Chapter 15 Lecture Notes: Metabolism

Educational Goals

1. Define the terms **metabolism**, **metabolic pathway**, **catabolism**, and **anabolism**.
2. Understand how **ATP** is formed from **ADP** and inorganic phosphate (**P_i**), and vice versa.
3. Understand how **Coenzyme-A** is used to *transfer* **acyl groups**.
4. Understand the roles of the **NAD^+/NADH** and **$FAD/FADH_2$** coenzymes in the *transfer of electrons*. Identify the **oxidized** and **reduced form** of each of these pairs.
5. Understand the differences between **linear**, **circular**, and **spiral** *metabolic pathways* and give an example of each.
6. Name the products formed during the **digestion** of *polysaccharides*, *triglycerides*, and *proteins*, and know the part(s) of the digestive track where each occurs.
7. Identify the initial reactant and final products of **glycolysis**, and understand how this pathway is controlled.
8. Understand and compare **glycolysis** and **gluconeogenesis** pathways.
9. Know the *fate of pyruvate* under **aerobic** and **anaerobic** conditions.
10. Define the terms ***hyperglycemic*** *and* ***hypoglycemic***.
11. Understand how the body controls **blood glucose concentration** by the release of **insulin** or **glucagon** into the bloodstream.
12. Understand and compare **glycogenesis** and **glycogenolysis**. Understand how these processes are involved in maintaining normal blood glucose concentration.
13. Understand and compare **type I**, **type II**, and **gestational diabetes**.
14. Identify the initial reactant and final products of the **citric acid cycle**; understand how this pathway is controlled.
15. Understand how the *oxidation of coenzymes* during **oxidative phosphorylation** is used to produce **ATP**.
16. Compare the **malate-aspartate shuttle** and the **glycerol 3-phosphate shuttle** and understand their significance in affecting the amount of **ATP** that can be produced from glucose.
17. Predict how many **ATP** are formed when **acetyl-CoA** undergoes ***stages*** **3** and **4** of catabolism.
18. Describe the catabolism of **triglycerides**, the **β-oxidation spiral**, and how *β-oxidation* differs from **fatty acid anabolism** (biosynthesis).
19. Given the structure of a **fatty acid**, predict how many **ATP** are formed when it undergoes the ***β-oxidation spiral***.
20. Understand and compare **lipolysis** and **fatty acid synthesis**.
21. Explain the biological origins of **ketosis** and **ketoacidosis**.
22. Understand how **transamination** and **oxidative deamination** are involved in the **catabolism of amino acids**.
23. Given the structure of an **amino acid** and **α-ketoglutarate**, predict the products of a **transamination reaction**.
24. Explain how ***quaternary ammonium groups*** ($-NH_3^+$) are removed from amino acids ***and*** eliminated from the body.

An Overview of Metabolism

_______________ is defined as *the entire set of life-sustaining chemical reactions that occur in organisms*.

- These reactions number in the thousands and include reactions such as those responsible for getting energy from food, processing and removal of waste, building up muscles, growth, photosynthesis in plants, cell division, and reproduction.

The entire set of metabolic reactions is organized into smaller sets of sequential reactions called **metabolic** __________________.

The species produced in the various reactions of a metabolic pathway are sometimes referred to as __________________.

Many of the reactions in metabolic pathways require enzymes; therefore organisms can control (accelerate or suppress) metabolic pathways, according to their current needs, by *upregulating*, *downregulating*, *inhibiting*, or *activating* one or more of the enzymes involved in the pathway.

Metabolic pathways can usually be classified as **catabolic** (catabolism) or **anabolic** (anabolism).

- ***Catabolic pathways*** involve the ________________ of larger organic compounds into smaller compounds.
- ***Anabolic pathways*** involve ________________ ______ of larger organic compounds from smaller ones.

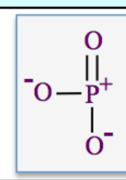
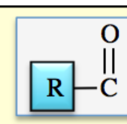
In this chapter, you will learn about the pathways that are involved in the metabolism of carbohydrates, proteins, and fats.

- An ultimate goal of these reactions is to convert the chemical potential energy contained in food into chemical potential energy in the form of ___________.

The Coenzymes Involved in Metabolism

A *coenzyme* is a species that must bind to an enzyme in order for the enzyme to function.

- In most cases, a coenzyme is actually one of the *substrates* (reactants) in the catalyzed reaction.
- The reason that certain *substrates* are ***also*** referred to as *coenzymes* is that these *substrates* are ***common substrates in many different enzymatic reactions*** in which they ***donate electrons, atoms, or groups of atoms*** to other substrates, ***or accept electrons***, ***atoms or groups of atoms*** from other substrates.
- The five group-transfer coenzymes that are central to the metabolism of food, along with the species each transfers are listed in the table on the right.

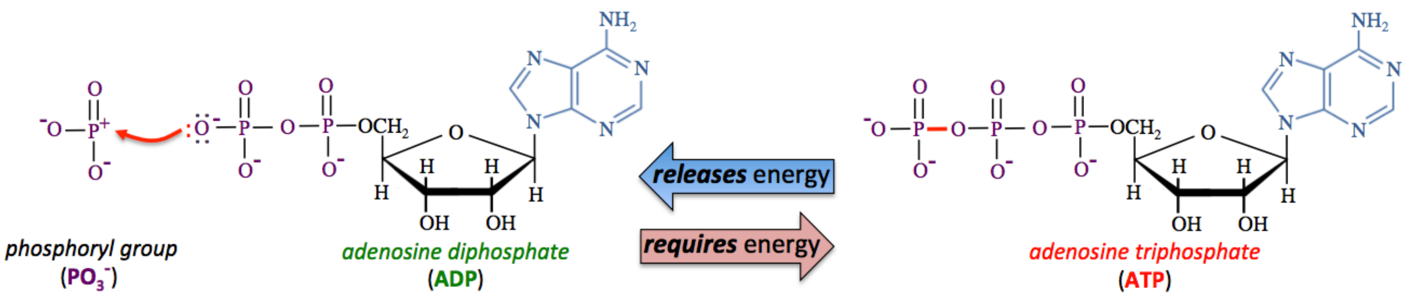
Coenzyme	Species that is Transferred
ADP/ATP	phosphoryl group = 
NAD^+/NADH	hydride ion ($H:^-$) **or** electrons
FAD/$FADH_2$	hydride ion ($H:^-$) **or** electrons
coenzyme A	acyl group = 
coenzyme Q	hydride ion ($H:^-$) **or** electrons

Phosphoryl Group-Transfer Coenzymes: ATP and ADP

ATP and **ADP** are classified as **coenzymes** because they are involved in the *transfer* of _____________ **groups** (PO_3^-) ***in many different enzymatically catalyzed reactions***.

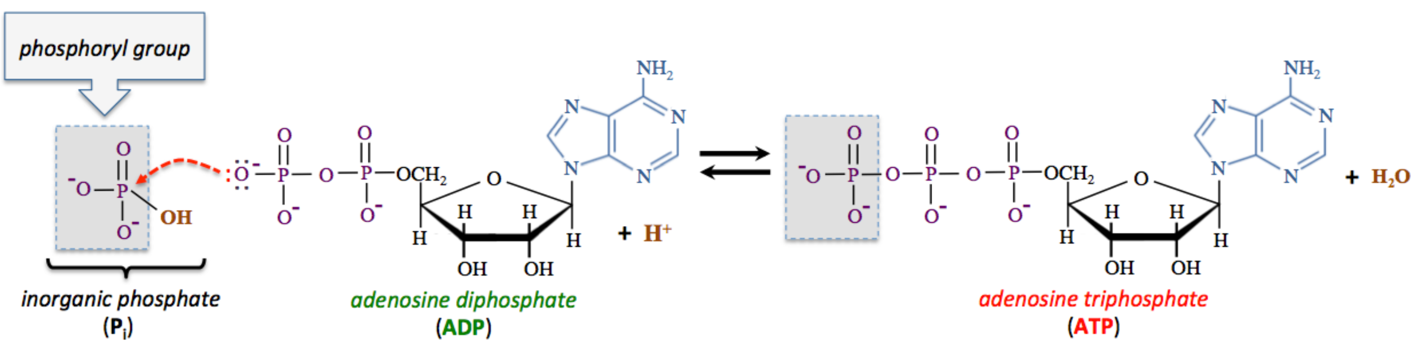
- When a compound gains/accepts a *phosphoryl group* in a reaction, we say that the compound became "**phosphorylated**."
- When a compound loses/donates a *phosphoryl group* in a reaction, we say that it was "**dephosphorylated**."

ATP and **ADP** are interconverted by the transfer of a *phosphoryl group*, as shown below.



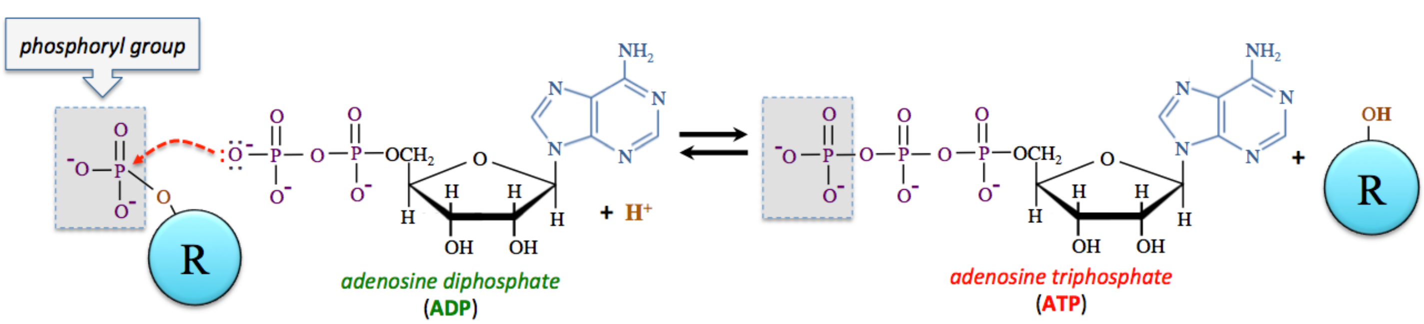
- Adding a *phosphoryl group* to **ADP** ____________ energy.
- Removing a *phosphoryl group* from **ATP** ____________ energy.

ATP is often formed by the reaction of **ADP** with *hydrogen phosphate* (HPO_4^{2-}) and an $\mathbf{H^+}$ ion, as shown below.



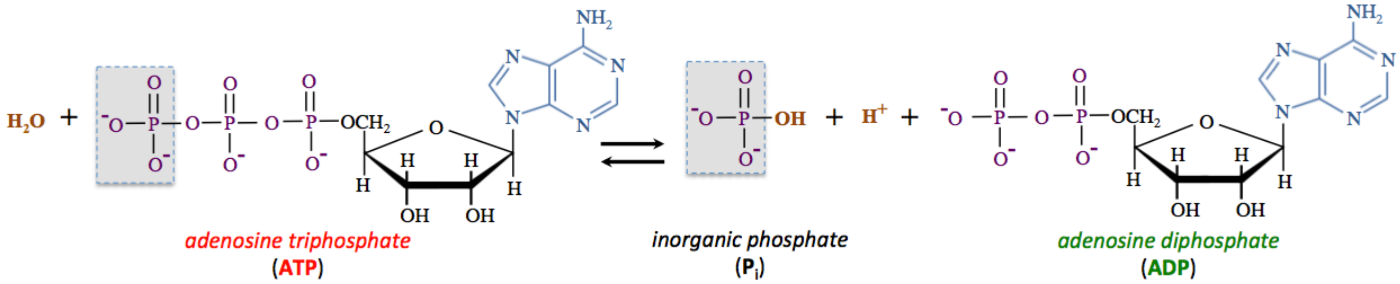
Biological literature refers to *hydrogen phosphate* as "______________ **phosphate"** (abbreviated as $\mathbf{P_i}$).

Another way that organisms convert **ADP** to **ATP** is by the reaction of **ADP** with an _______________ molecule *that contains a phosphoryl group*. In this case, a *phosphoryl group* is transferred ***from*** the organic molecule ***to*** **ADP,** as shown in the chemical equation below.



