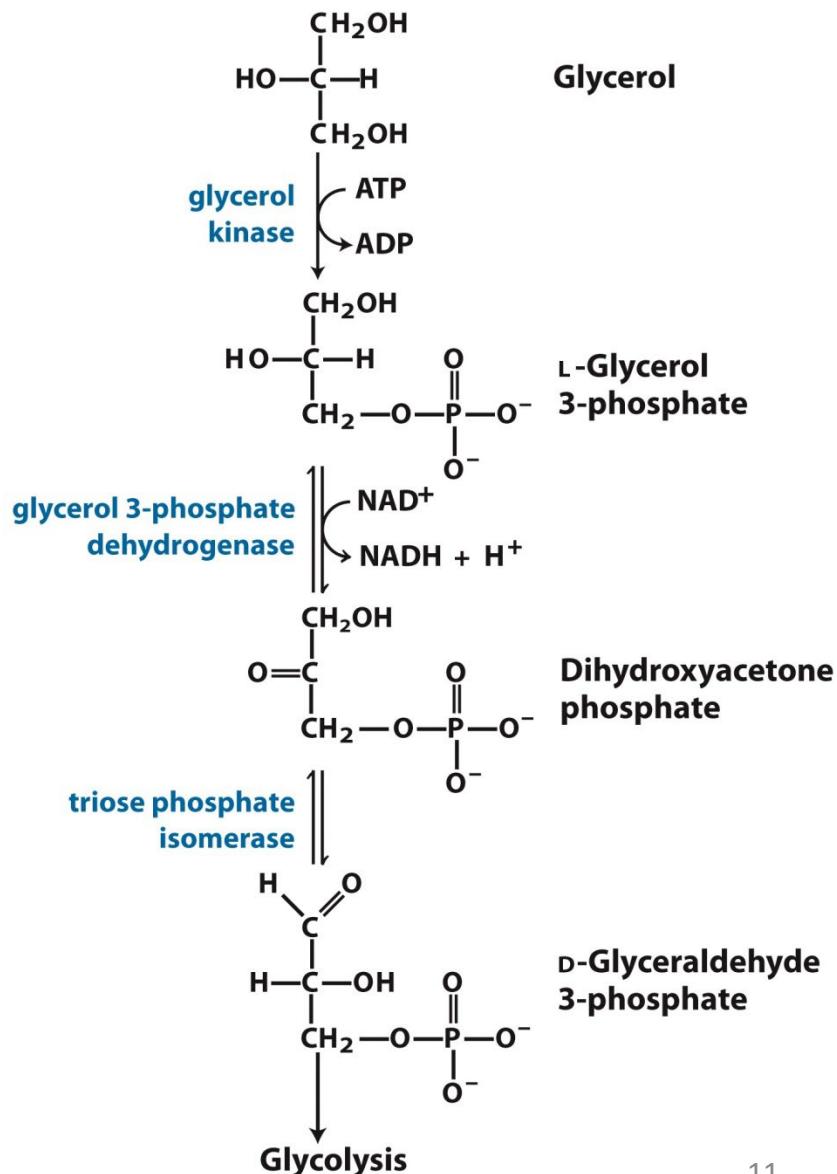


Acetyl coenzyme A, showing its constituents

- Konrad Bloch and Feodor Lynen were awarded the 1964 Nobel Prize in Physiology and Medicine for their discoveries linking acetyl-CoA and fatty acid metabolism.
- Fritz Lipmann won the Nobel Prize in 1953 for his discovery of the cofactor coenzyme A.

# Glycerol is consumed in glycolysis

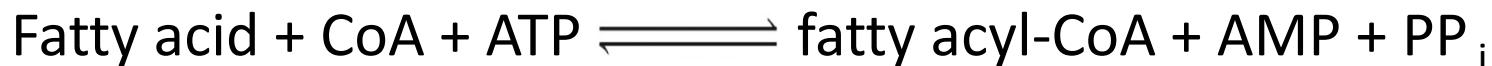
- Glycerol formed by lipolysis is absorbed by the liver and phosphorylated to form **glycerol 3-phosphate** which is then oxidized to dihydroxyacetone phosphate
- It is then isomerized to **glyceraldehyde 3-phosphate**, an intermediate molecule in both the glycolytic and the gluconeogenic pathways



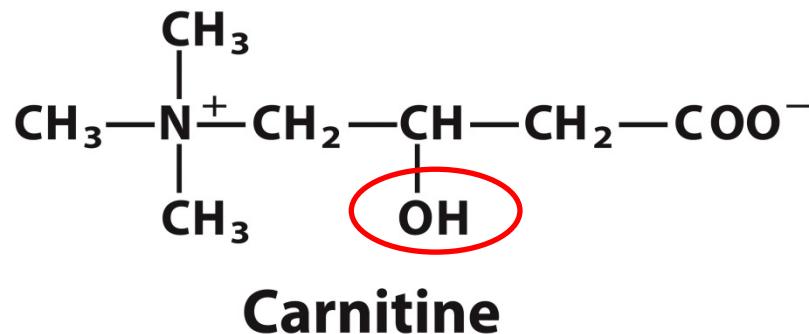
# Fatty acids catabolism

## Step 1: transportation to mitochondria by carnitine shuttle

- 1) Fatty acids are transformed to fatty acyl-CoA by acyl-CoA synthetases



- 2) Fatty acyl-CoA are transiently attached to the hydroxyl group of carnitine to form fatty acyl-carnitine, which enters mitochondria through the acyl-carnitine/carnitine transporter



- 3) Finally fatty acyl group is enzymatically transferred from carnitine to intra-mitochondrial coenzyme A to form back fatty acyl-CoA

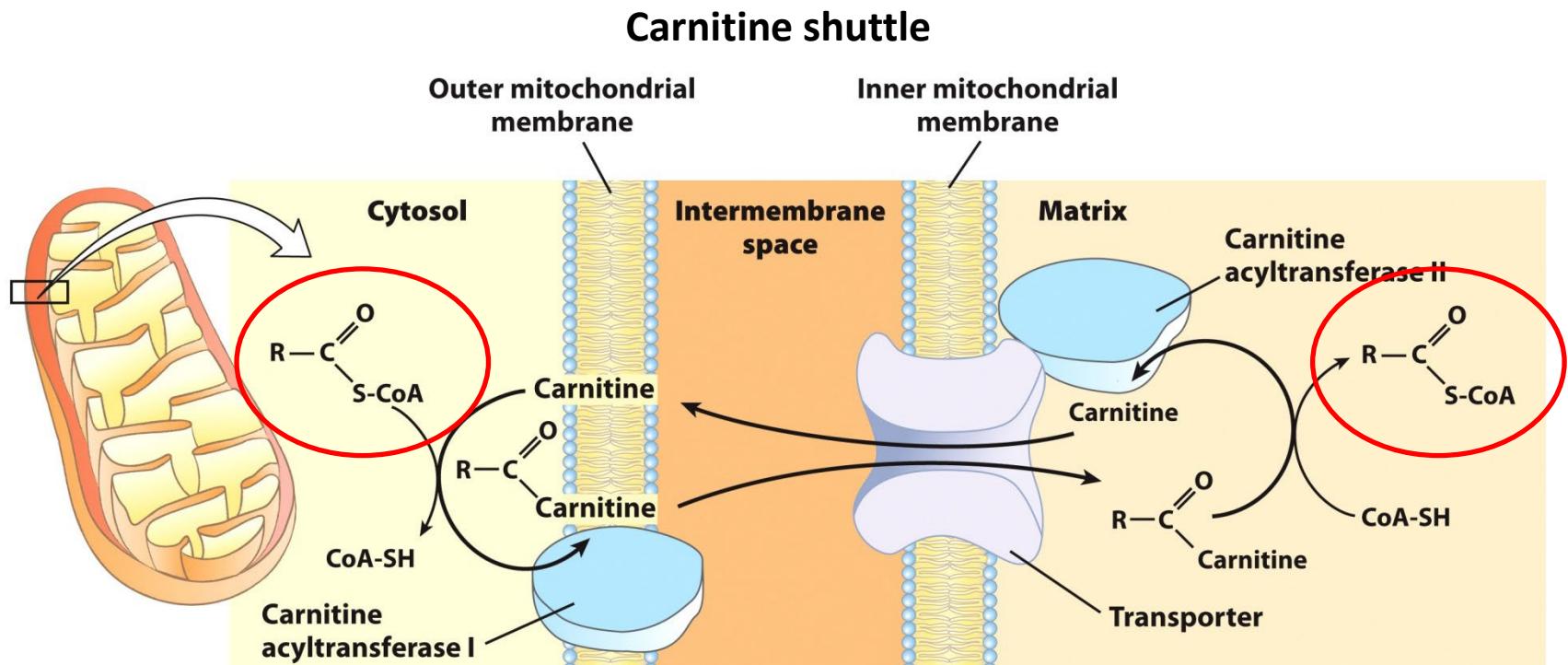


Figure 17-6

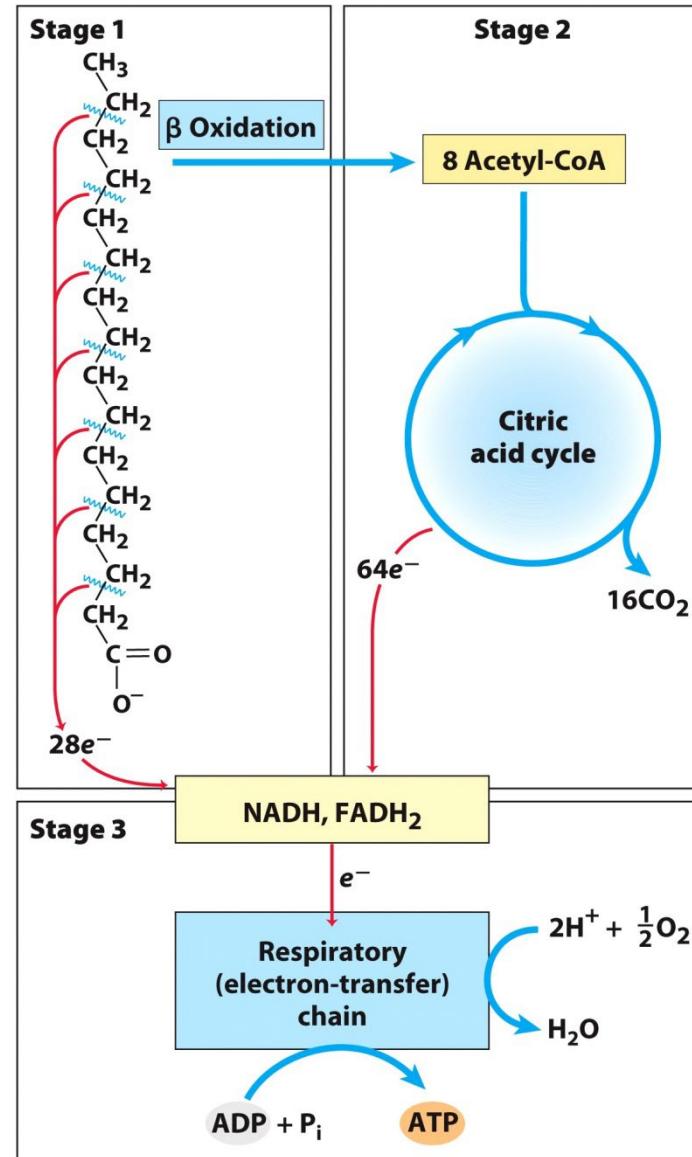
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Cytoplasm

Mitochondria

# Oxidation of fatty acids in mitochondria

- First stage:  $\beta$ -oxidation - fatty acids undergo oxidative removal of successive two-carbon units in the form of acetyl-CoA
- Second stage: acetyl-CoA are oxidized to  $\text{CO}_2$  in citric acid cycle
- Third stage: Reduced electron carriers NADH and FADH<sub>2</sub> produced in the first two stages donate electrons to the mitochondrial respiratory chain to produce ATP



# $\beta$ -oxidation

- Step 1: Dehydrogenation by three acyl-CoA dehydrogenase. Three isozymes: very-long-chain acyl-CoA dehydrogenase (VLCAD), acting on 12-18 carbons; medium chain (MCAD) on 4-14 carbons; short chain (SCAD) on 4-8 carbons
- Step 2: Adding  $H_2O$  (hydration) by enoyl-CoA hydratase
- Step 3: Dehydrogenation
- Step 4: Split off the carboxyl-terminal two-carbon fragment by thiolysis (thiol R-SH cleaves one molecule into two)