You will see hydrogen ions ($\mathbf{H^+}$) as reactants *in many of the reactions in this chapter*. Because these reactions occur in aqueous solutions, $\mathbf{H^+}$ is ***readily available*** from $\mathbf{H_2O}$, and can also come from $\mathbf{H_3O^+}$ or the *acid forms* of other species that are present.

Energy is ***released*** from **ATP** when it is converted to **ADP**. This energy is used by organisms to drive energy-requiring reactions or physical processes that would otherwise not occur spontaneously. *One* way that energy can be released from **ATP** is by reacting it with **H_2O** to ***form*** **ADP**, *inorganic phosphate*, and an **H^+** ion. Although this reaction is spontaneous (ΔG is negative), the reaction rate is quite slow, therefore organisms employ enzymes in order for the reaction to proceed at a useful rate. The chemical equation for this reaction is shown below.



ΔG = -*7300* Joules per mole of ATP

Note that **H^+** is *produced* in this reaction. You will see **H^+** ions as products *in many of the reactions in this chapter*. Keep in mind that the **H^+** ions that are produced in aqueous solutions do not remain solvated as *isolated ions*; they quickly react with water to form **H_3O^+**. Alternatively, **H^+** can react with **OH^-** or the *base form* of another species that is present.

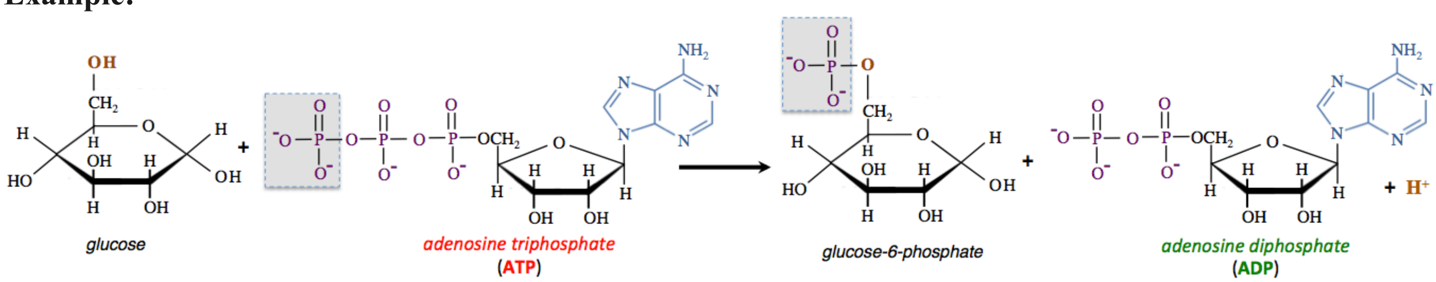
Another way that organisms extract energy from **ATP** is to "energize" organic compounds by transferring a phosphoryl group *directly* to the compound. In this reaction, **ATP** is ***dephosphorylated*** and an organic compound is ***phosphorylated***, as shown in the reaction below:

$$\textbf{ATP} + \text{organic compound} \rightleftarrows \textbf{ADP} + \text{phosphorylated organic compound} + \mathbf{H^+}$$

Chemical potential energy ***released*** by the conversion of **ATP** *to* **ADP** is *transferred to the phosphorylated organic product*.

- It is for this reason that we say "the organic compound is energized" in the reaction.

Example:

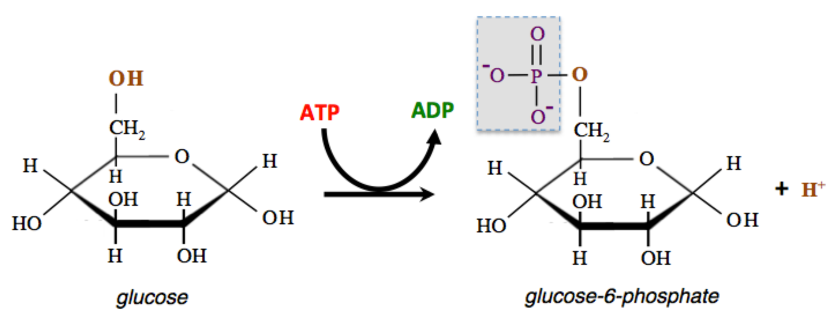


In this particular reaction, the reverse reaction occurs so slowly that it is negligible.

- In such cases, we refer to the reaction as an "_____________________ **reaction**."

When writing a chemical equation for an irreversible reaction, only a forward (left to right) arrow is used, as shown *above*.

Biochemical literature often uses an *alternative* chemical equation format. For example, the reaction shown above is often written as:



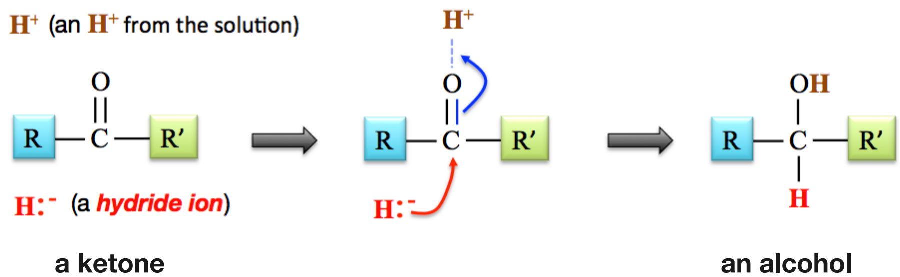
Electron-Transfer Coenzymes and Their Role as Oxidizing and Reducing Agents

Oxidation-reduction reactions, which involve the transfer of one or more electrons, are quite common in organisms.

Many of these reactions involve the transfer of an electron by way of the ***hydride ion*** (**H:**$^-$).

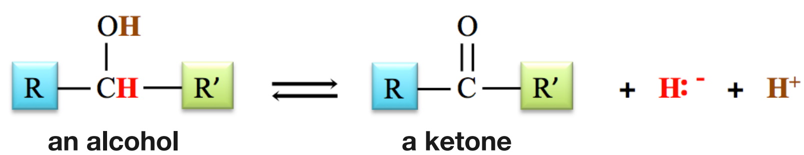
A ***reduction*** occurs when a ______________ ion forms a bond with an organic compound.

- The transfer of a hydride ion is a reduction because of hydride's "extra" electron.
  - For example, aldehydes or ketones are ***reduced*** when a ***hydride ion*** forms a bond with them.



An ___________ occurs when a *hydride ion* (**H:**$^-$) and an **H**$^+$ ion are *removed* from an organic compound.

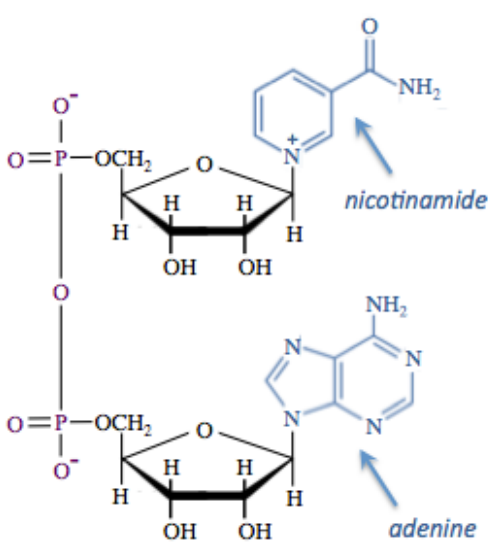
- For example, 2º alcohols can be ***oxidized*** to ketones, as shown in the chemical equation below.



  - This is considered an oxidation because the hydride ion carries away the "extra" electron.

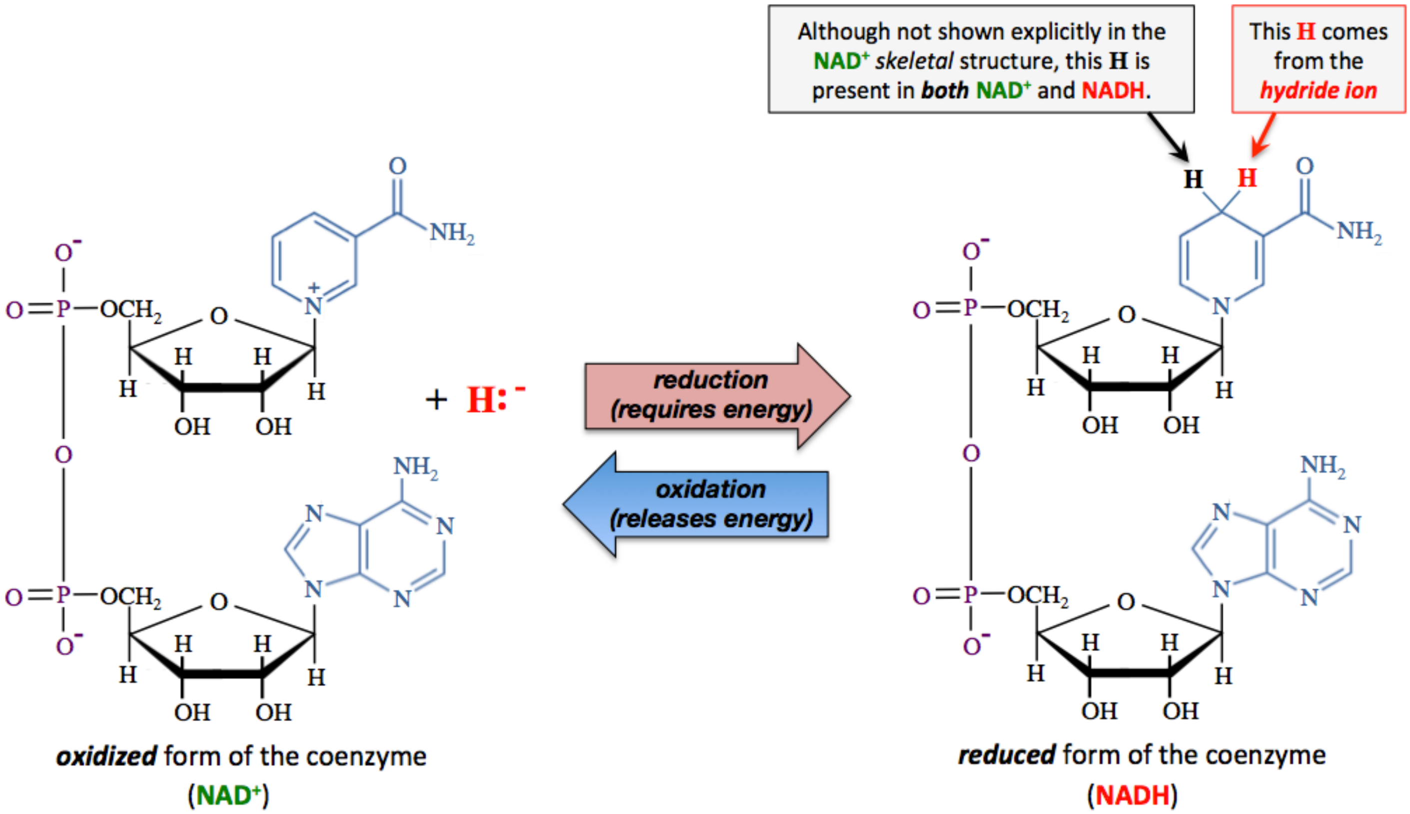
Nicotinamide adenine dinucleotide (**NAD**$^+$) and flavin adenine dinucleotide (**FAD**) are classified as **coenzymes** because they are common substrates, involved in the transfer of ________________, ***in many different enzymatically catalyzed reactions***.

Nicotinamide Adenine Dinucleotide (NAD$^+$**)**



nicotinamide adenine dinucleotide
(NAD$^+$)

The structural formula of **NAD**$^+$ is shown on the left. **NAD**$^+$ contains *two* nucleotide residues. One of the nucleotides has an ***adenine*** base, and the other contains a ***nicotinamide*** base.



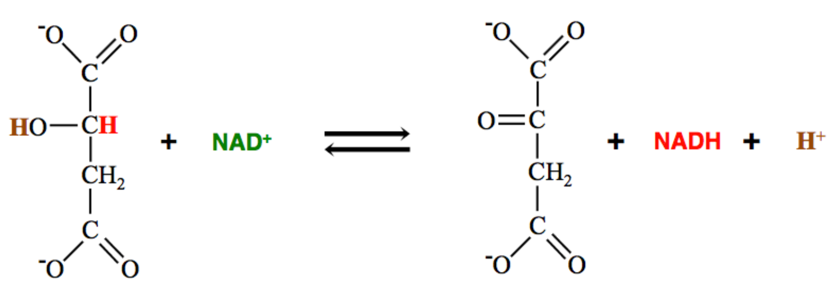
When **NAD**$^+$ *accepts* a hydride ion from another species, it is ***reduced*** to **NADH**.

- It is for this reason that **NADH** is referred to as a ***reduced form of the coenzyme*** or a "_______________ __________________."
- The reduction of **NAD**$^+$ ***requires*** energy.

When **NADH** *donates* a hydride ion (to another species) it is ***oxidized*** to **NAD**$^+$.

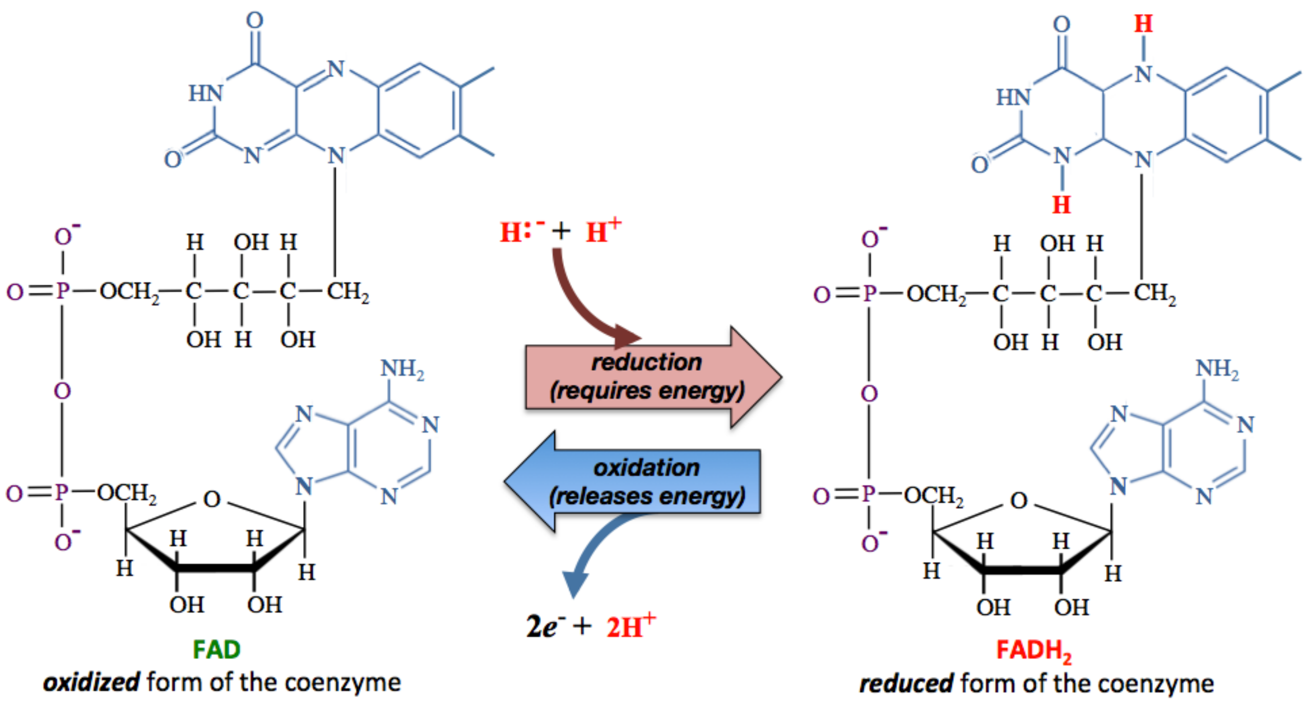
- **NAD**$^+$ is referred to as the ***oxidized form of the coenzyme*** or an "_____________ ______________."
- Oxidation of **NADH** ***releases*** energy.

Example: The oxidation of an organic compound using **NAD**$^+$ as the *oxidizing agent:*



- In this reaction, *malate* is oxidized and **NAD**$^+$ is reduced.

Flavin Adenine Dinucleotide (FAD)



When **FAD** *accepts* a hydride ion from another species (and an H^+ from solution), it is ***reduced*** to **$FADH_2$**.

- The reduction of **FAD** *requires* energy.

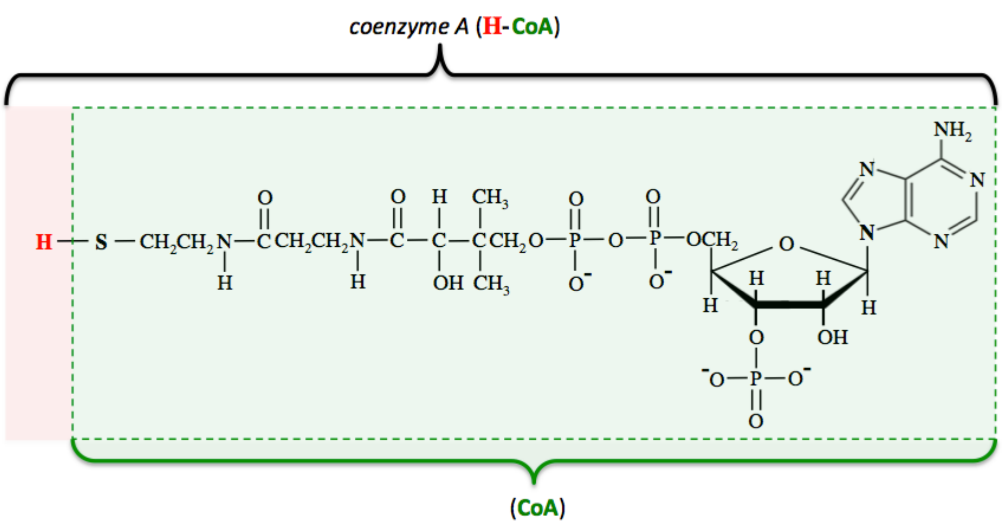
$FADH_2$ is **oxidized** to **FAD** by *donating* ***two*** electrons (and two H^+ ions) to other species.

- The oxidation of **$FADH_2$** *releases* energy.

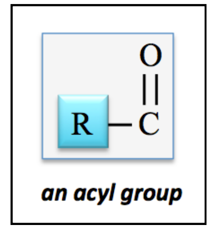
Much like **NAD^+/NADH** and **FAD/$FADH_2$**, **Coenzyme Q** (*not shown*), transfers electrons and hydrogen ions when it cycles between its oxidized and reduced forms.

Acyl Group-Transfer Coenzyme: Coenzyme A

Coenzyme A (**H-CoA**) is used in many metabolic reactions. Its structural formula is shown below.



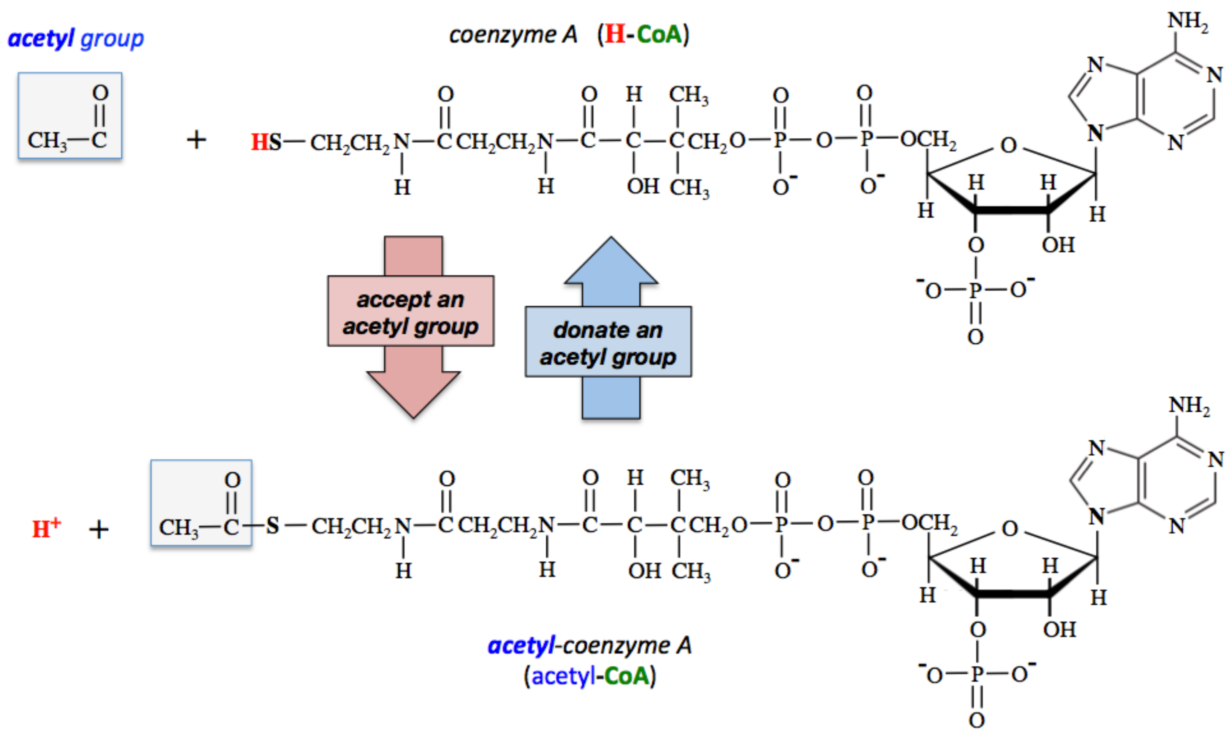
Coenzyme A is classified as a **coenzyme** because it is involved in the *transfer* of an ________ ***group*** *in many different enzymatically catalyzed reactions*.



- An *acyl group* consists of a carbonyl group bonded to an organic group (**R**), as shown *on the right.*
- When *coenzyme A* (**H-CoA**) accepts an ***acyl group***, the *acyl group* replaces the *left-most* hydrogen in the *coenzyme A* structure.

An ***acyl group*** that is central to the metabolism of food is the ______________ **group**.

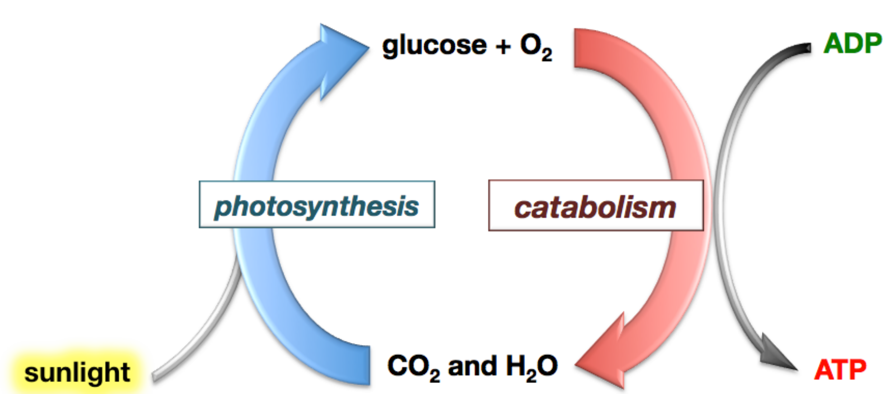
- *Acetyl groups* are donated and accepted by *coenzyme A*, as shown below:



Carbohydrate Metabolism

The energy that is contained in food can be traced back to the ___________.

- Energy from sunlight is captured by plants during *photosynthesis* as they convert CO_2 and H_2O into *glucose* and O_2.
- Without energy from sunlight, the reaction of CO_2 with H_2O to produce glucose and O_2 is not spontaneous.
- The input of energy from sunlight provides the energy that is required to convert CO_2 and H_2O to glucose and O_2.