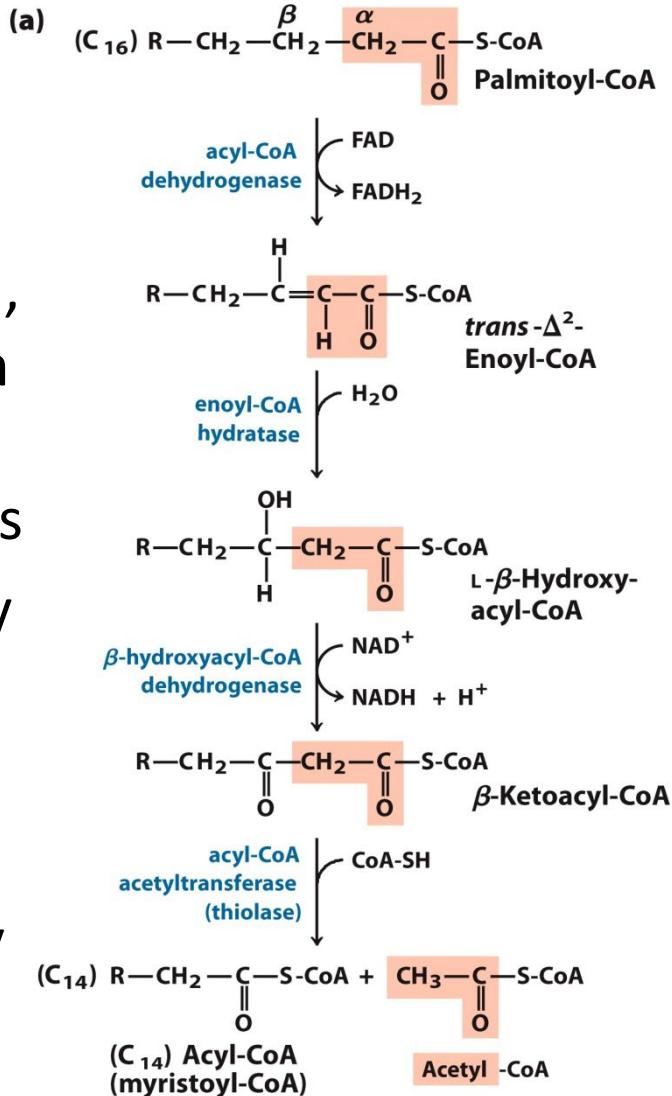
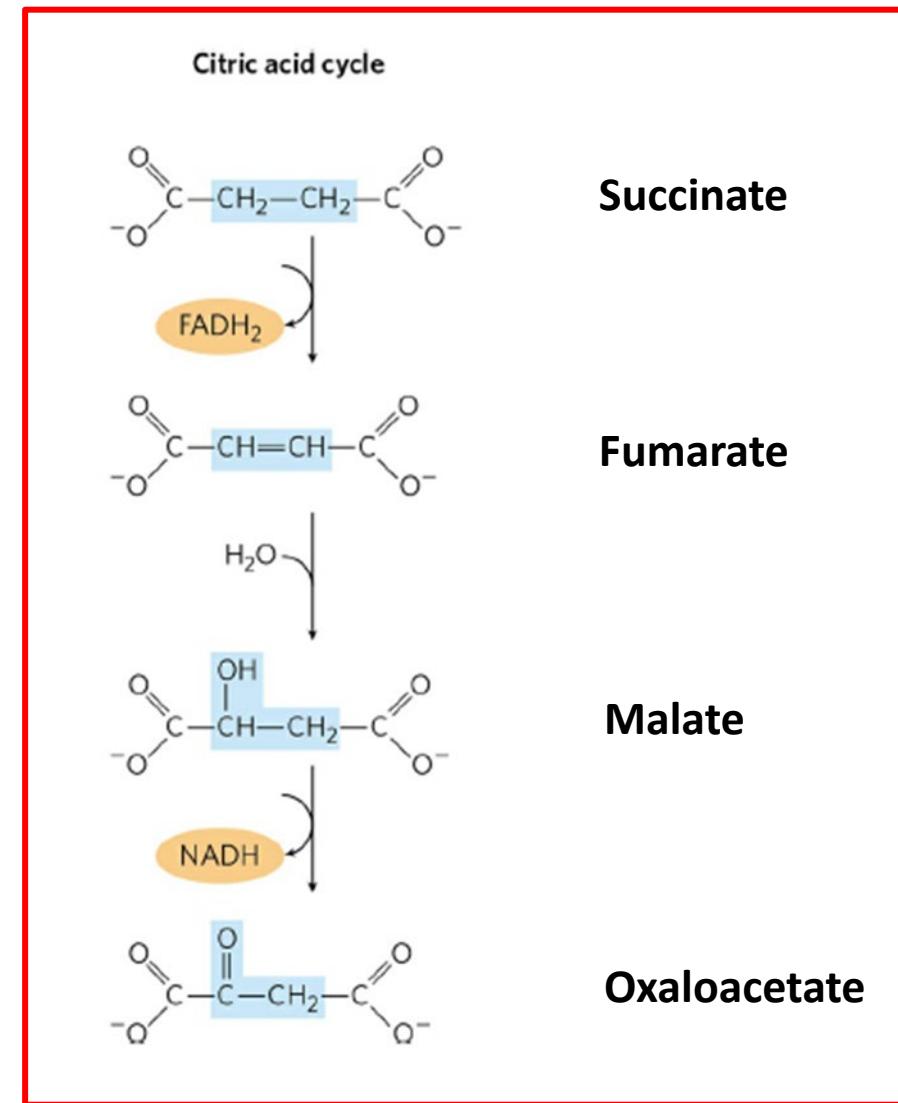
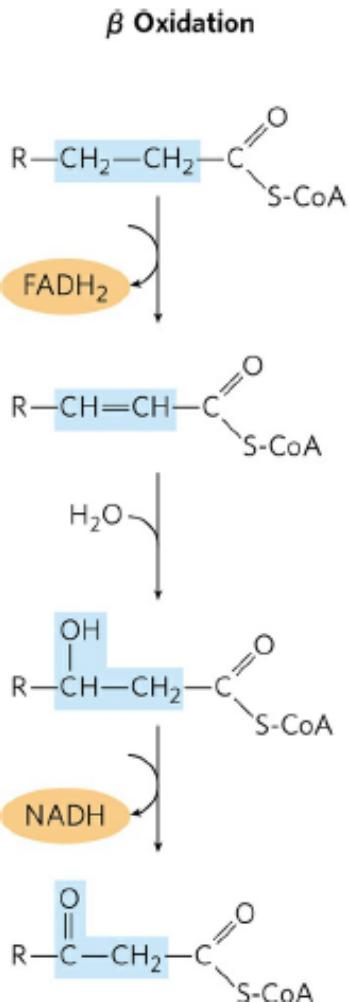


Figure 17-8

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# $\beta$ -oxidation: similar reaction sequences as citric acid cycle

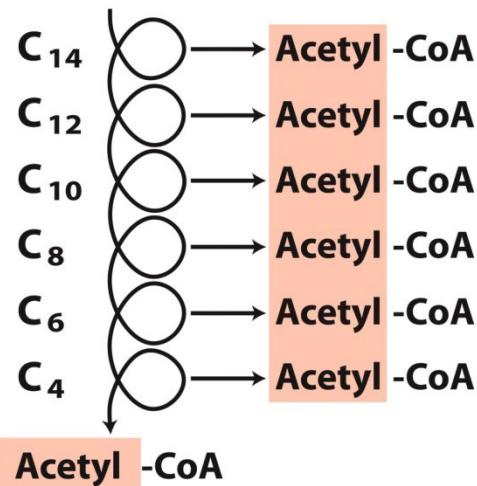


# The trifunctional protein complex

- For fatty acid chains longer than 12, trifunctional protein (TFP), a multienzyme complex associated with the inner mitochondrial membrane, is involved
- TFP is a heterooctamer of  $\alpha_4\beta_4$  subunits. Each  $\alpha$  subunit contains two activities: enoyl-CoA hydratase and  $\beta$ -hydroxyacyl-CoA dehydrogenase (step 2 and 3 of  $\beta$ -oxidation). The  $\beta$  subunit contains thiolase activity (step 4)
- This tight association of three enzymes allows efficient substrate channeling from one active site to the next
- When the fatty acids are shortened to 12 or fewer carbons, further oxidations are catalyzed by a set of four soluble enzymes in mitochondrial matrix.

# Generation of multiple acetyl-CoA by $\beta$ -oxidation in cycles

- $\beta$ -oxidation is carried out in cycles, generating a number of acetyl-CoA



For a 14 carbon fatty acid (fatty acyl-CoA):  
Number of acetyl-CoA =  $14/2 = 7$   
Number of  $\beta$ -oxidation cycles =  $(14-2)/2 = 6$

- For palmitic acid, a 16 carbon fatty acid:

Number of acetyl-CoA =  $16/2 = 8$   
Number of  $\beta$ -oxidation cycles =  $(16-2)/2 = 7$

Figure 17-4b  
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# Yield of ATP in the degradation of palmitic acid

- In  $\beta$ -oxidation, the number of acetyl CoA formed is 8 and the number of successive oxidation cycle in total is 7
- In each  $\beta$ -oxidation cycle, 1 NADH and 1 FADH<sub>2</sub> are produced
- In each citric acid cycle of acetyl CoA, 3 NADH and 1 FADH<sub>2</sub> are produced
- In total, one 16-carbon palmitic acid produces 108 molecules of ATP

**TABLE 17-1 Yield of ATP during Oxidation of One Molecule of Palmitoyl-CoA to CO<sub>2</sub> and H<sub>2</sub>O**

	Enzyme catalyzing the oxidation step	Number of NADH or FADH <sub>2</sub> formed	Number of ATP ultimately formed*
$\beta$ -oxidation	Acyl-CoA dehydrogenase	7 FADH <sub>2</sub>	10.5
	$\beta$ -Hydroxyacyl-CoA dehydrogenase	7 NADH	17.5
Citric acid cycle	Isocitrate dehydrogenase	8 NADH	20
	$\alpha$ -Ketoglutarate dehydrogenase	8 NADH	20
	Succinyl-CoA synthetase		8†
	Succinate dehydrogenase	8 FADH <sub>2</sub>	12
	Malate dehydrogenase	8 NADH	20
	Total		108

\*These calculations assume that mitochondrial oxidative phosphorylation produces 1.5 ATP per FADH<sub>2</sub> oxidized and 2.5 ATP per NADH oxidized.

†GTP produced directly in this step yields ATP in the reaction catalyzed by nucleoside diphosphate kinase (p. 526).