In photosynthesis, energy from the sun's light does not vanish; it is converted to ________________ ______________ ______________ within _________________.

- Plants store excess *glucose* as ***starch***.

Organisms, including humans, use a series of **catabolic** chemical reactions to ***slowly*** _______________ ***carbohydrates and other food***, eventually converting it back to CO_2 and H_2O.

Energy that is released in these oxidations is converted to chemical potential energy within _______.

All three classes of macronutrients in food, carbohydrates, triglycerides (fats), and proteins, are catabolized in ***four stages***:

Stage 1: ____________________________________

Stage 2: ____________________________________

Stage 3: ____________________________________

Stage 4: ____________________________________

Stage 1: Digestion of Carbohydrates

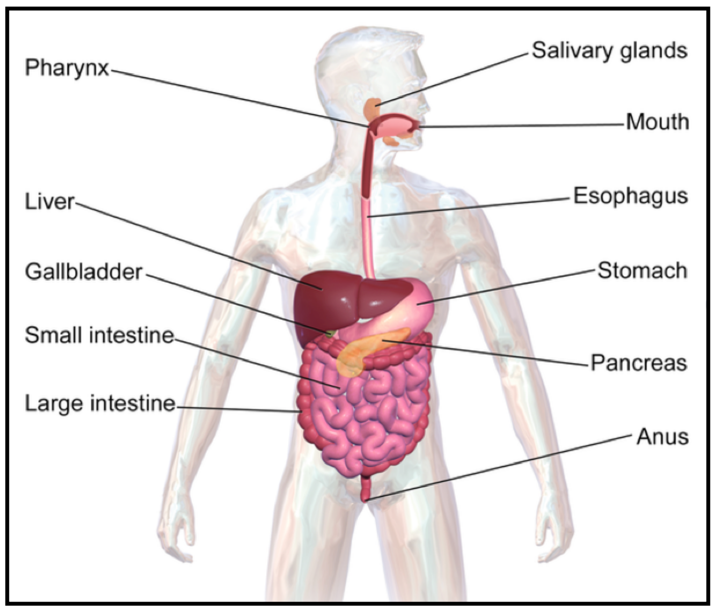
Digestion is the process in which the body breaks down carbohydrate, protein, and triglyceride polymers into their _________________ residues.

- For example, carbohydrate polymers are converted to monosaccharides.

Digestion occurs in the **digestive system**.

The *digestive system*, sometimes referred to as the **digestive track** or **gastrointestinal (GI) track**, includes the organs that are responsible for digesting food and eliminating the *un*digestible components of food. The major organs of the human digestive system are shown on the right.

Major Organs of the Human Digestive System



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During the digestion of carbohydrate polymers, most oligosaccharides (2-10 monosaccharide residues) and polysaccharides (> 10 monosaccharide residues) can be broken down to _________________________.

- These reactions are catalyzed by ________________ _________________.

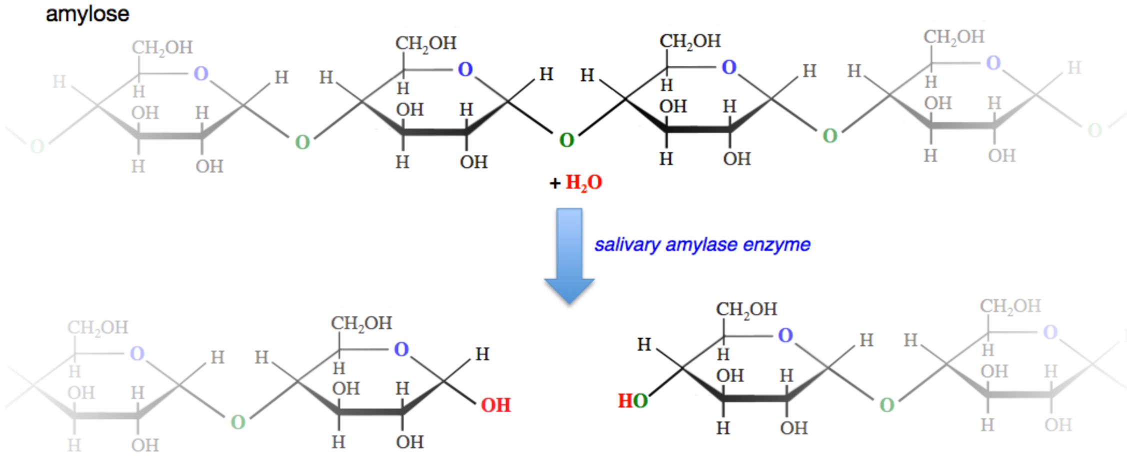
Approximately 50% of our dietary carbohydrates are in the form of **starch**.

- Starch has two components, amylose and amylopectin, both of which are composed entirely of __________________ residues.

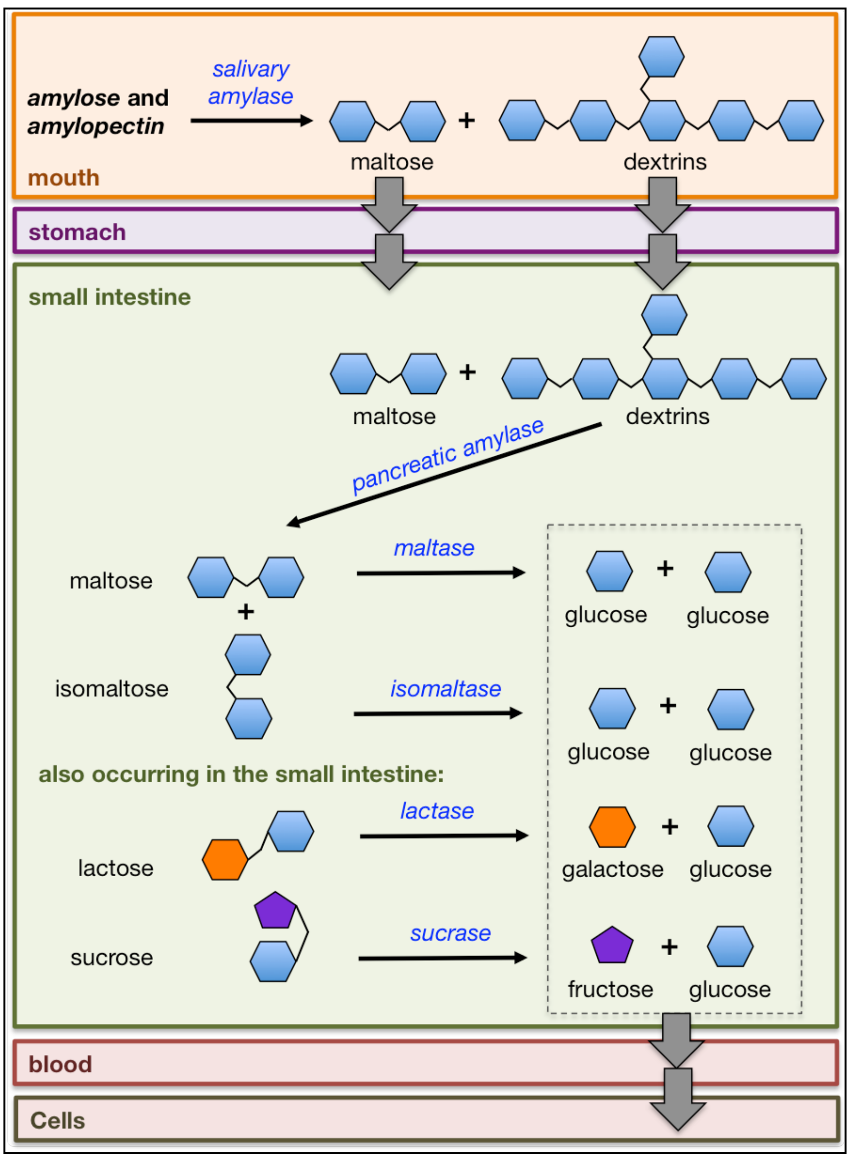
Digestion of amylose and amylopectin (starch) begins in the _______________.

Saliva contains _____________ _____________ ***enzymes***, which catalyze the hydrolysis of some of the **α-(1→4)** glycosidic bonds in amylose and amylopectin.

In the hydrolysis of carbohydrates, water molecules are used to lyse (break) _______________ ***bonds***.



An Illustrative Overview of the Digestion of Carbohydrates



Salivary amylase catalyzes the hydrolysis of amylose and amylopectin to form *maltose* (an **α-(1→4)** glucose-glucose disaccharide) and small oligosaccharides called **dextrins**.

Dextrins are oligosaccharides that generally contain between *three* and *eight* glucose residues.

The maltose, dextrins, and other non-starch dietary carbohydrates then pass through the stomach, where carbohydrate digestion temporarily stops because the *salivary amylase* is denatured by the stomach's low pH (very acidic) environment.

Digestion continues in the small intestine with the help of more digestive enzymes.

Pancreatic amylase catalyzes the hydrolysis of *dextrins* to form *maltose* and *isomaltose*. *Isomaltose* is an **α-(1→6)** glucose-glucose disaccharide that comes from the branching points in amylopectin.

Maltase and *isomaltase* enzymes catalyze the hydrolysis of maltose and isomaltose (respectively) into glucose.

The ***non starch*** dietary carbohydrates, *lactose* and *sucrose,* are converted to monosaccharides with the help of *lactase* and *sucrase* enzymes, respectively.

- Lactose is hydrolyzed to galactose and glucose.
- Sucrose is hydrolyzed to fructose and glucose.

It is critical that oligosaccharides and polysaccharides be converted to monosaccharides in order for the sugars to pass through the intestine wall and into the bloodstream so that they are available to cells throughout the body.

Monosaccharides are transported into the cells by passive diffusion through transmembrane proteins.

Not all dietary carbohydrates can be digested.

- For example, cellulose cannot be digested because humans do not have a dietary enzyme capable of hydrolyzing **β-(1→4)** glucose-glucose glycosidic bonds. Cellulose cannot pass through the small intestine and therefore passes through the digestive track until it is excreted in feces.

Stage 2: Acetyl-Coenzyme A Production

When glucose enters a cell, it can then undergo **stages 2**, **3**, and **4** of catabolism.

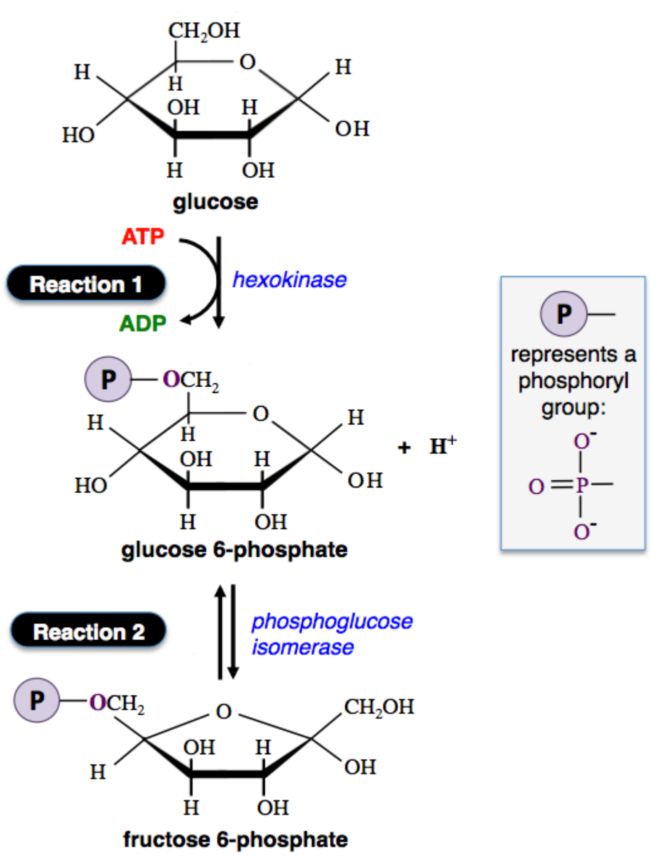
In **stage 2** of carbohydrate catabolism, ***glucose*** is converted into **acetyl-coenzyme A**, CO_2, and H_2O.

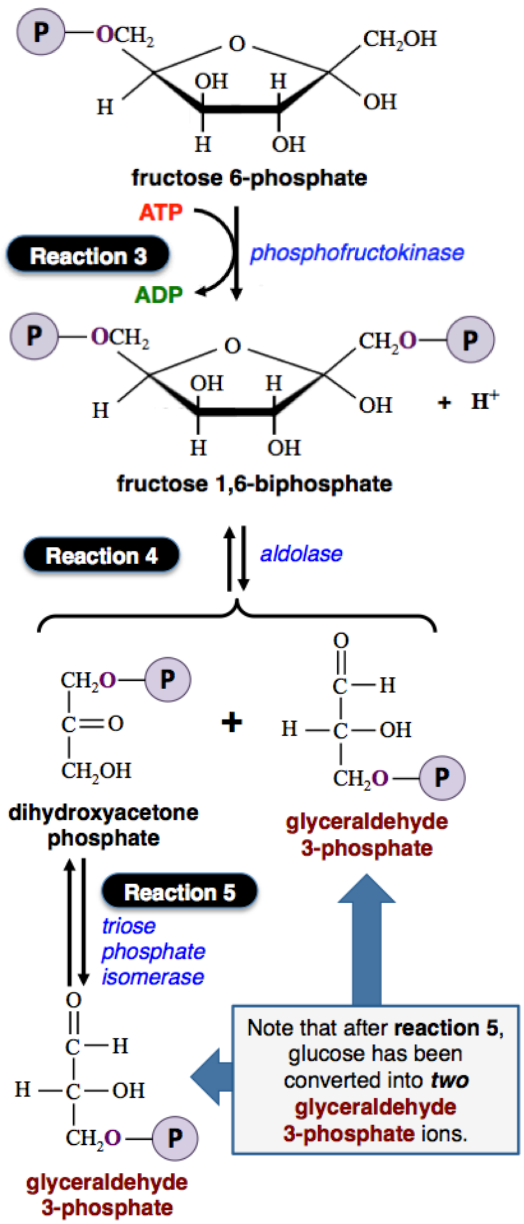
This process begins with a *catabolic pathway* called ________________.

Glycolysis is a series of ________ sequential reactions that ultimately converts one glucose molecule to two pyruvate ions and two H_2O molecules.

NOTE: I want to minimize any possible student anxiety by informing you that is not my intention for you to memorize these reactions, the names of the intermediates, or the names of the enzymes that are involved.

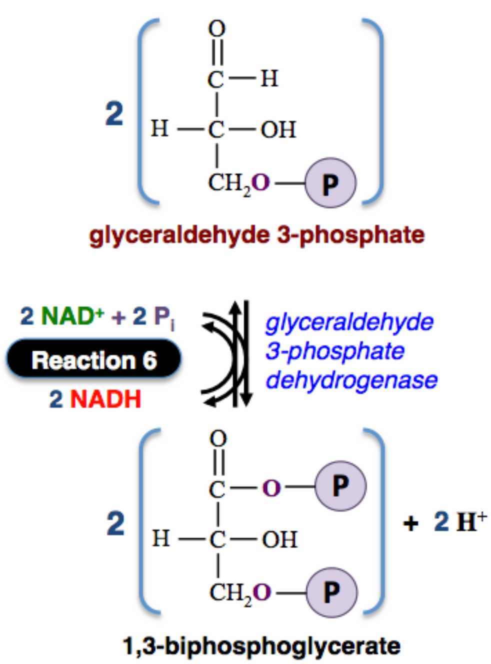
The **reactions of glycolysis**:





Notice that *one* ***glyceraldehyde 3-phosphate*** is produced in **reaction 4** and a second ***glyceraldehyde 3-phosphate*** is produced in **reaction 5**. Therefore, each of the *subsequent* reactions in the pathway ***will occur twice for each molecule of glucose that undergoes glycolysis***.

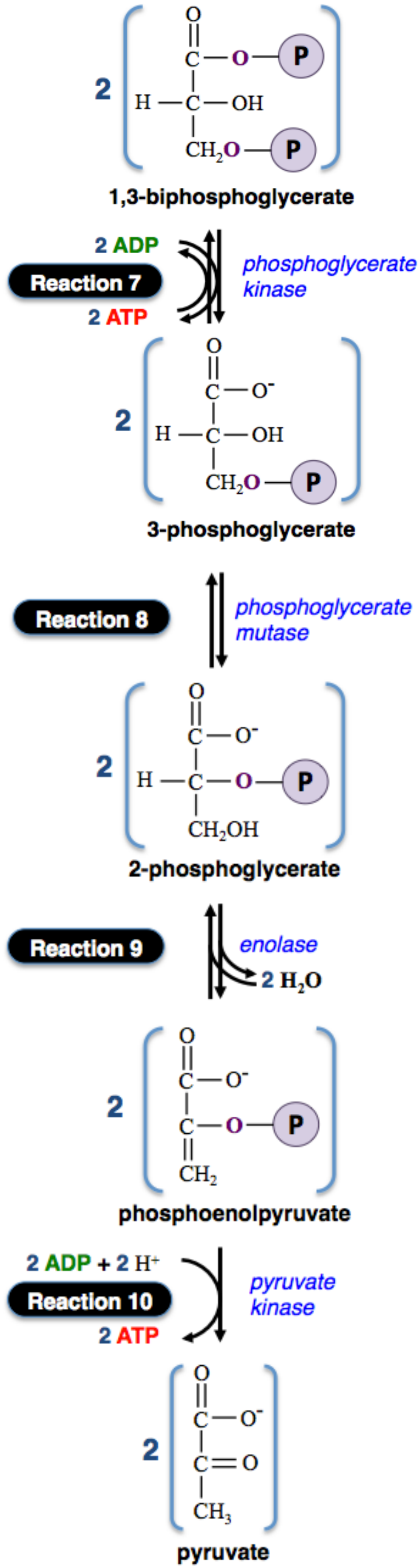
It is for this reason the reactants and products in the chemical equations that follow have a stoichiometric coefficient of "**2**."



Reaction 6) In this reaction, ***glyceraldehyde 3-phosphate*** is ***oxidized***. *An oxidation cannot occur without a reduction.* In this case, $\mathbf{NAD^+}$ is ***reduced*** to **NADH**. This occurs when a hydride ion ($\mathbf{H:^-}$) is transferred from glyceraldehyde 3-phosphate's carbonyl carbon to $\mathbf{NAD^+}$. The reduction of $\mathbf{NAD^+}$ to **NADH** requires energy, that energy comes from glyceraldehyde 3-phosphate.

The energy that is acquired by **NADH** can later be used to convert **ADP** to **ATP**.

- You will learn how that happens when I discuss **stage 4** of metabolism.



The reactions of glycolysis result in a net gain of ***two*** **ATP** and ***two*** **NADH**.

When there is a sufficiently high concentration of **ATP**, pyruvate, or other pathway products, then the rate of glycolysis can be slowed down. If the **ATP** concentration becomes low, then glycolysis can be accelerated. The rate of the glycolysis pathway is controlled by enzyme inhibitors and enzyme activators of the enzymes involved in the **irreversible reactions** (**1**, **3**, and **10**).

- For example, **ATP** and phosphoenol pyruvate (the product of **reaction 9**) act as inhibitors of the *phosphofructokinase* enzyme that catalyzes **reaction 3**.

Summary of Glycolysis

The chemical equation for the ***overall*** glycolysis pathway is:

$$\textbf{glucose} + 2\ \textbf{ADP} + 2\ \textbf{P}_i + 2\ \textbf{NAD}^+ \rightleftarrows 2\ \textbf{pyruvate ions} + 2\ \textbf{ATP} + 2\ \textbf{NADH} + 2\ \textbf{H}_2\textbf{O} + 2\ \textbf{H}^+$$

The **ten reactions** of glycolysis result in a net gain of _________ **ATP** and _________ **NADH**.

Not ***all*** of the energy from **glucose** is transferred to the **ATP** and **NADH** formed in glycolysis.

- Some energy was lost as *heat* during the reactions, however, **most** of glucose's chemical potential energy remains in the two ***pyruvate ions***.

Glycolysis is characterized as a ______________ ***metabolic pathway***.

- A *linear metabolic pathway* is a series of reactions that are not repeated.

Understanding Check:

a. How many **ATP** are produced when ***six*** glucose molecules undergo glycolysis?
b. How many **NADH** are produced when ***six*** glucose molecules undergo glycolysis?

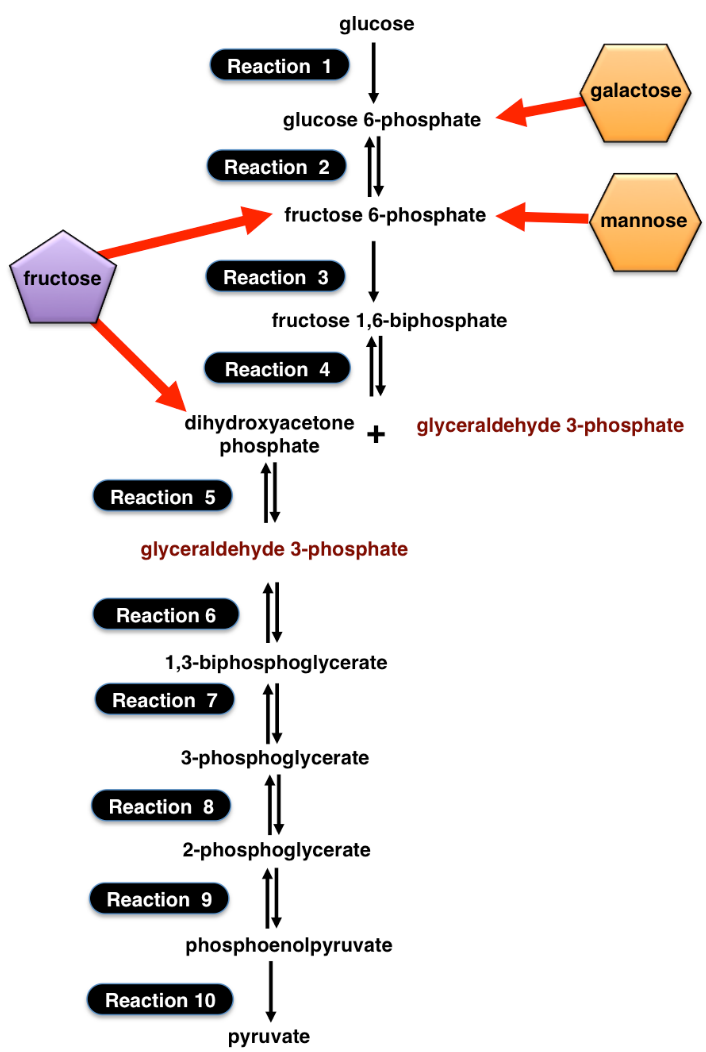
Before we take a look at the *fate of the pyruvate* that is produced in glycolysis, let's consider how ***non glucose monosaccharides*** are metabolized.

The Entry of Non Glucose Monosaccharides into Glycolysis

Although ***glucose*** is the major product of ***carbohydrate digestion***, *it is not the only monosaccharide that is produced.*

Other monosaccharides can be catabolized when they are ***converted to*** _____________ ***in the glycolysis pathway***.

- For example, fructose, galactose, and mannose monosaccharides are produced in carbohydrate digestion and can be converted to the glycolysis intermediates as shown on the right.

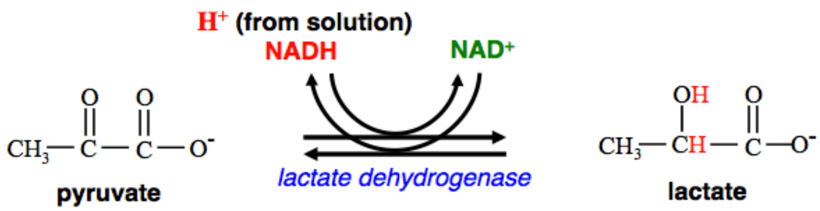


The Fate of Pyruvate

The fate of the pyruvate that is produced by *aerobic organisms* (organisms that require O_2 to grow), such as humans and most other organisms, *depends on the availability of* _________________ *in cells*.