## Carnitine shuttle

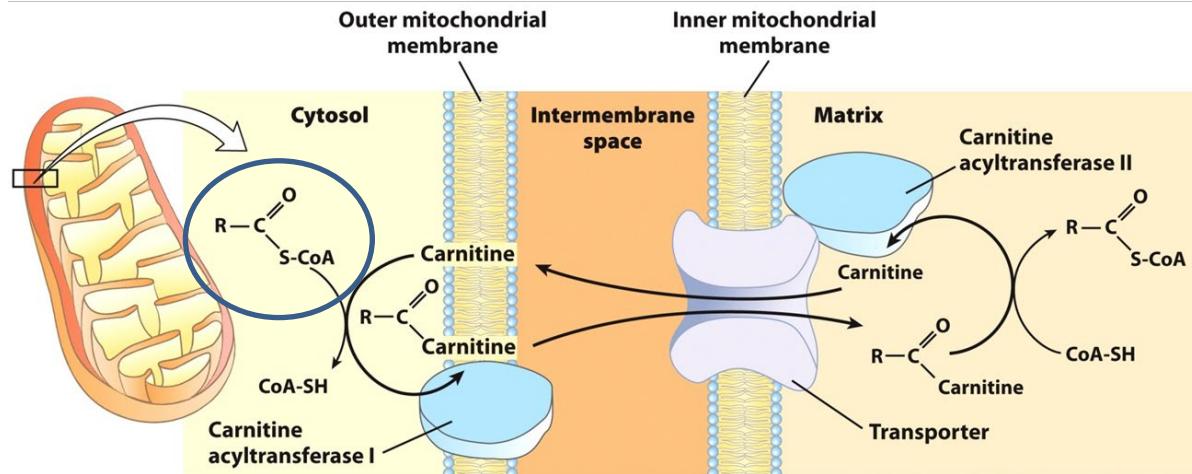


Figure 17-6  
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- Palmitic acid is converted to palmitoyl-CoA for the transportation (from cytosol into mitochondria) by carnitine shuttle



- Two phosphates are removed from ATP so the energy consumption equals to 2 ATP
- Total energy generated by palmitic acid degradation is:

$$108 - 2 = 106 \text{ ATP}$$

# Study question

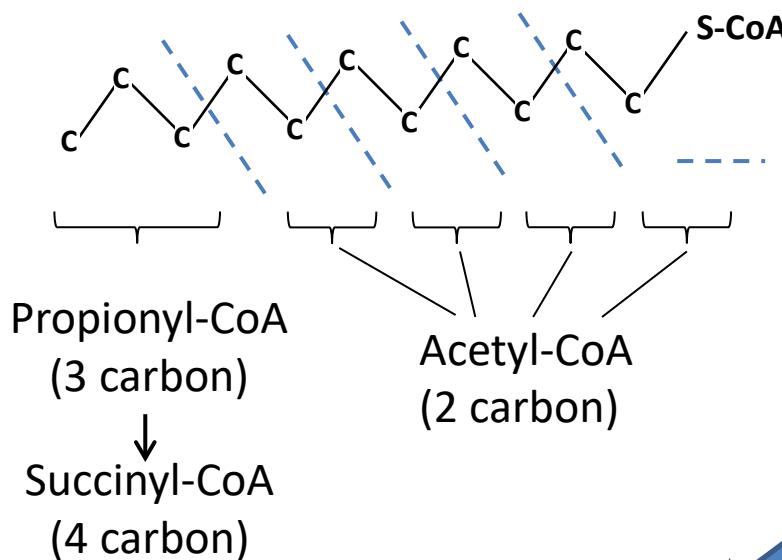
Why can hibernating animals survive the long winter without drinking water?



# Oxidation of odd-number fatty acids

- Most naturally occurring lipids contain fatty acids with an even number of carbon in the chain. Fatty acids with **odd number** are common **in plants and some marine organisms**
- Odd number fatty acids are also oxidized by successive  $\beta$ -oxidation. In the last pass of  $\beta$ -oxidation, 5-carbon fatty acids are converted into acetyl-CoA and **propionyl-CoA**

Example: 11 carbon fatty acid



For a 11 carbon fatty acid (fatty acyl-CoA):

$$\text{Number of acetyl-CoA} = (11-3)/2 = 4$$

$$\text{Number of } \beta\text{-oxidation cycles} = 4$$

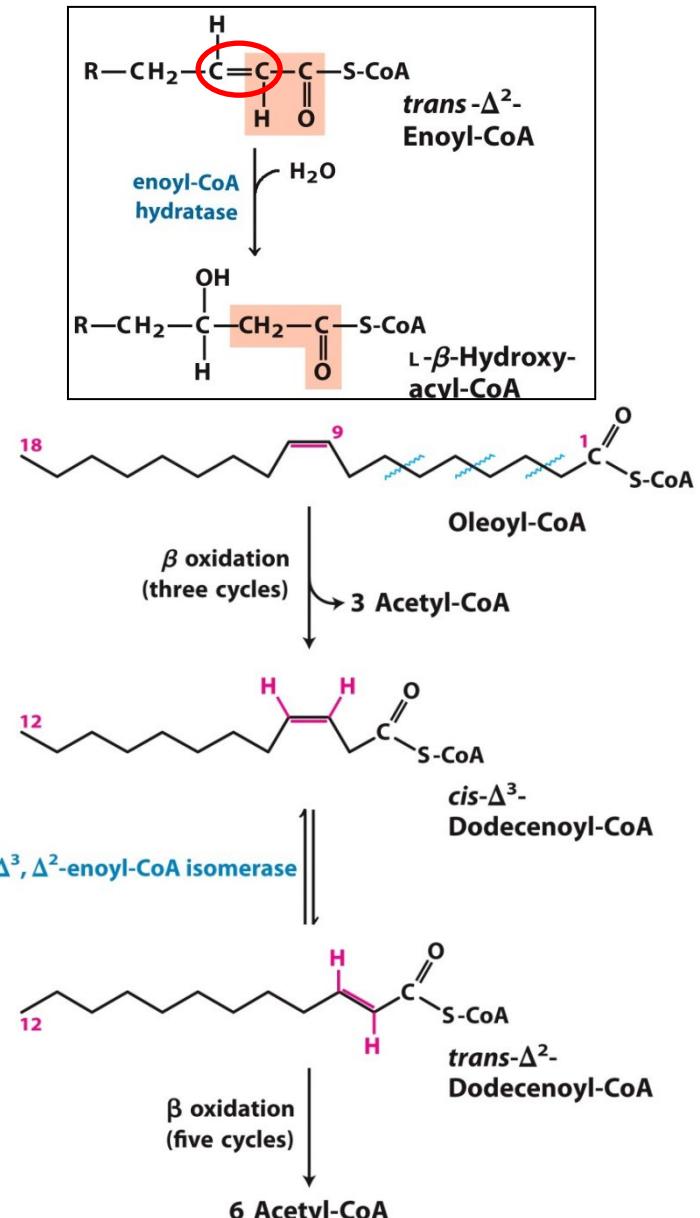
Propionyl-CoA will be converted through multiple-step reactions to **succinyl-CoA**; these reactions requires **vitamin B12**

Citric acid cycle

# Oxidation of unsaturated fatty acids

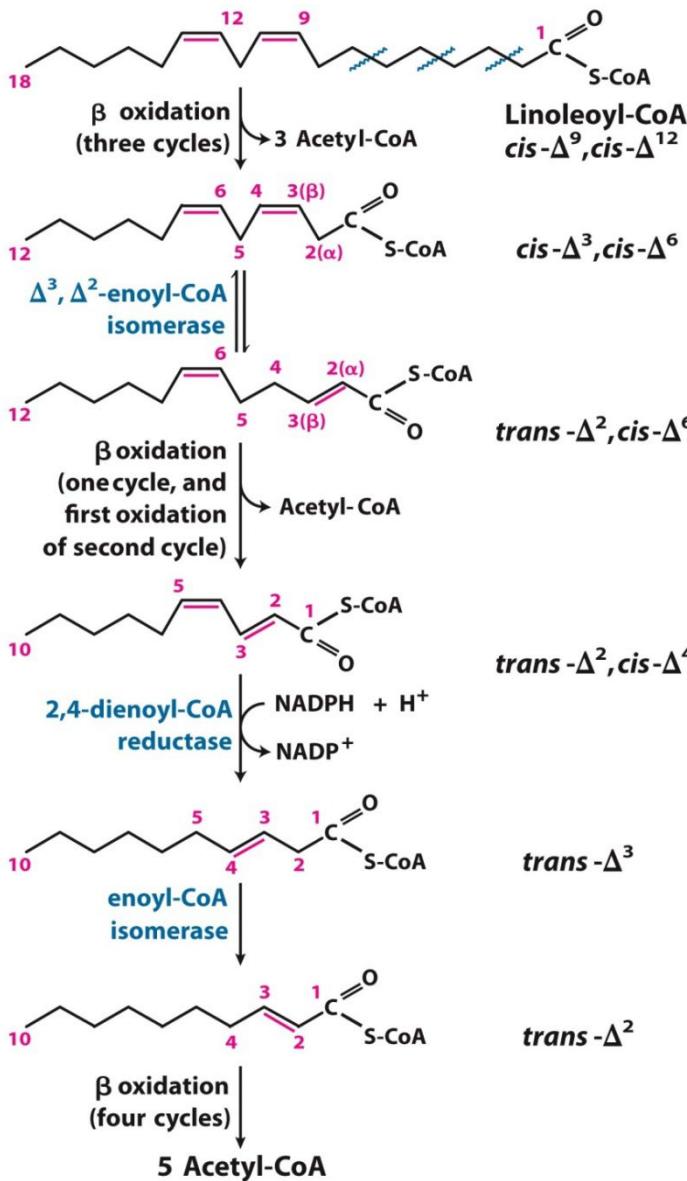
- Most of the fatty acids in the triacylglycerols and phospholipids in plants and animals are **unsaturated**
- The substrate of enoyl-CoA hydratase (second step of  $\beta$ -oxidation) has double bond between  $\alpha$  (2) and  $\beta$  (3) carbon
- In fatty acids, double bonds are in **cis-configuration** which enoyl-CoA hydratase cannot work on
- **Isomerase** is involved in changing the **cis-configuration** to **trans-configuration**

$\beta$ -oxidation – the second step



# Oxidation of poly-unsaturated fatty acids

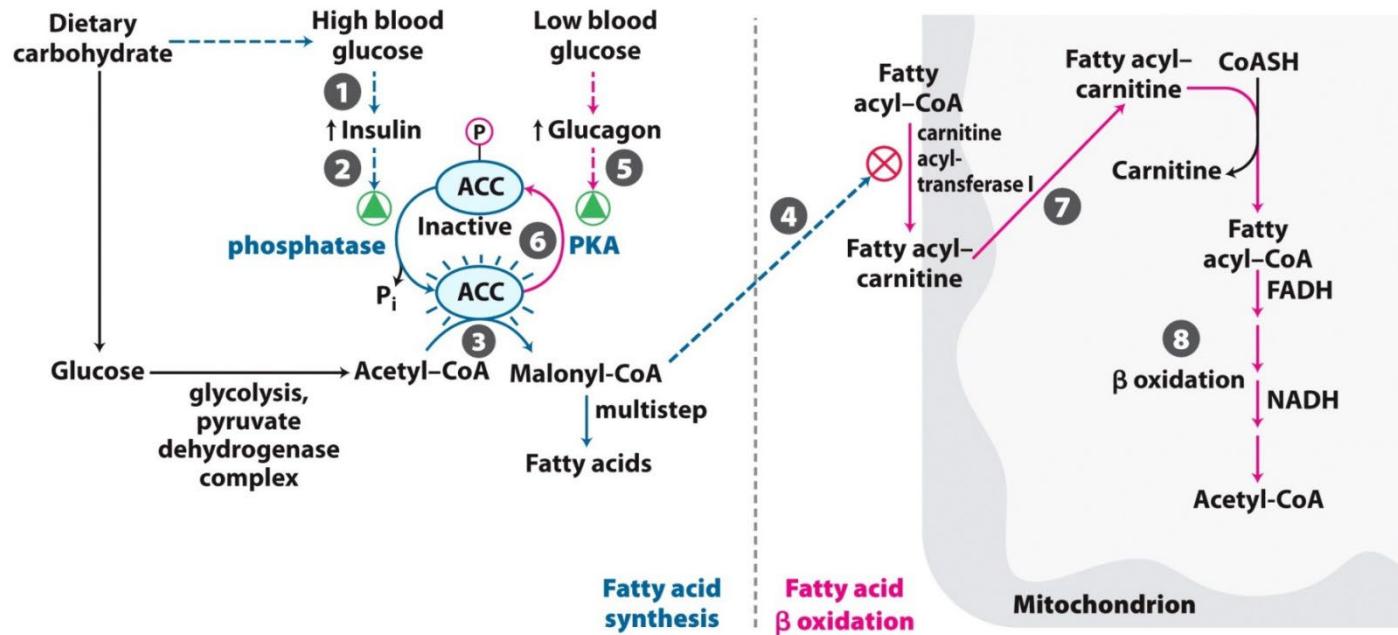
Eg. linoleate (18-carbon), two cis-double bonds at carbon atoms 9 and 12



- Reductase is required for the oxidation of polyunsaturated fatty acids
- So two additional enzymes, **reductase** and **isomerase** are involved in the complete degradation of unsaturated fatty acids