During strenuous physical activity, the oxygen in muscle cells becomes depleted (**anaerobic condition**).

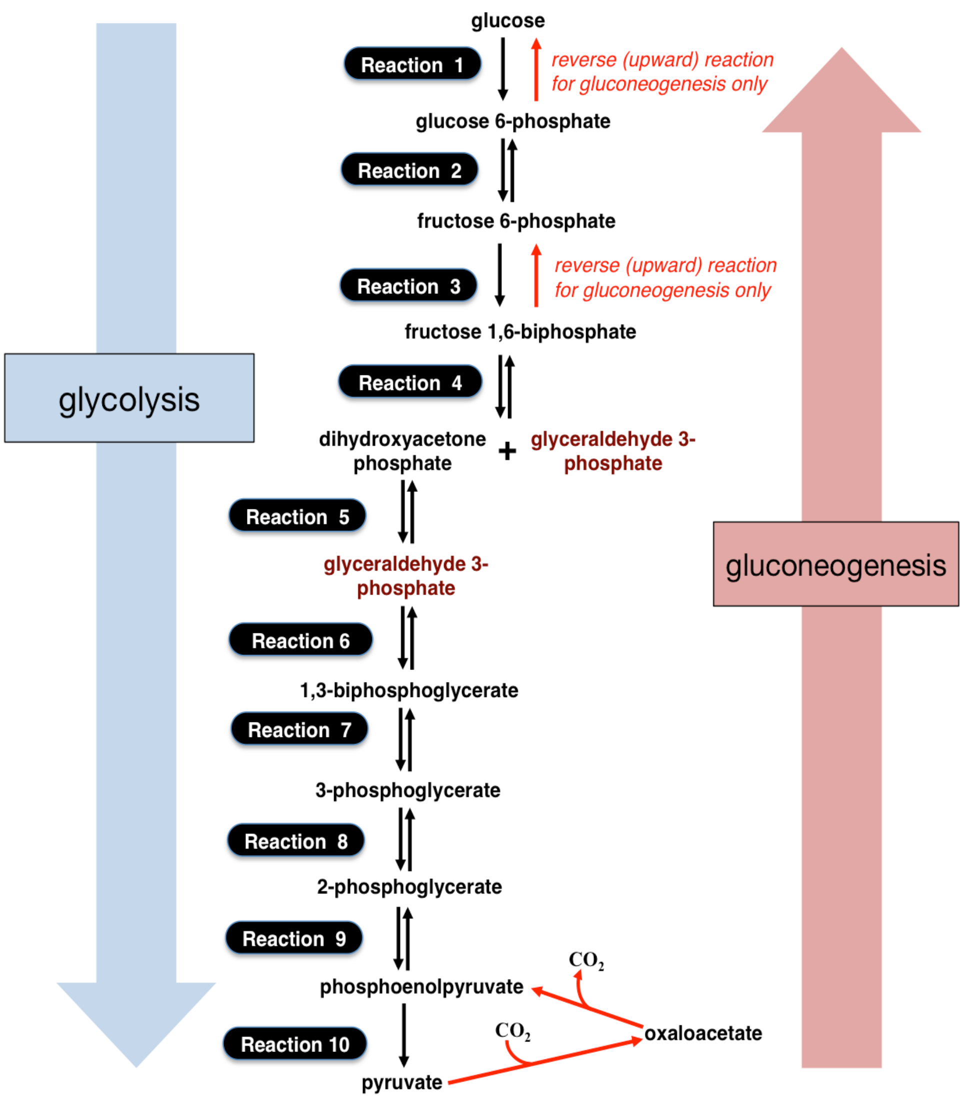
- When this occurs, the *pyruvate* that is made in glycolysis remains in the cytoplasm and is converted (***reduced***) to ________________, as shown in the reaction below.



The presence of lactate in a muscle causes the muscle to tire and feel sore.

Lactate is released by muscle cells into the circulatory system and then taken up by _____________ cells. **In the liver, lactate can be cycled *back to pyruvate*.**

After lactate is transformed back to pyruvate, it can be converted to glucose and stored for future use.



The conversion of ***non carbohydrate species to glucose*** is called ________________________.

- The conversion of lactate and pyruvate to glucose is an example of *gluconeogenesis*.

The *gluconeogenesis* and *glycolysis* pathways share many reactions. The differences occur at the three *irreversible* glycolysis reactions (reactions 1, 3, and 10), as shown in the figure on the left.

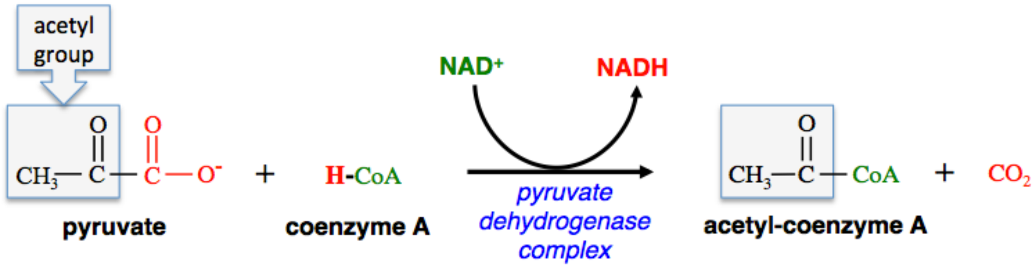
Gluconeogenesis does not use reaction 10 of glycolysis, and it uses different enzymes in order to enable the reverse of reactions 1 and 3 of glycolysis.

Gluconeogenesis takes place primarily ***in the liver***.

In the figure above, *glycolysis* proceeds in the ***downward*** direction, and *gluconeogenesis* proceeds in the ***upward*** direction.

When oxygen is present (_____________ **conditions**), much more energy can be derived from pyruvate.

Under aerobic conditions, pyruvate passes from the *cytoplasm* into the _____________________ and is then converted to ***acetyl-coenzyme A*** and CO_2 (as shown in the equation below).



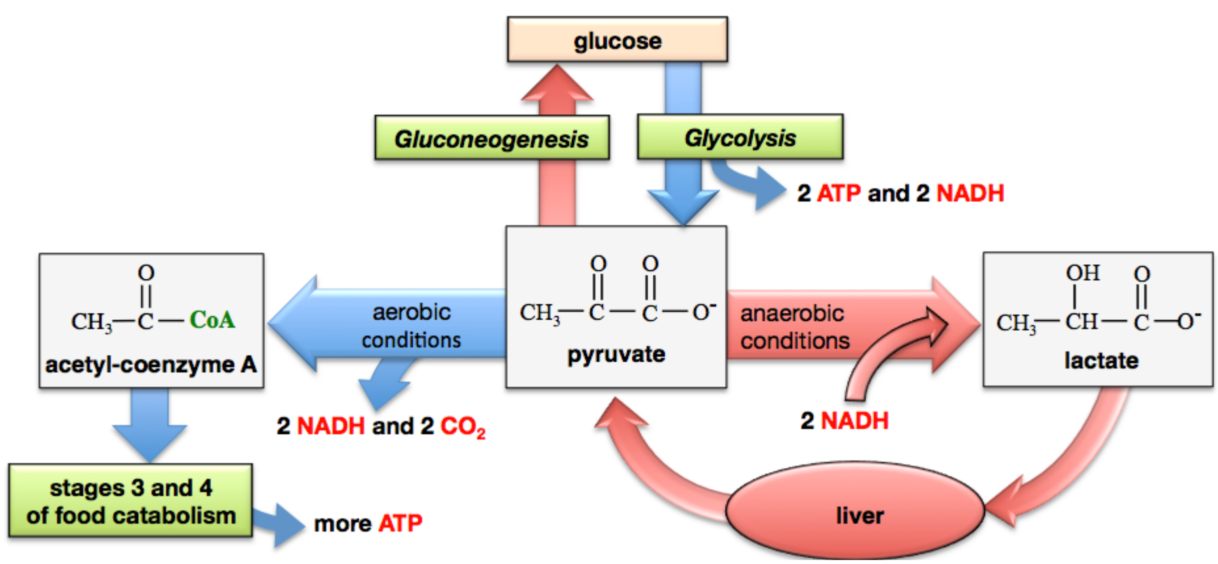
In this reaction, pyruvate is ***oxidized*** and ***decarboxylated***.

- The decarboxylation produces $\mathbf{CO_2}$.
- In the oxidation process, electrons from pyruvate are passed through intermediate compounds (not shown), until they are eventually transferred, along with a hydrogen, to $\mathbf{NAD^+}$.
- Energy *released* by the oxidation of pyruvate is transferred to **NADH**.
- ________________________ is produced.

The acetyl groups are relatively high-energy because they still contain much of the energy that was originally in glucose.

In the next stage of catabolism (the citric acid cycle), the energy contained in the acetyl groups is used to produce more **NADH** and more **ATP**.

Summary of Stage 2 of Carbohydrate Catabolism and the Fate of Pyruvate

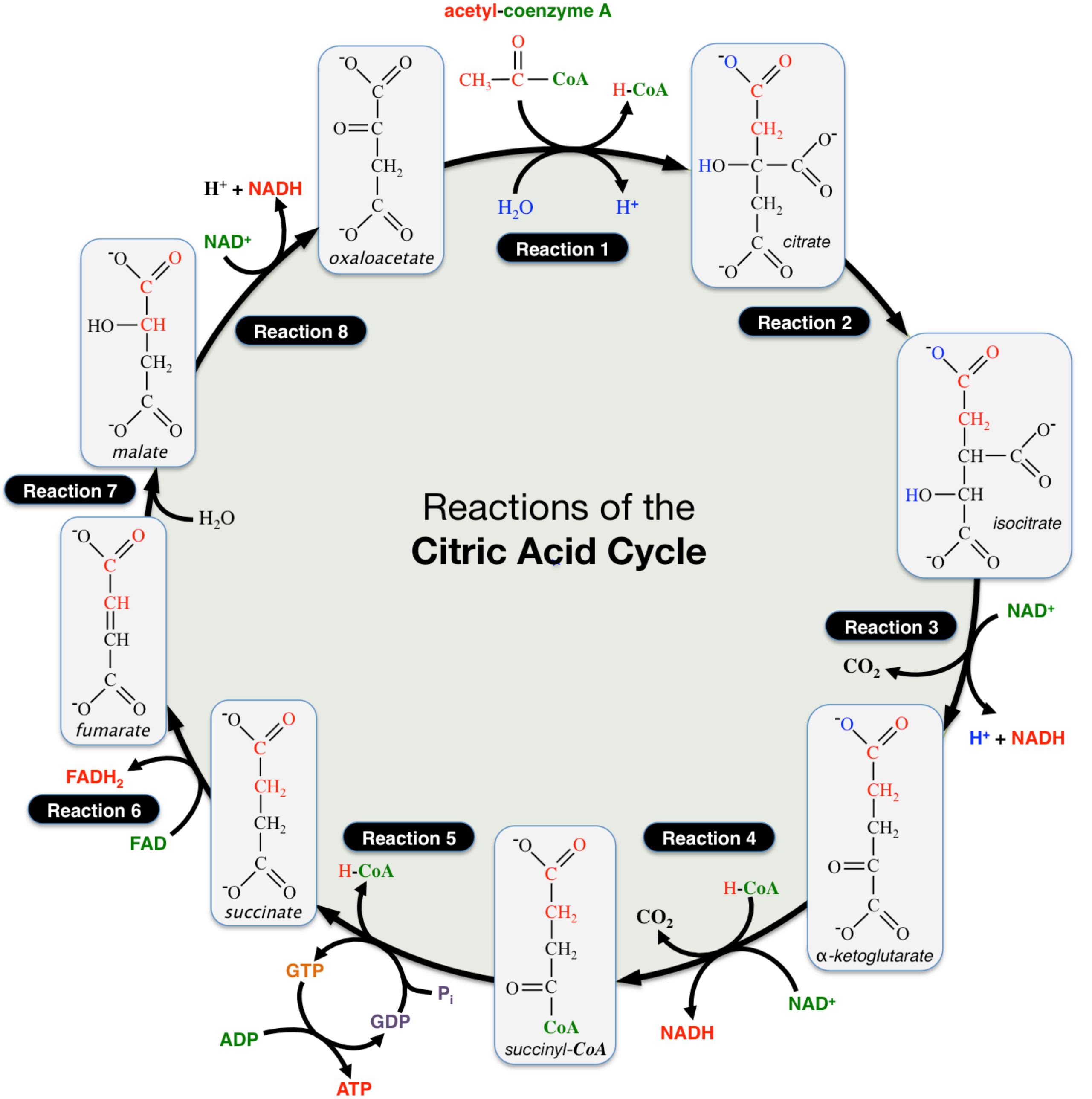


In Stage 2 of carbohydrate catabolism, **under aerobic conditions**, ***one*** glucose molecule has produced two ***acetyl-coenzyme A*** *ions,* and provided the energy for the formation of *four* **NADH** and *two* **ATP**.