# Regulation of fatty acid oxidation

Availability/energy needs: glucose VS fatty acid

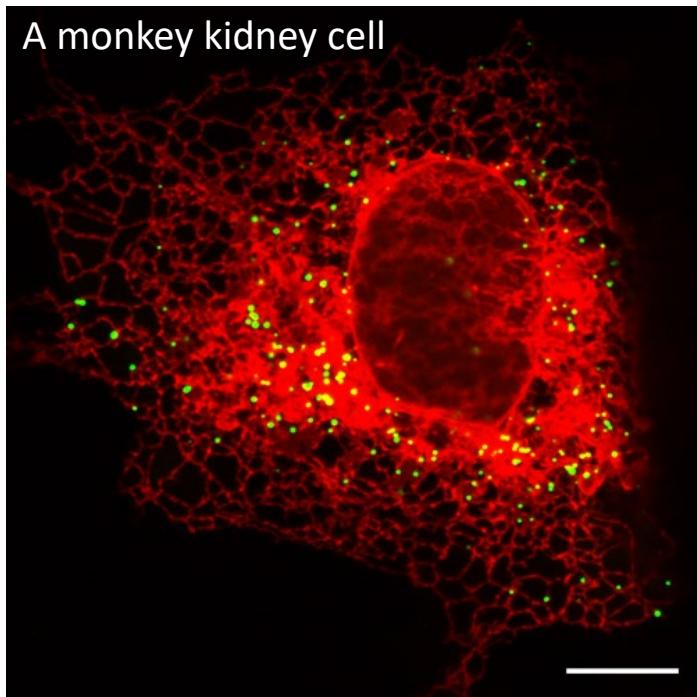


1 & 2: High glucose level upregulates insulin; activation of acetyl-CoA carboxylase (ACC) which promotes fatty acid synthesis (conversion of acetyl-CoA to malonyl-CoA)

4. Malonyl-CoA is the first intermediate in the biosynthesis of long chain fatty acids from acetyl-CoA, and its concentration controls carnitine acyltransferase I activity: high level malonyl-CoA (caused by high glucose level) inhibits fatty acid degradation & favors fatty acid synthesis

# Fatty acid degradation in peroxisome

- Peroxisomes are membrane-enclosed organelles of animal and plants. The functions include degradation of fatty acids (especially the very long and branched) and the reduction of reactive oxygen species - hydrogen peroxide



**Red:** ER (Endoplasmic Reticulum) marker

**Green:** peroxisomal marker

- It is the major location for fatty acid degradation in yeast and plant

# Summary (I) (fatty acid oxidation)

- Fatty acids, in the form of fatty acyl-CoA, are transported into mitochondria by carnitine shuttle
- Fatty acids undergo oxidative removal of successive two-carbon units in the form of acetyl-CoA ( $\beta$ -oxidation)
- Even-number fatty acids are converted to acetyl-CoA
- Odd-number fatty acids are converted to acetyl-CoA and succinyl-CoA. The last step of the degradation involves the coenzyme vitamin B<sub>12</sub>.
- $\beta$ -oxidation and the degradation of acetyl-CoA in citric acid cycle can both generate energy in the form of ATP from the mitochondrial electron transport chain
- Oxidation of unsaturated fatty acids involves two more enzymes: reductase and isomerase (change the double bond from cis- to trans-configuration)

# The ketone body pathway

# The cause of ketone body formation

- The fate of acetyl-CoA to enter the citric acid cycle depends on the availability of **oxaloacetate** for the formation of citrate
- The concentration of oxaloacetate is lowered if carbohydrate is unavailable or improperly utilized
- The lack of oxaloacetate causes **acetyl-CoA** being diverted to the keto genesis pathway

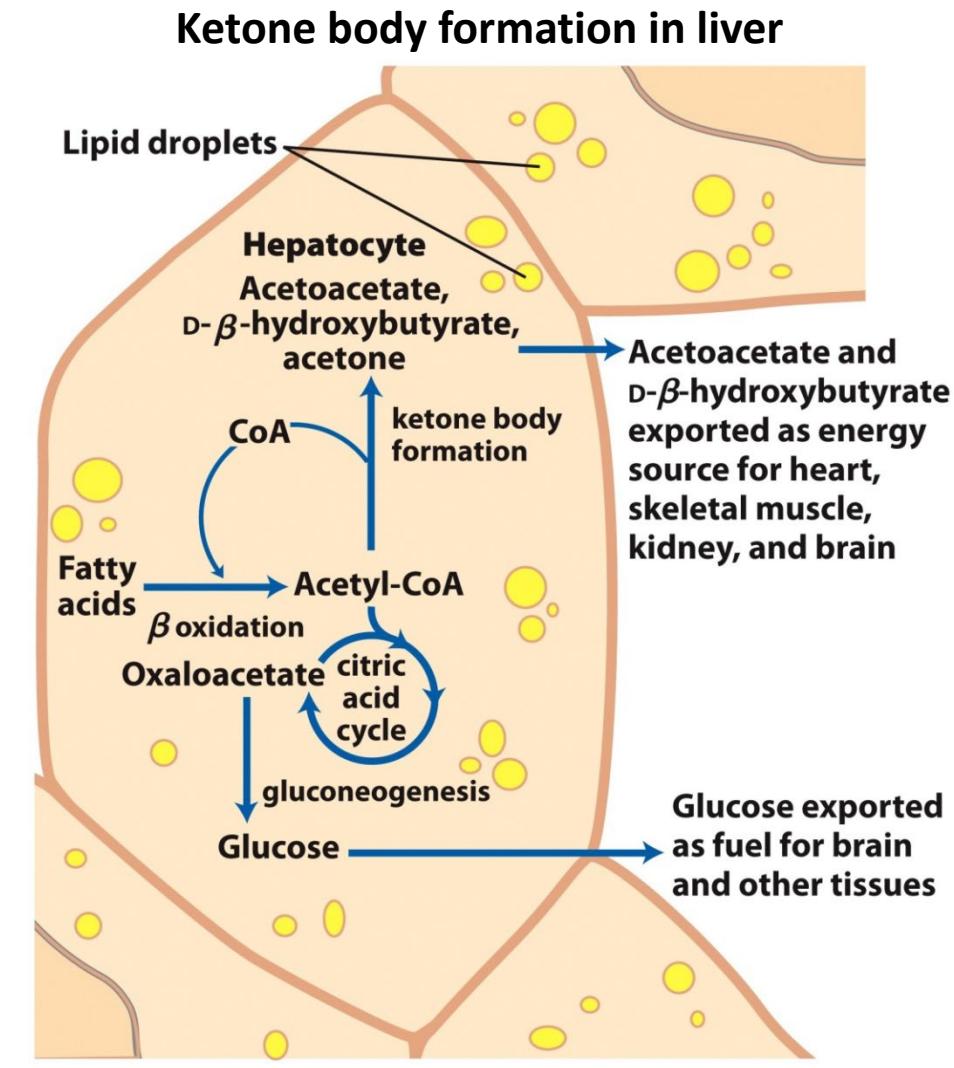
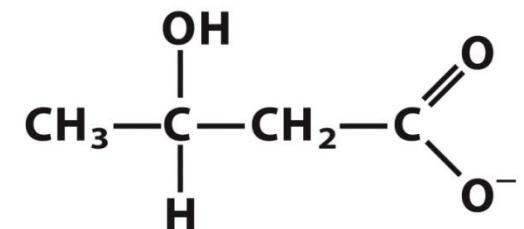
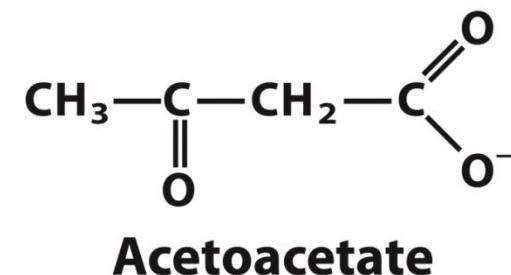
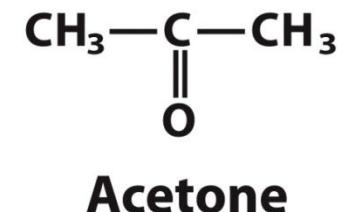
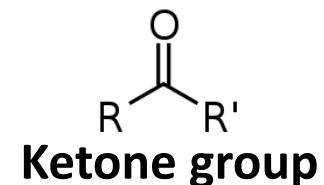


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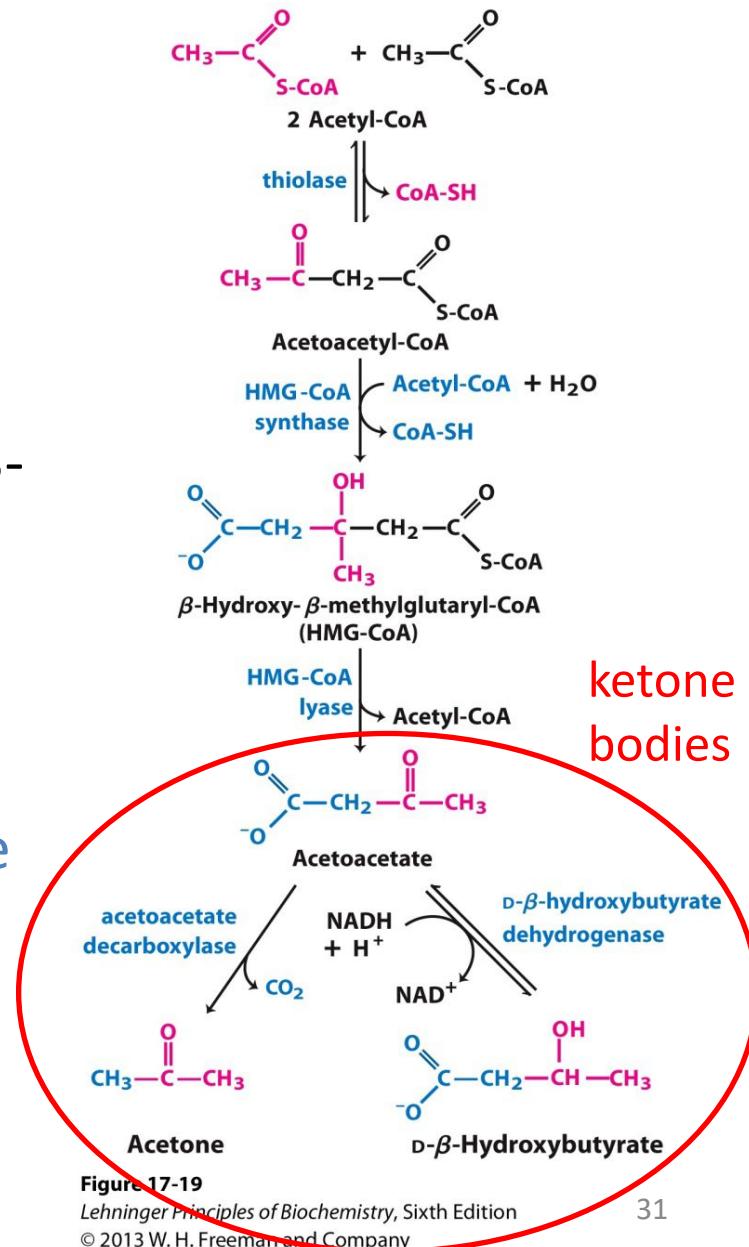
# What are ketone bodies?

- Ketone bodies, three molecules containing ketone group, are produced from acetyl-CoA without any other carbon molecule in liver
- Acetone once formed is exhaled in the breath
- Acetoacetate and  $\beta$ -hydroxybutyrate are transported to other tissues by blood. They are then converted back to acetyl-CoA and oxidized in the citric acid cycle to provide energy for tissues like muscles and kidney
- The brain prefers to use glucose as fuel but can be adapted to utilize acetoacetate or  $\beta$ -hydroxybutyrate under starvation



# Pathway of ketone body formation

- The first step is the condensation of two acetyl-CoA to form acetoacetyl-CoA catalyzed by thiolase
- Another acetyl-CoA condenses with acetoacetyl-CoA to form 3-hydroxy-3-methyl-glutaryl CoA (HMG-CoA) by HMG-CoA synthase
- HMG-CoA lyase removes acetyl-CoA from HMG-CoA to form acetoacetate
- Acetoacetate can either be decarboxylated to acetone or be converted to  $\beta$ -hydroxybutyrate



# Acetoacetate and $\beta$ -hydroxybutyrate are fuels for tissues outside liver

- Once exported outside liver,  $\beta$ -hydroxybutyrate is oxidized to acetoacetate
- Acetoacetate can be converted to acetoacetyl-CoA by the transfer of a CoA group from succinyl-CoA (an intermediate in the citric acid cycle)
- Acetoacetyl-CoA can be converted to two acetyl-CoA

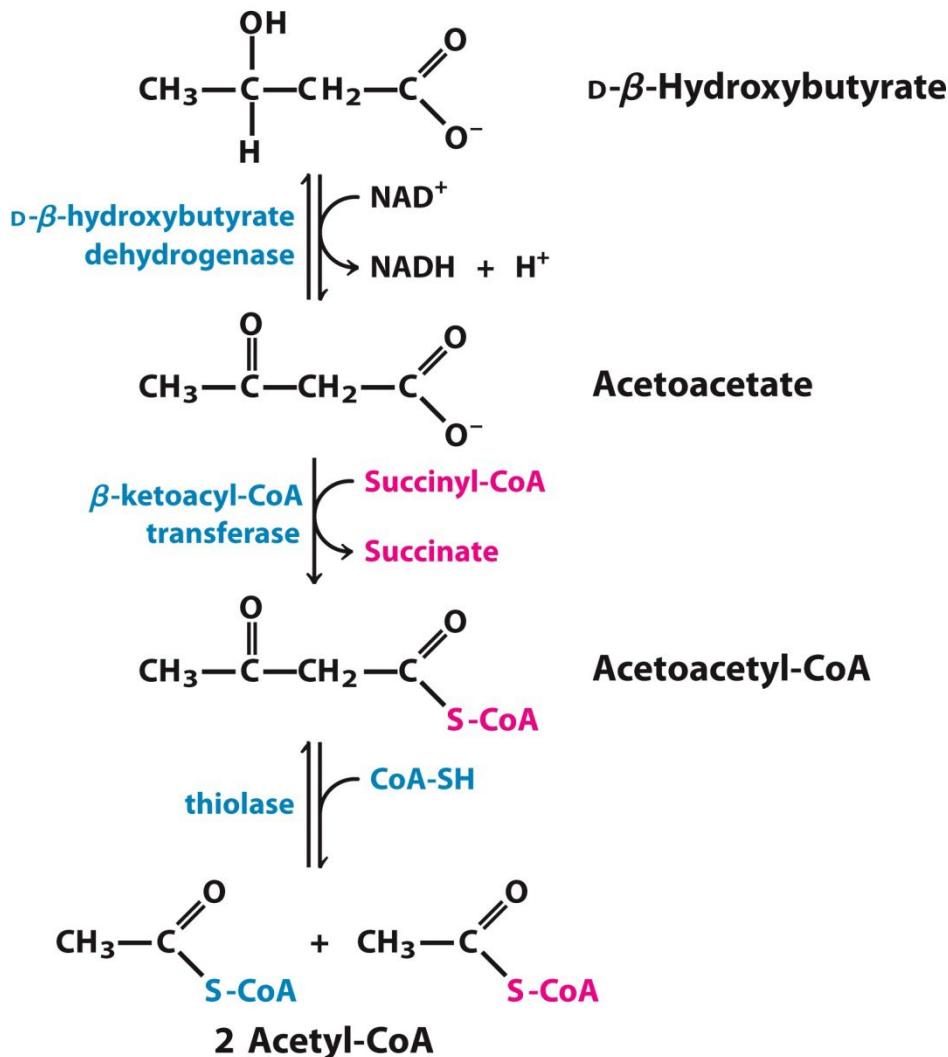


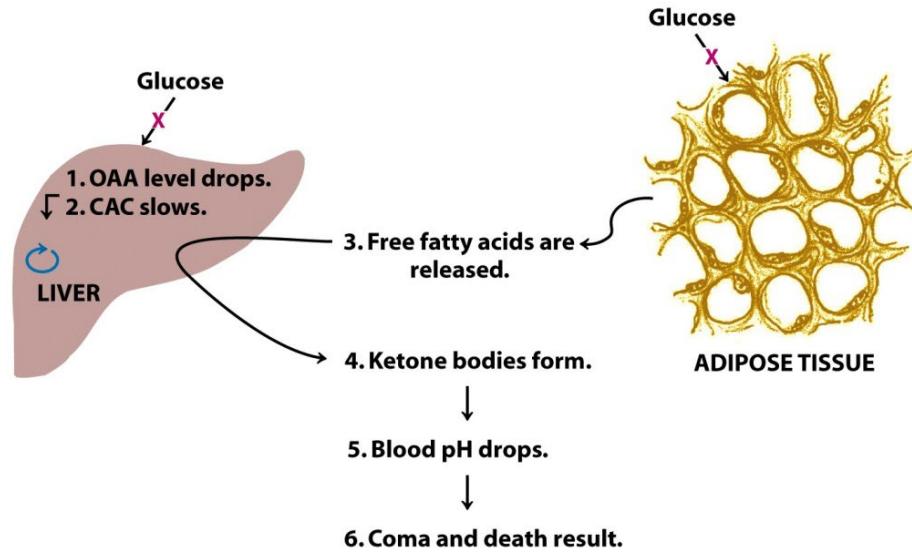
Figure 17-20

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# Diabetes and ketone bodies

- Diabetes mellitus is a chronic metabolic disease in which there are **high blood glucose levels** over a prolonged period
- Two major types:
  - In **Type I** or insulin-dependent diabetes mellitus (IDDM), **little or no insulin is produced**
  - In **Type II** or non-insulin-dependent diabetes mellitus (NIDDM), there is **reduced insulin secretion and the body does not respond to insulin**
- As of 2014, an estimated 387 million people have diabetes worldwide, with type 2 diabetes making up about 90% of the cases. In Hong Kong about **1 in 10 people** has this disease

- During starvation or in diabetes patient, deficiency in insulin signaling causes defects in uptake of blood glucose - low glucose levels inside cells



- The lack of cellular glucose causes low level of oxaloacetate
- Acetyl-CoA can not enter the citric acid cycle and instead are used to generate ketone bodies (overproduction of ketone bodies)

- Acetone is produced in large quantity and it is toxic
- Both acetoacetate and  $\beta$ -hydroxybutyrate are acidic; lower blood pH (acidosis) and urinary excretion of ketone bodies (ketosis)

## Summary (II) (ketone body pathway)

- The lack of oxaloacetate, an intermediate in citric acid pathway, causes acetyl-CoA being diverted to generate ketone bodies in liver
- Ketone bodies are comprised of acetone, acetoacetate and  $\beta$ -hydroxybutyrate
- Acetone is exhaled. Acetoacetate and  $\beta$ -hydroxybutyrate are transported out of liver and can be converted back to acetyl-CoA (thus energy) in tissues
- In diabetes patient, ketone bodies are overproduced due to low level of cellular oxaloacetate causing both acidosis (low blood pH) and ketosis (high level of ketone bodies in blood and urine)

# The pentose phosphate pathway

# Glucose utilization pathways

- Energy storage:  
Glycogen, starch,  
sucrose.
- Functional polymer:  
Polysaccharides (eg.  
glycoproteins, lipid  
polysaccharides).
- Energy generation:  
Glycolysis or pentose  
phosphate pathway.

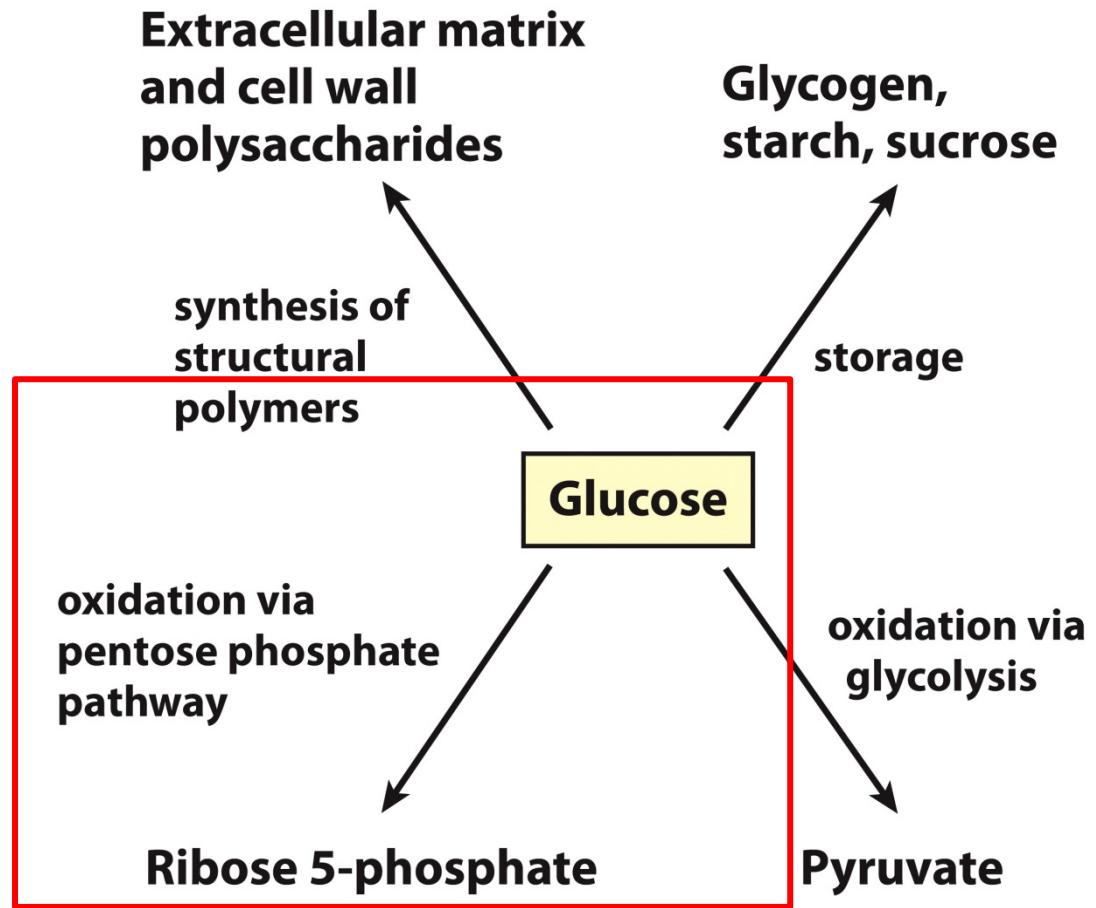


Figure 14-1  
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# Pentose phosphate pathway

- **What?**

- The process serves to generate NADPH and 5-carbon sugar (pentose ribose 5-phosphate) from glucose 6-phosphate
- Also called phosphogluconate pathway or the hexose monophosphate pathway

- **Why?**

- Produce precursors (ribose 5-phosphate) for DNA, RNA and coenzymes such as ATP, NADH, FADH<sub>2</sub> and coenzyme A
- Provide electron donor NADPH for reductive biosynthesis or countering damaging effects of oxygen radicals.

- **Where?**

1. Rapid dividing cells: cells in bone marrow (stem cells and progenitor cells of blood cell lineage), skin, intestinal mucosa and tumor cells
2. Tissues that carry out extensive synthesis of fatty acid (liver, adipose, lactating mammary gland) cholesterol and steroid hormones synthesis (liver, adrenal glands, gonads)
3. Cells that are exposed to oxygen (such as?)

# Overview of the pentose phosphate pathway

- The **oxidative phase**:
  - Oxidation of glucose-6-phosphate to ribose 5-phosphate
  - NADPH is generated
- The **nonoxidative phase**:
  - Interconversion of three-, four-, five-, six-, and seven-carbon sugars
  - Recycle excess five-carbon sugars back to glucose 6-phosphate
- All these reactions take place in the **cytosol**