Stage 3: The Citric Acid Cycle

The **citric acid cycle** is also referred to as the **Krebs Cycle** because it was H. A. Krebs who, in 1937, discovered these reactions and recognized their significance in energy-transfer reactions.

NOTE: you ***do not*** need to memorize these reactions, the names of the intermediates, or the names of the enzymes that are involved.



The *citric acid cycle* is characterized as a ___________________ **metabolic pathway**.

- A *circular pathway* is a repeating series of reactions in which the final product is __________ an *initial* reactant.
- In the first reaction, acetyl-coenzyme A (acetyl-CoA) reacts with oxaloacetate. In the citric acid cycle, *oxaloacetate* is not only a *reactant* in the first reaction; it is ***also*** the *product* of the last reaction.

Acetyl-CoA brings two carbons in its acetyl group (these carbons are shown in red font in the video).

When one acetyl-CoA is completely processed in the citric acid cycle, _______**NADH**, ______**$FADH_2$**, _______ **ATP**, and ***two*** CO_2 molecules are produced.

In this process, energy that was originally contained in acetyl-CoA is converted to chemical potential energy within **NADH, $FADH_2$** and **ATP**.

Reactions of the Citric Acid Cycle

Reaction	Type of Reaction	Enzyme	Energy Transferred to:	Notes
1	acetyl group transfer	*citrate synthase*		An ***acetyl group*** is transferred to oxaloacetate.
2	isomerization	*aconitase*		The product and reactant are *constitutional isomers*.
3	oxidation/reduction *and* decarboxylation	*isocitrate dehydrogenase*	**NADH**	This reaction is irreversible. ***Isocitrate*** is decarboxylated and its hydroxyl group is oxidized to a carbonyl group. A *hydride ion* (**H:**$^-$) is transferred from *isocitrate* to **NAD^+**, thereby reducing **NAD^+** to **NADH**. This reaction is the body's main regulation point for the citric acid cycle. When cells are "energy rich," **ATP** and **NADH** concentrations are high. **ATP** and **NADH** ***inhibit*** the *isocitrate dehydrogenase* enzyme. When energy is in demand, **ADP** and **NAD^+** concentrations are high. **ADP** and **NAD^+** ***activate*** *isocitrate dehydrogenase*.
4	oxidation/reduction and decarboxylation	*α-ketogulutarate dehydrogenase*	**NADH**	This irreversible process has multiple steps (not shown). Two electrons are transferred from α-ketogulutarate to an intermediate species. Ultimately, the two electrons and a **H^+** ion are transferred from an intermediate to **NAD^+** to form **NADH**.
5	acyl group transfer *and* phosphorylation	*succinyl-CoA synthase*	**ATP**	Humans have a *succinyl-CoA synthase* enzyme that produces **GTP** (*guanosine triphosphate*). Energy in **GTP** is used to produce an **ATP**. We have another *succinyl-CoA synthase* enzyme that produces **ATP** directly.
6	oxidation/reduction	*succinate dehydrogenase*	**$FADH_2$**	$-CH_2-CH_2-$ is ***oxidized*** to -CH=CH- **FAD** is ***reduced*** to **$FADH_2$**. The **FAD**/**$FADH_2$** coenzyme is permanently bound to the succinate dehydrogenase enzyme.
7	hydration	*fumarase*		Hydration of an alkene.
8	oxidation/reduction	*malate dehydrogenase*	**NADH**	***Malate's*** 2° alcohol is ***oxidized*** to a ketone. **NAD^+** is ***reduced*** to **NADH**.

Summary of the Citric Acid Cycle

The ***overall*** chemical equation for the ***citric acid cycle*** metabolic pathway is:

$$\textbf{\textit{acetyl}-CoA} + 3\ NAD^+ + FAD + ADP + P_i + 2\ H_2O \rightleftarrows 2\ CO_2 + 3\ NADH + FADH_2 + ATP + H\text{-}CoA + 3\ H^+$$

Potential energy from an acetyl-CoA that undergoes the citric acid cycle is converted to potential energy in ***three*** **NADH**, ***one*** **$FADH_2$**, and ***one*** **ATP**. Some energy is lost as *heat*.

The CO_2 produced in the *citric acid cycle* and in **stage 2** of metabolism, is one of the end-products of food metabolism.

- CO_2 is the most-oxidized form of carbon in organic compounds, and therefore has a very low energy content.
- Energy that was present in the food and food metabolites that contained these carbons has been extracted in the catabolism process.

Understanding Check: Calculate the net gain of NADH, $FADH_2$, and ATP from ***one glucose molecule*** that undergoes the ***first three stages of catabolism***.

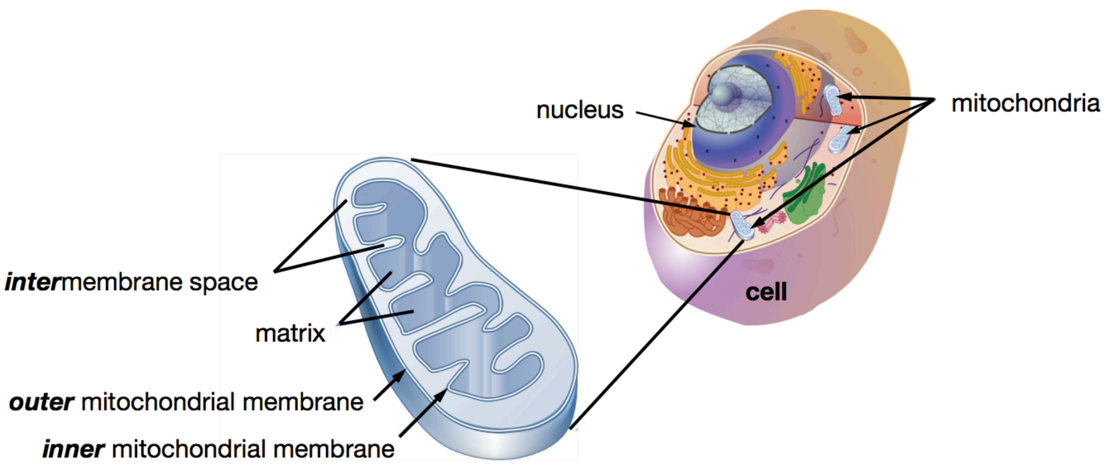
- Keep in mind that glycolysis produces ***<u>two</u>*** pyruvate ions, which results in the production of two acetyl-CoA.

Stage 4: Oxidative Phosphorylation

Glycolysis occurs in the ____________________ of the cell.

The reactions of the citric acid cycle occur in the ________________________.

The Structure of the Cell and a Magnification of an Individual Mitochondrion.



A mitochondrion consists of an _________ **membrane** bilayer and an __________ **membrane** bilayer.

The region ***between*** the *outer* and *inner membranes* is called the ___________________ _____________.

The region within the inner membrane is called the ______________.

Pyruvate oxidation/decarboxylation and *the reactions* of the citric acid cycle occur in the ***matrix*** region.

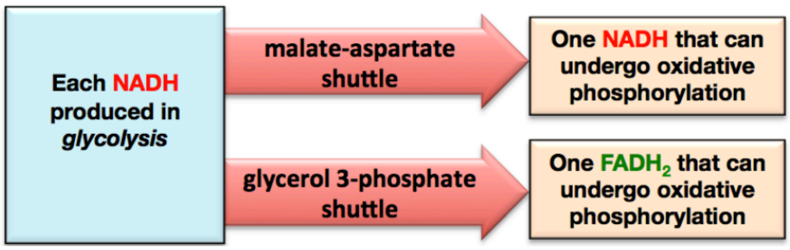
The pyruvate that is produced in **glycolysis** is able to pass from the cytoplasm, through both the inner *and* outer mitochondrial membranes, into the ***matrix*** region.

The next stage of carbohydrate catabolism, **oxidative phosphorylation** (**stage 4**), requires that ________ be located ***within* the *mitochondrial matrix***.

- Since pyruvate oxidation/decarboxylation ***and*** the reactions of the citric acid cycle occur in the *mitochondrial matrix*, the **NADH** created in those processes can immediately undergo oxidative phosphorylation.
- The **NADH *that is produced by glycolysis*** is able to pass through the ***outer*** *mitochondrial membrane* and enter the *intermembrane space*; however, it is ***not*** able to pass through the ***inner*** *mitochondrial* membrane to enter the ***matrix*** region.
    - In order for the energy from these **NADH** to be utilized, they must be processed through an "**NADH** ____________."

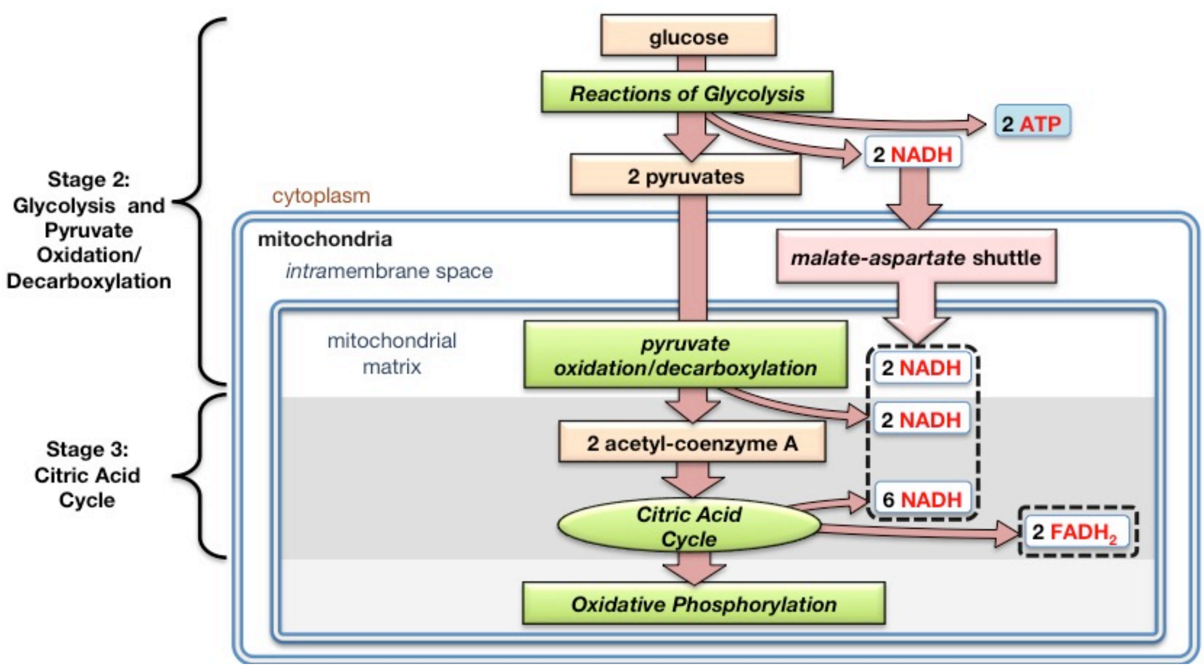
The two most important **NADH** shuttles are the **malate-aspartate shuttle** and the **glycerol 3-phosphate shuttle**.