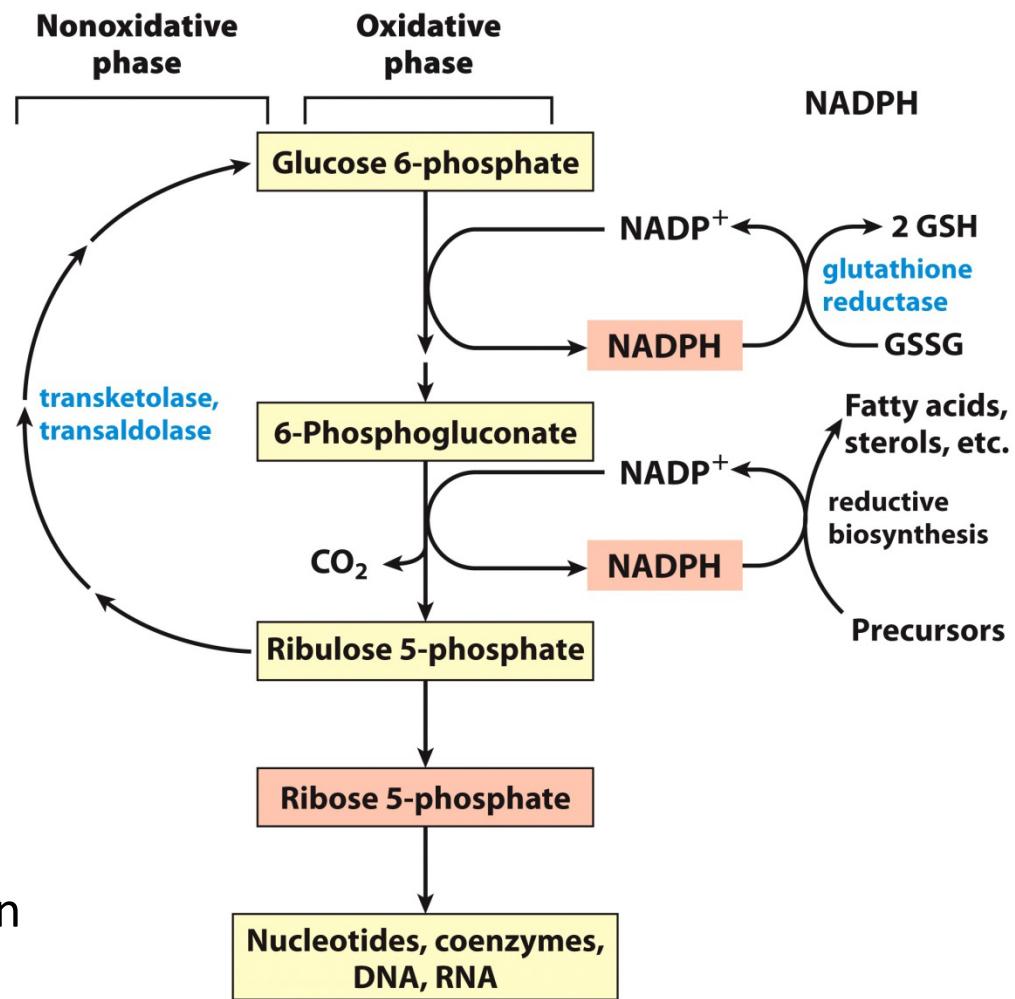
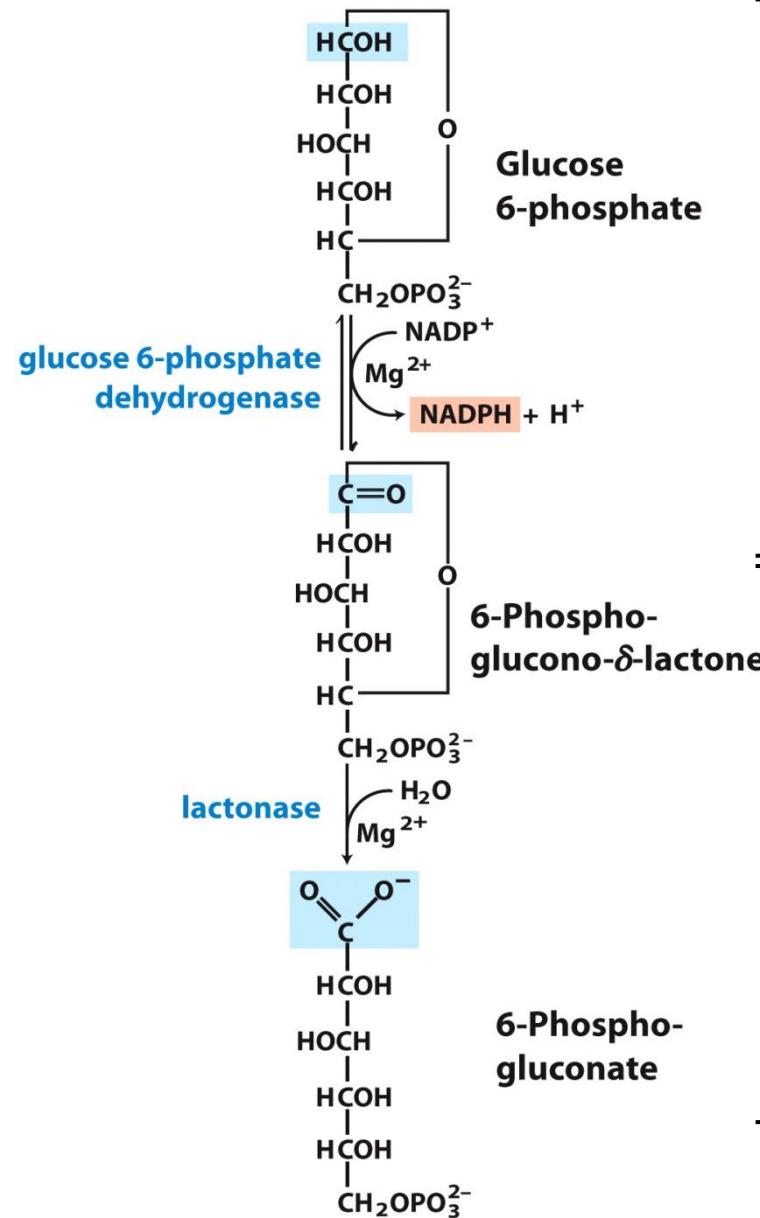


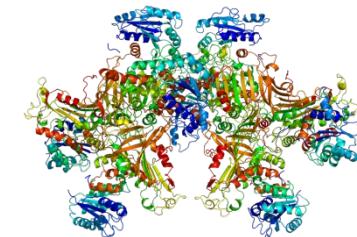
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# The oxidative phase



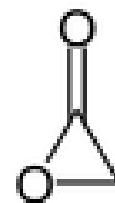
## Step 1: Glucose-6-phosphate dehydrogenase

- Generates the first NADPH
- The product is **6-Phosphoglucono- $\delta$ -lactone**. Lactone is a cyclic ester, which is formed from the condensation between a carboxylic acid (-COOH) and an alcohol (-OH).

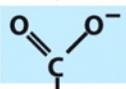


## Step 2: Lactonase

- Lactone is hydrolyzed by lactonase to produce a linear molecule: **6-Phosphogluconate**.

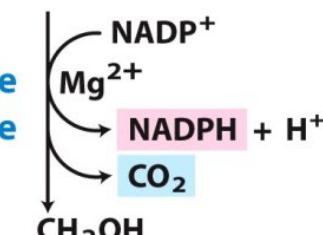


$\alpha$ -acetolactone



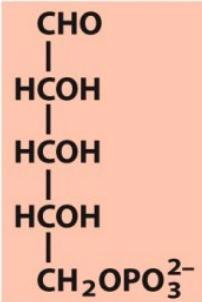
**6-Phospho-gluconate**

**6-phosphogluconate dehydrogenase**



**D-Ribulose 5-phosphate**

**phosphopentose isomerase**



**D-Ribose 5-phosphate**

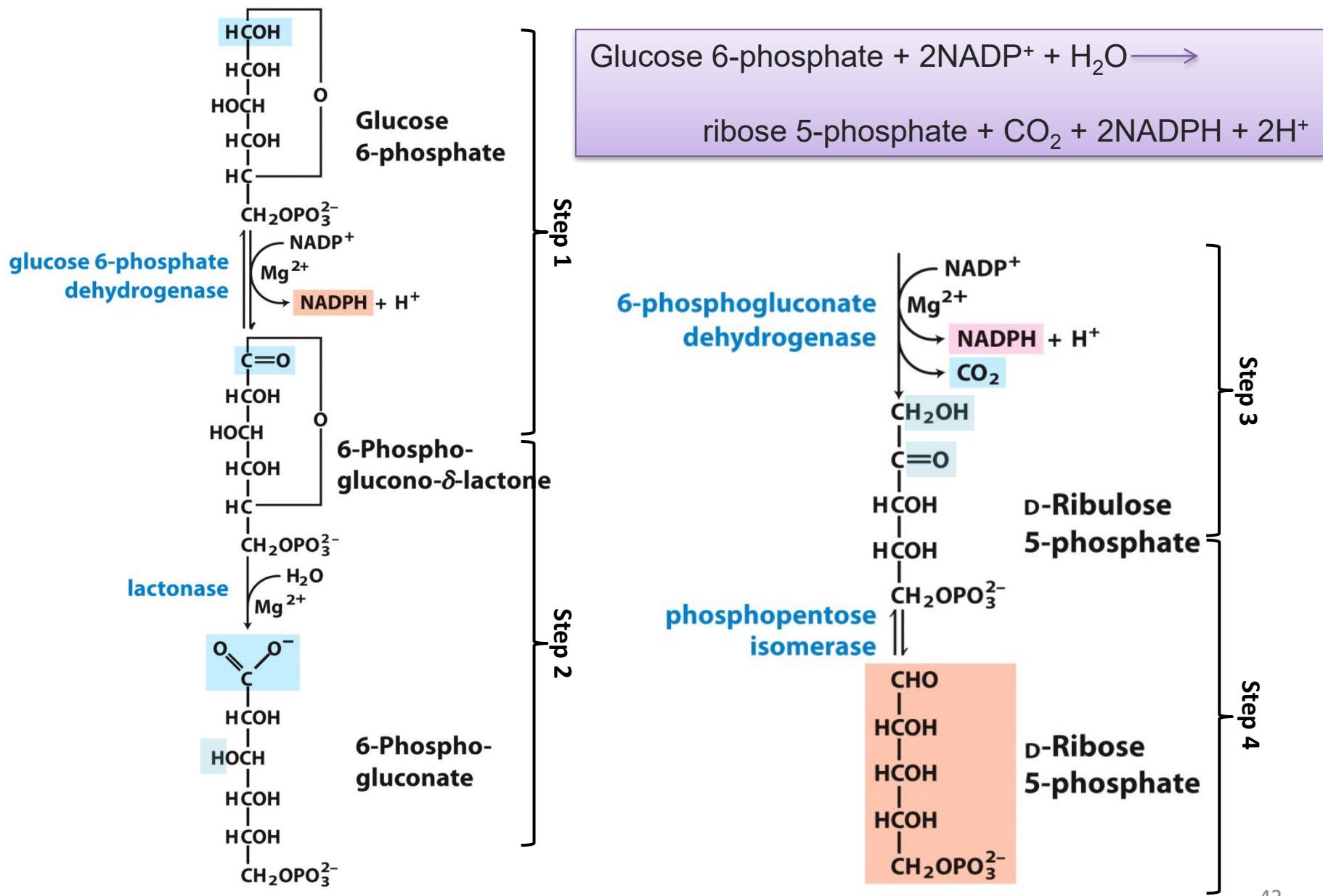
### Step 3: 6-Phosphogluconate dehydrogenase

- Generates the second NADPH and one  $\text{CO}_2$
- Produces ketopentose ribulose 5-phosphate

### Step 4: Phosphopentose isomerase

- Produces pentose ribose 5-phosphate

# The oxidative phase complete reaction

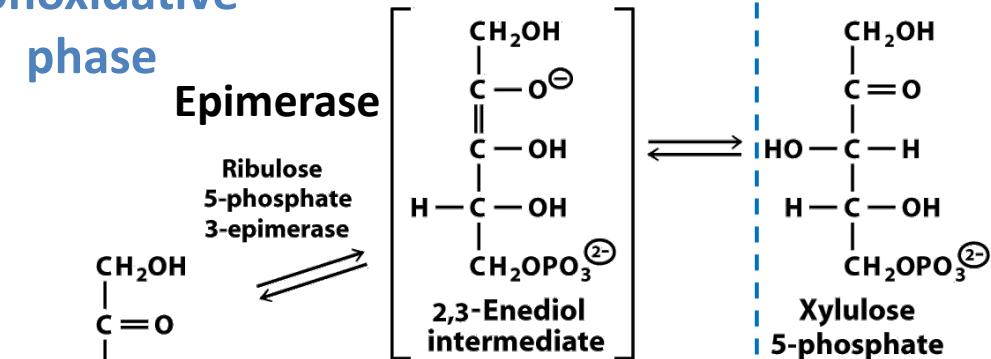


# The different fates of ribulose 5-phosphate

Nonoxidative phase

**Epimerase**

Ribulose 5-phosphate 3-epimerase



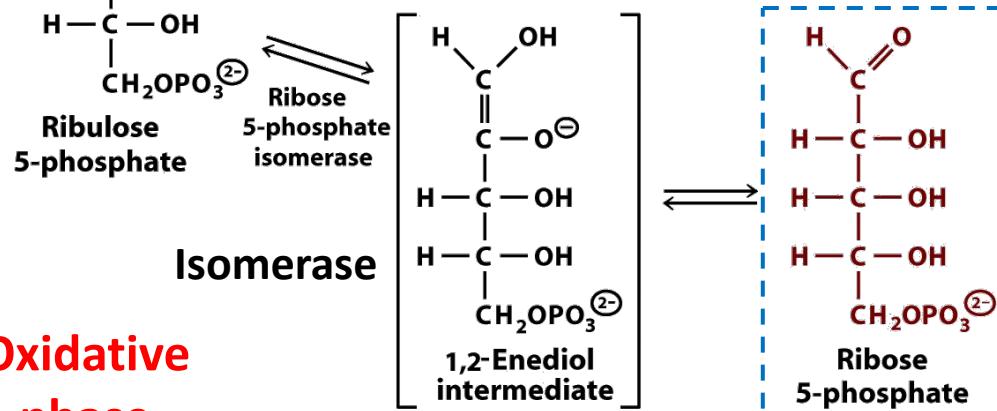
In some cases, more NADPH than ribose 5-phosphate is needed:

- most of pentose phosphates are converted back to glucose 6-phosphate

Oxidative phase

**Isomerase**

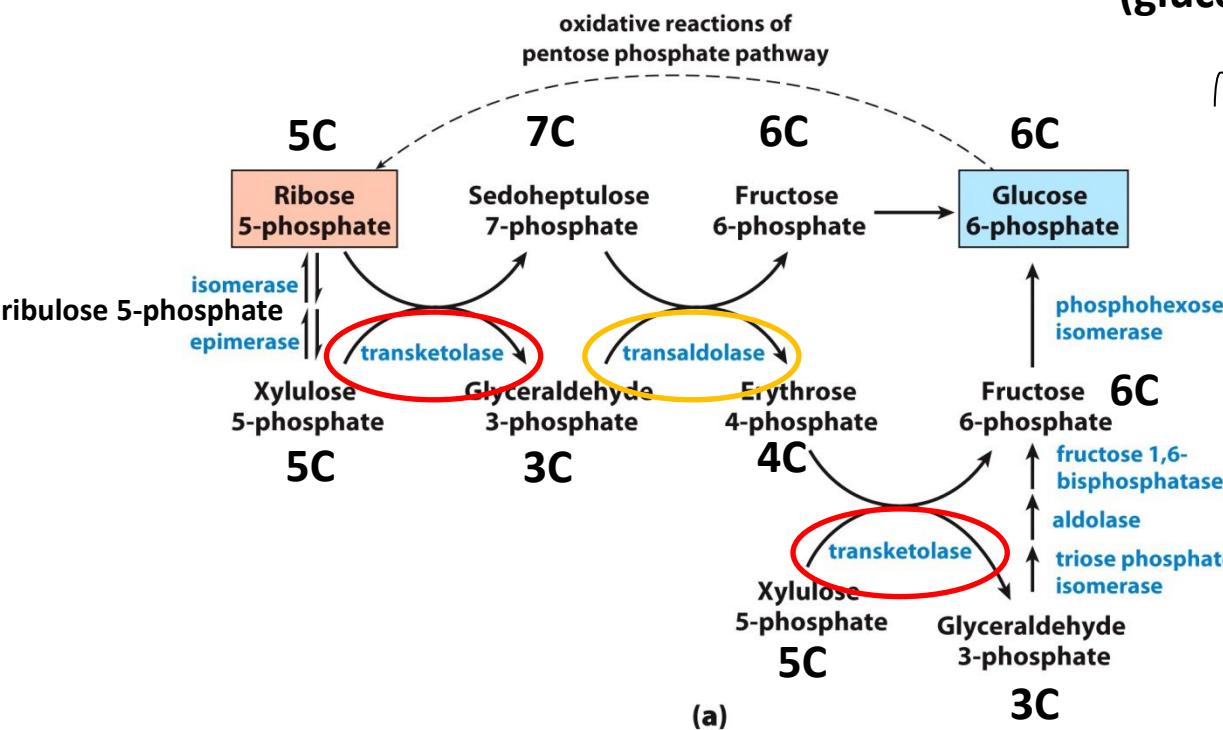
Ribose 5-phosphate isomerase



If both NADPH and nucleotides are required (e.g. in rapidly dividing cells):

- all ribulose 5-phosphate is isomerized to ribose 5-phosphate and the pathway is completed at this stage

# The nonoxidative reactions pathway



Schematic for generating 5 hexoses (glucose 6-phosphate) from 6 pentoses

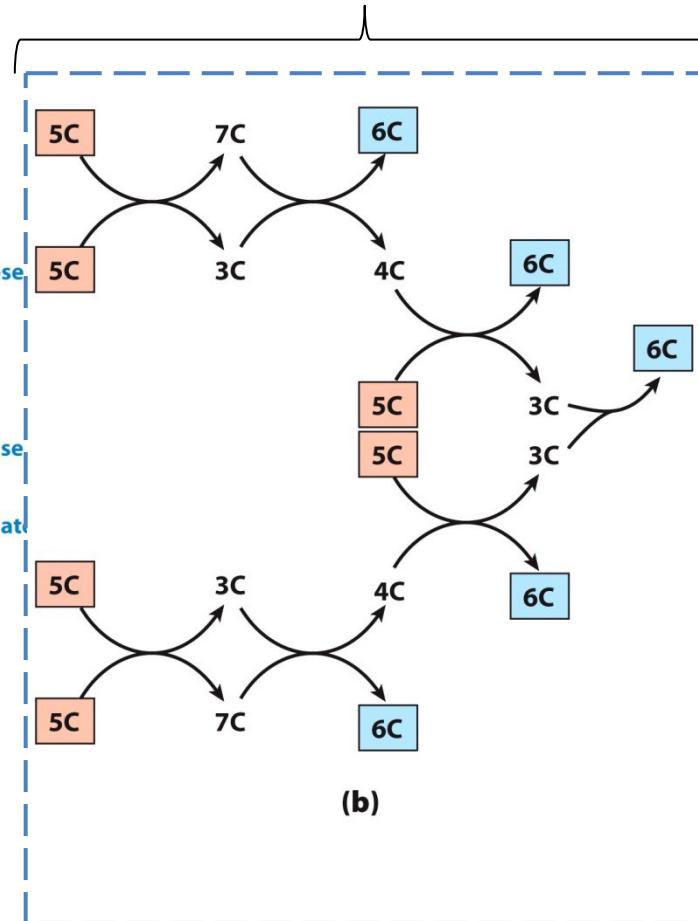


Figure 14-23

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The nonoxidative reactions involve the enzymes **Transketolase** and **Transaldolase**

# The nonoxidative phase complete reaction

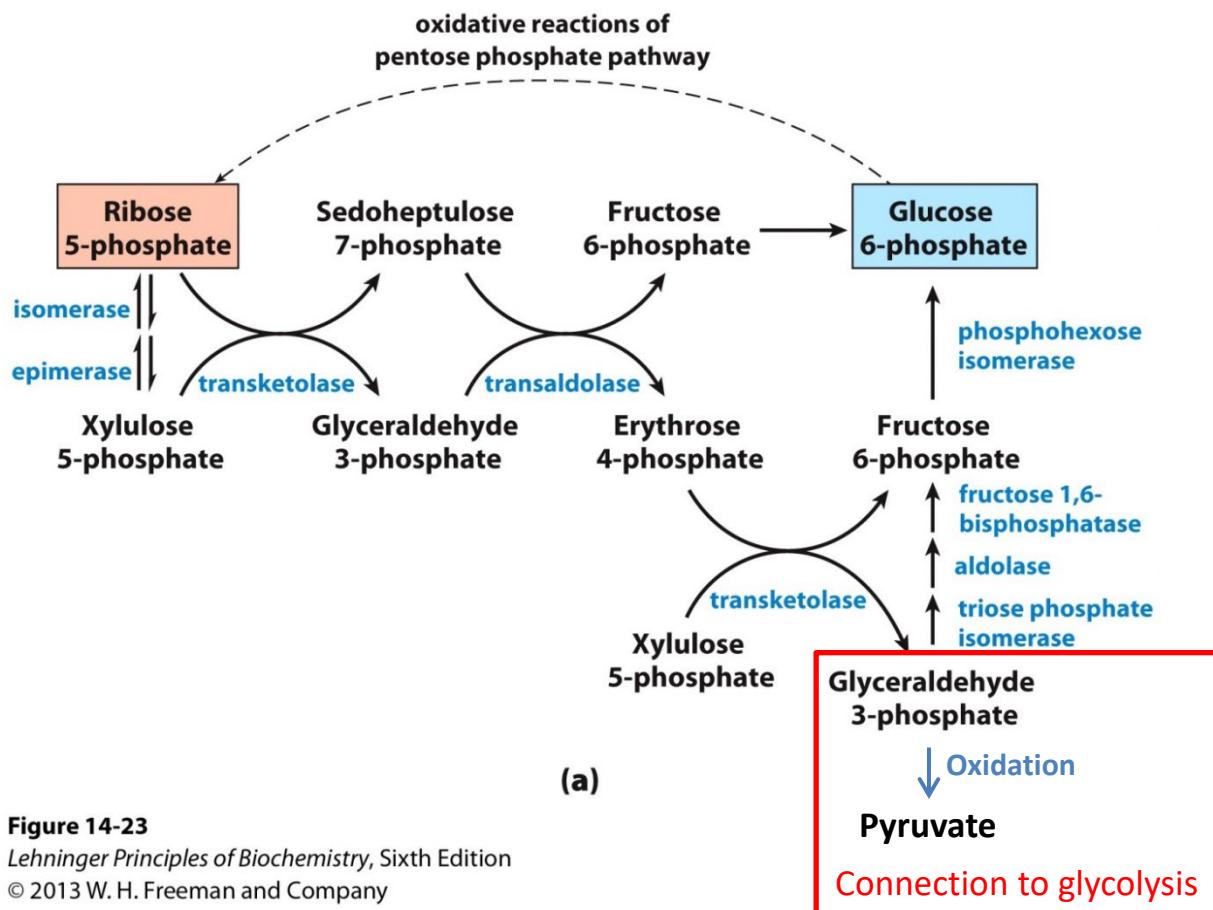
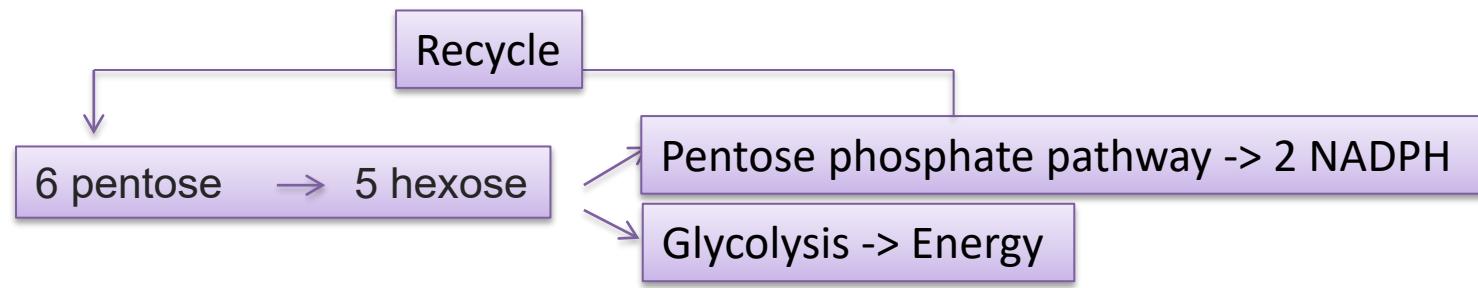


Figure 14-23

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# Regulation of pentose phosphate pathway

- The entering of pentose phosphate pathway is controlled by the level of NADP<sup>+</sup>.

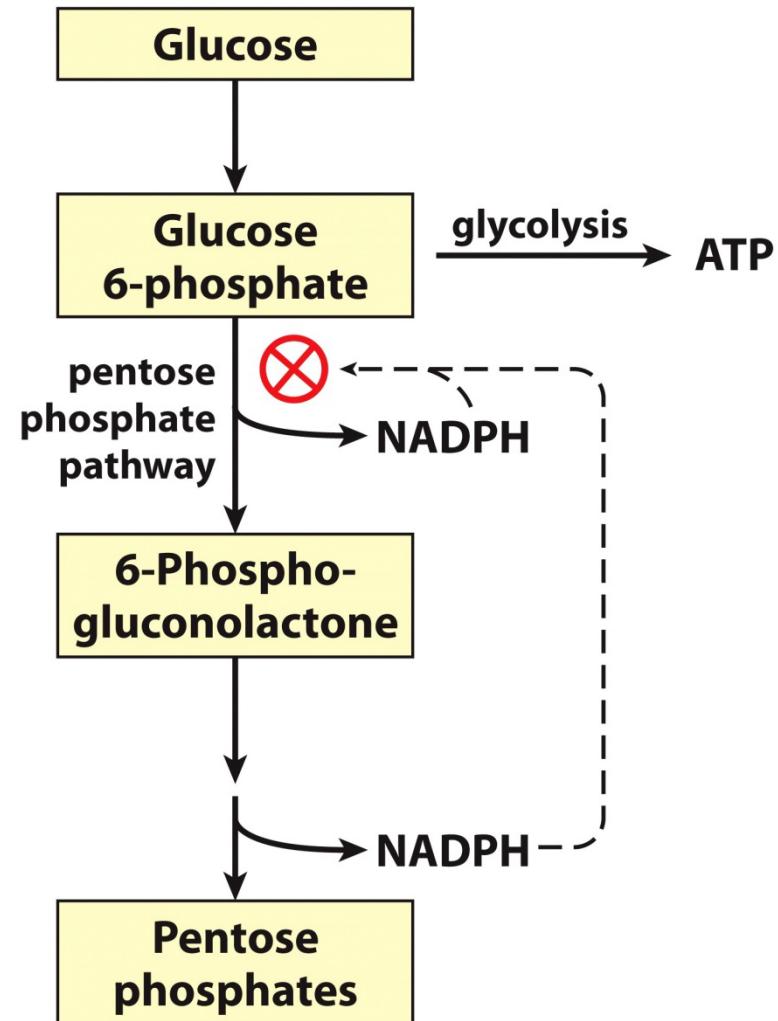
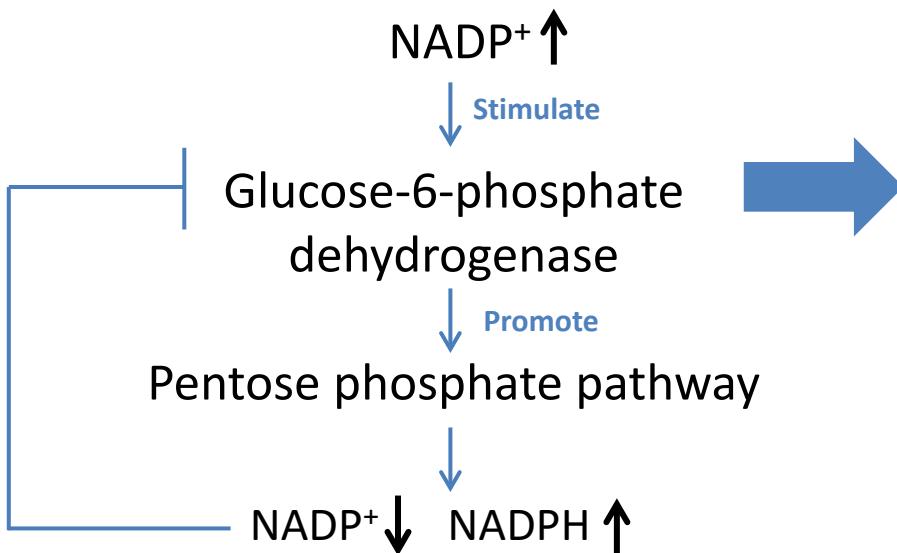
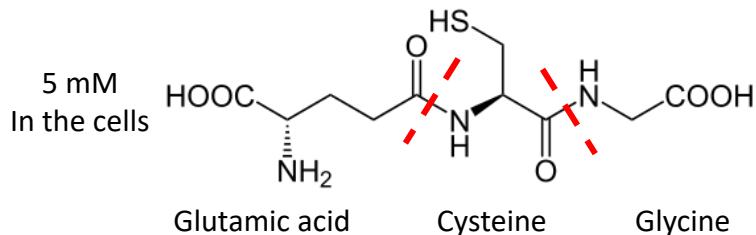


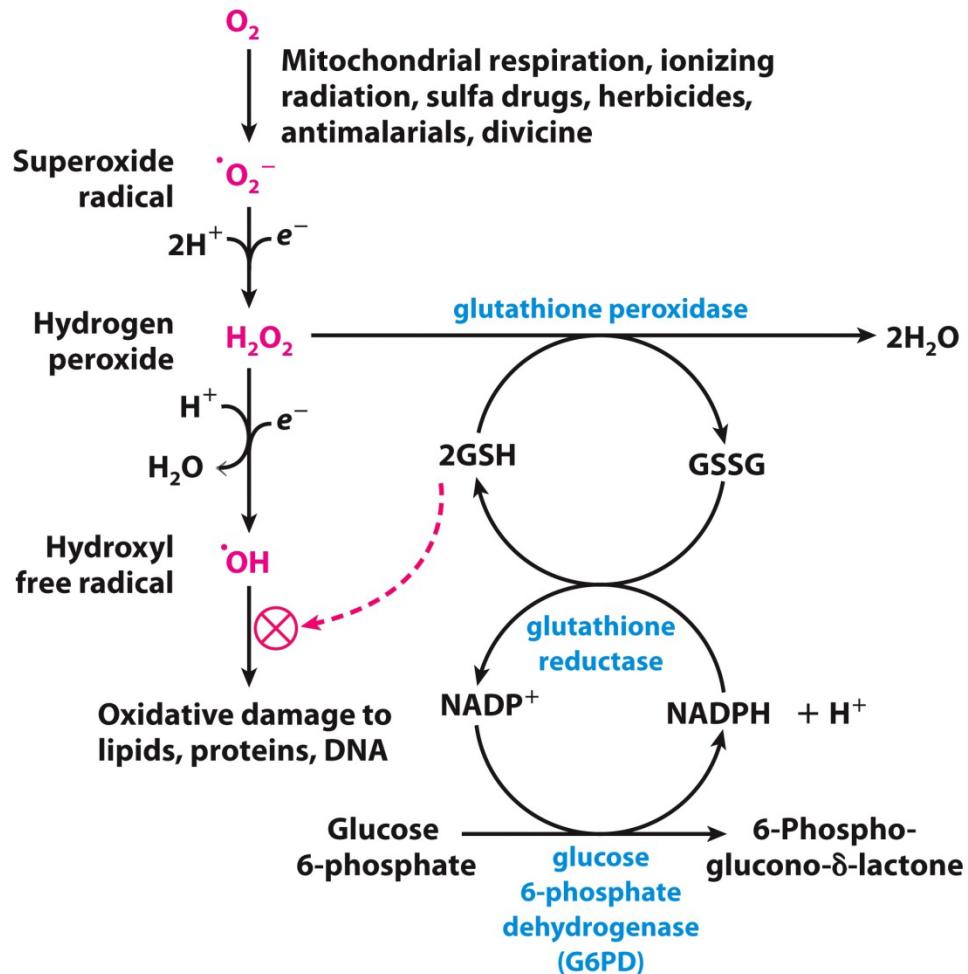
Figure 14-28  
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# NADPH and glutathione in oxidative stress

- Glutathione (GSH) is a short peptide composing of cysteine, glutamate and glycine

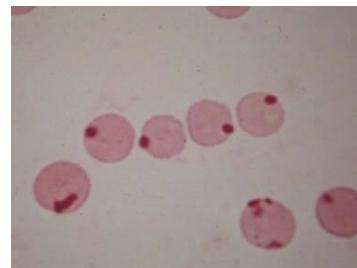
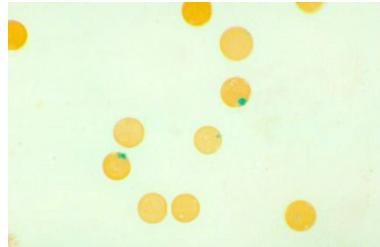


- Detoxification of hydrogen peroxide ( $H_2O_2$ ), which produces hydroxyl free radical ( $\cdot OH$ ), needs glutathione, glutathione peroxidase, glutathione reductase and NADPH



Box 14-4 figure 1  
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# Hereditary anemia and Heinz body

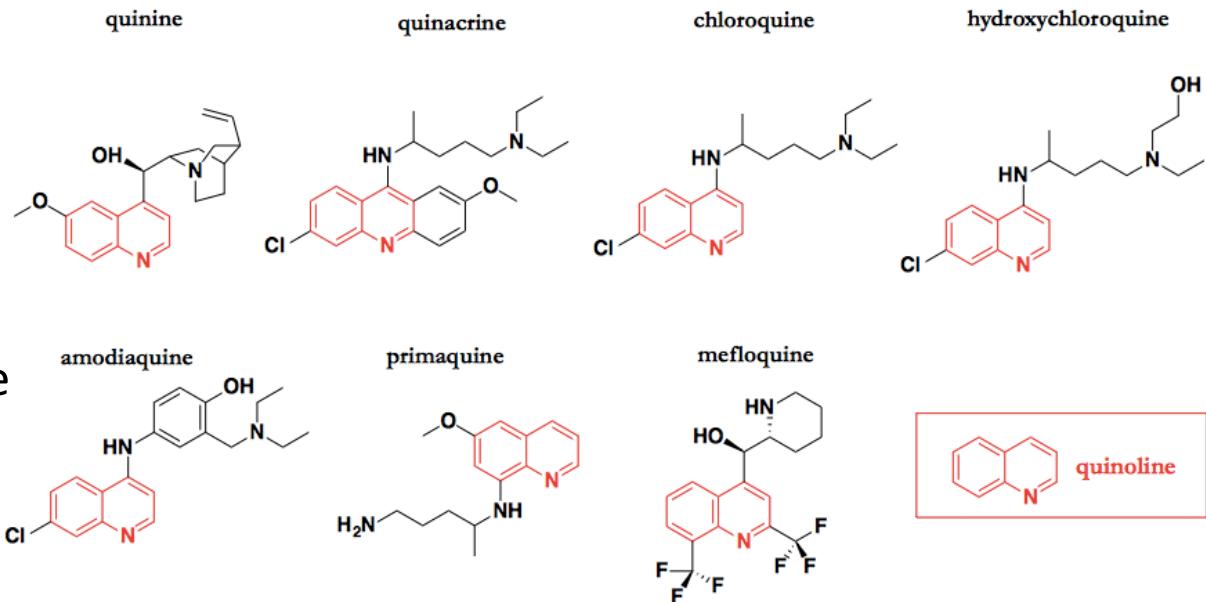


- G6PD deficiency person mostly asymptomatic but is more prone to oxidative damage induced by stresses and eating fava beans
- Red blood cells use lots of  $O_2$  for the generation of ATPs; need NADPH to protect them from oxidative stresses
- Without G6PD and NADPH, free radicals attract the globins which become denatured and forms a little ball (the “Heinz body”)
- The gene for G6PD is on the X chromosome (thus males are much more likely to have full expression of the disease); the disease is more common in African Americans

# Oxidative stress and malaria

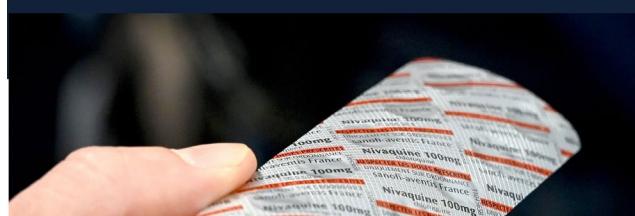
- G6PD deficiency population have an advantage of resistance to parasite malaria infection because of higher level of oxidative stress in erythrocytes

- Quinoline derivatives stem from quinine (top left), a natural product isolated from the bark of the Andean cinchona tree



## CDC warns against using form of chloroquine that killed man, sickened his wife

An Arizona couple, both in their 60s, became deadly ill after they ingested fish food that contained chloroquine phosphate.



- Pharmaceutical **chloroquine** phosphate and hydroxychloroquine sulfate are approved by the FDA to treat malaria
- Treatment for COVID-19 not proven

# Summary (III) (Pentose phosphate pathway)

- The pentose phosphate pathway
  - generates two NADPH and a pentose ribose 5-phosphate from glucose 6-phosphate
  - contains an oxidative phase and a nonoxidative phase
- Importance:
  - for rapid dividing cells which use ribose 5-phosphate for the synthesis of DNA, RNA and coenzymes
  - for tissues that need NADPH for reductive biosynthesis or countering damaging effects of oxygen radicals
- Nonoxidative phase recycles ribose 5-phosphate (produces 5 hexoses from 6 pentoses)
- NADPH is required for the antioxidant function of glutathione
  - G6PD deficiency population is less resistant to oxidative damage but more resistant to malaria