- The **malate-aspartate shuttle** works by oxidizing the **NADH** to **NAD^+** in the intermembrane space, then transferring the electrons through the inner mitochondrial matrix to an **NAD^+** that ***is* ____________ *inside the matrix,*** *thereby producing an* **NADH** that *can undergo oxidative phosphorylation*.
- In the **glycerol 3-phosphate shuttle**, **NADH** is oxidized in the intermembrane space by transferring electrons to an inner mitochondrial membrane-bound **FAD**, ***thereby producing an*** **$FADH_2$** that *can undergo oxidative phosphorylation.*



Example Problem: From one glucose molecule, determine how many **NADH** and **$FADH_2$** would be available for *oxidative phosphorylation* (stage 4 of metabolism). Assume that both **NADH** formed in glycolysis use the **malate-aspartate shuttle**.

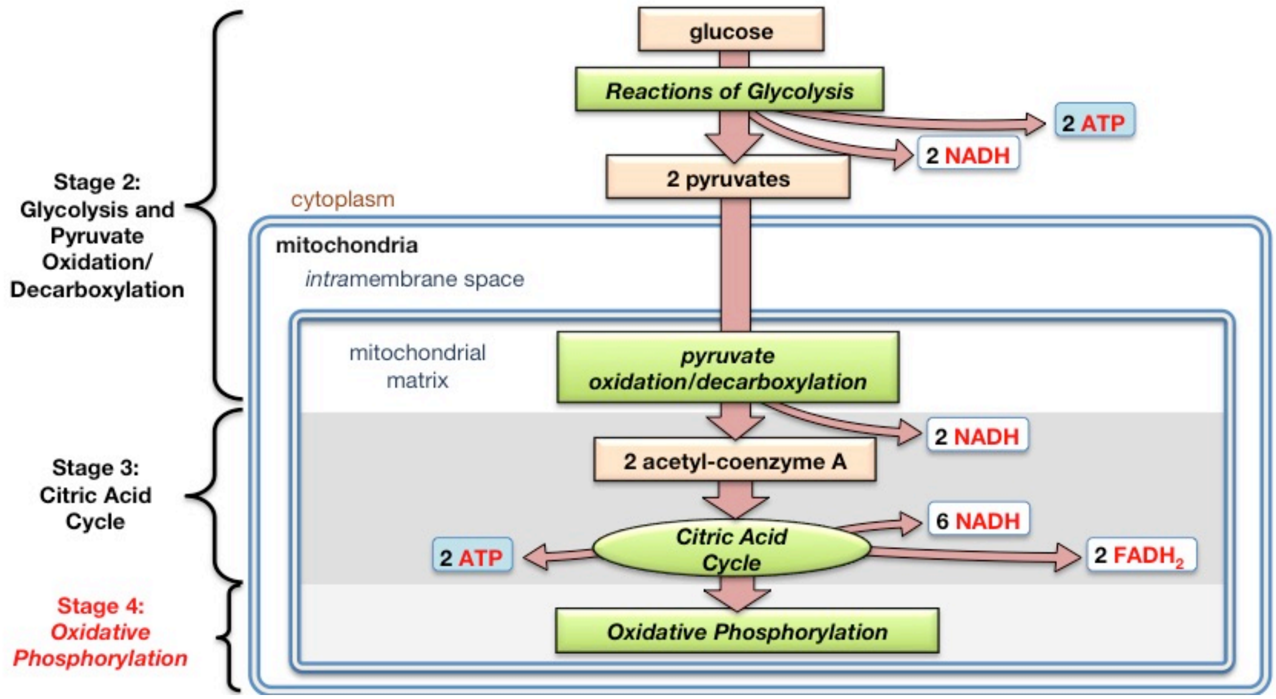
Solution: Start this problem with the amount of **NADH** and **$FADH_2$** that are formed ***from one glucose*** molecule in stages 1 to 3 of glucose catabolism. In the previous **UNDERSTANDING CHECK** problem (**chapter 15, part 5**), you found that **10 NADH**, and **2 $FADH_2$** are produced from one glucose molecule.



The ***two*** **NADH** that are produced in ***glycolysis*** cannot pass through the inner mitochondrial membrane and enter the matrix region where oxidative phosphorylation takes place. Therefore, it is necessary that "**NADH** *shuttles*" be used. In the **malate-aspartate shuttle**, each NADH produced in *glycolysis* results in one **NADH** that can undergo oxidative phosphorylation. In this case, there would be **10 NADH** and **2 $FADH_2$** available for oxidative phosphorylation.

You try one: From one glucose molecule, determine how many NADH and $FADH_2$ would be available for *oxidative phosphorylation* (stage 4 of metabolism). Assume that both NADH formed in glycolysis use the **glycerol 3-phosphate shuttle**.

The primary goal of food catabolism is the production of **ATP**.



At this point in my narrative of carbohydrate catabolism:

- Only ***four*** **ATP** have been produced from one glucose **so far**.
- Most of the chemical potential energy that has been extracted from glucose is still in the form of _____________ _____________(**NADH** and **$FADH_2$**).

In **stage 4** of catabolism (*oxidative phosphorylation*), chemical potential energy contained in the *reduced coenzymes* is __________________ to **ATP**.

Oxidative phosphorylation is the process in which ___________ from **NADH** or **$FADH_2$** are transferred, through a series of electron transfer intermediates, to dissolved oxygen (O_2) in order to provide the energy required to produce **ATP**.

In this process, **ADP** and an inorganic phosphate (P_i) are converted to **ATP**.

The formation of **ATP** from **ADP** and P_i would ***not*** occur spontaneously without the input of energy that is provided when electrons are transferred to O_2.

Because of the availability of H^+ in solution (from H_2O, H_3O^+, or the *acid form* of any other species present), when electrons are transferred to oxygen, the following reaction occurs:

$$O_2 + 4H^+ + 4 \text{ electrons} \rightarrow 2H_2O$$

In the reaction above, O_2 is________________; it gains electrons

O_2 is the ***final*** ______________ of electrons in food catabolism.

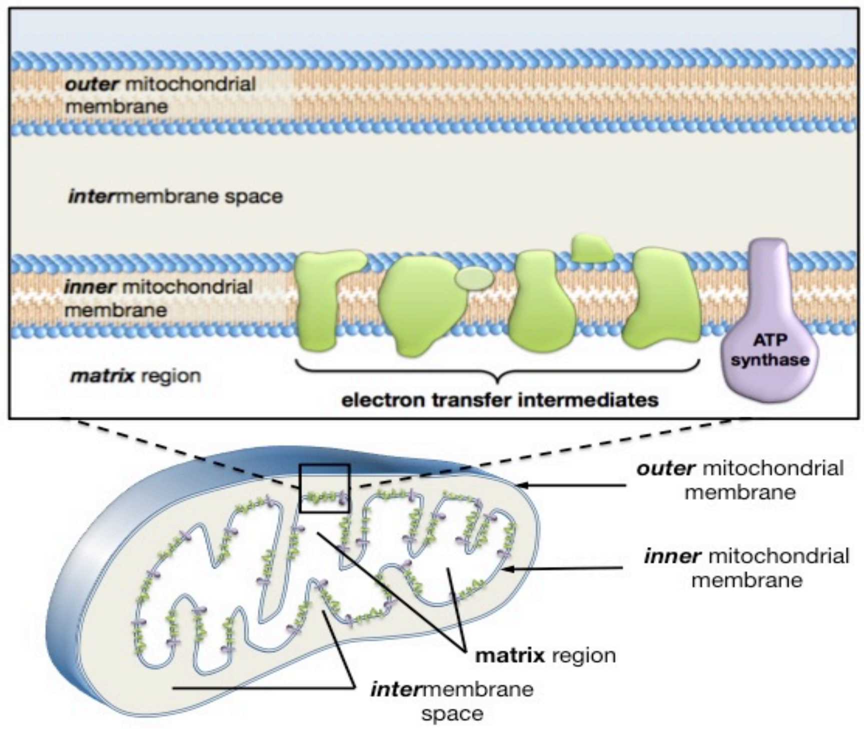
The energy released by the transfer of electrons from **NADH** or **FADH$_2$**, through the electron transfer intermediates, to O_2 is not immediately used to drive the production of **ATP**.

Instead, this energy is used to move hydrogen ions from a region of lower hydrogen ion concentration (the mitochondrial matrix) to a region of higher hydrogen ion concentration (the intermembrane space).

By doing so, the energy that is released by the transfer of electrons is converted to

_____________________ ***potential energy***.

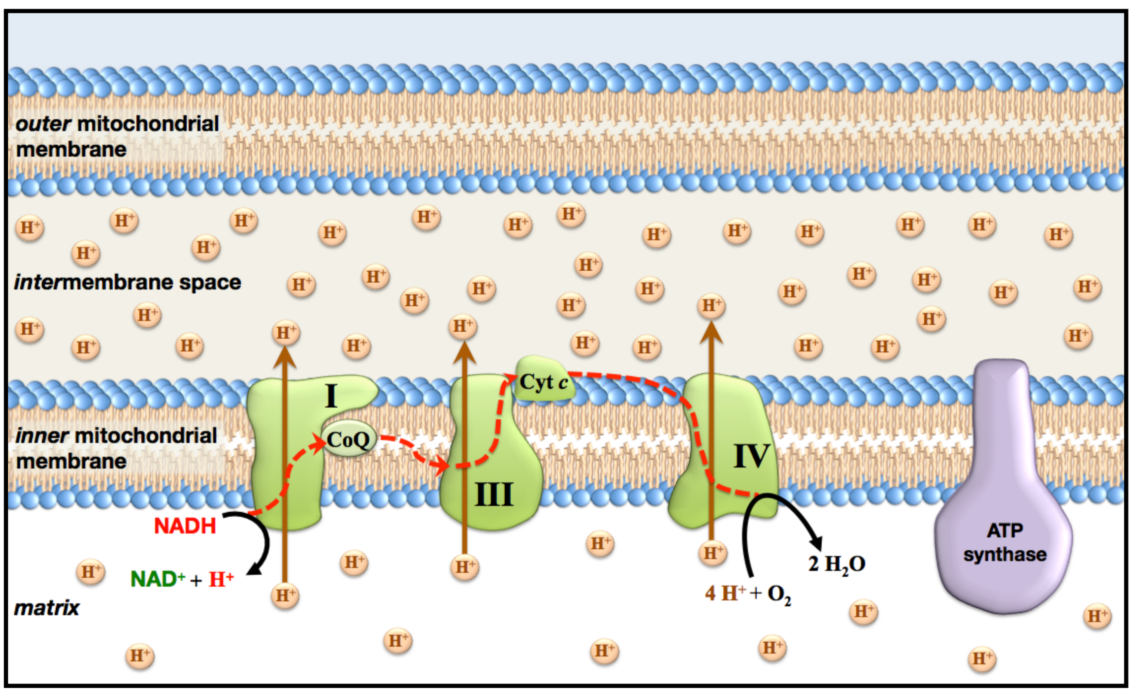
- Physically, this is very similar to "charging" a battery



Oxidative phosphorylation does not happen in exactly the same way for **NADH** as it does for **FADH$_2$**.

Electron Transfers and Hydrogen Ion Transport From NADH Oxidation

The process begins with the ________________ of **NADH** in the matrix region.



The electrons that are released in the oxidation of **NADH** are sequentially passed between electron transfer intermediates (shaded green) along the path that is indicated by the dashed red curve.

- Two of the electron transfer intermediates, ***coenzyme Q*** (**CoQ**) and ***cytochrome C*** (**Cyt c**), are quite *mobile*.
- The other electron transfer intermediates are *transmembrane* **proteins complexes** (labeled **I**, **III**, and **IV**).

In order for the electrons to "move through" these protein complexes, they are transferred ***within*** *the complexes* by sequential oxidations and reductions of neighboring prosthetic groups or cofactors (not shown in the figure).

The movement of electrons through the protein complexes releases energy (analogous to water being released from a dam).

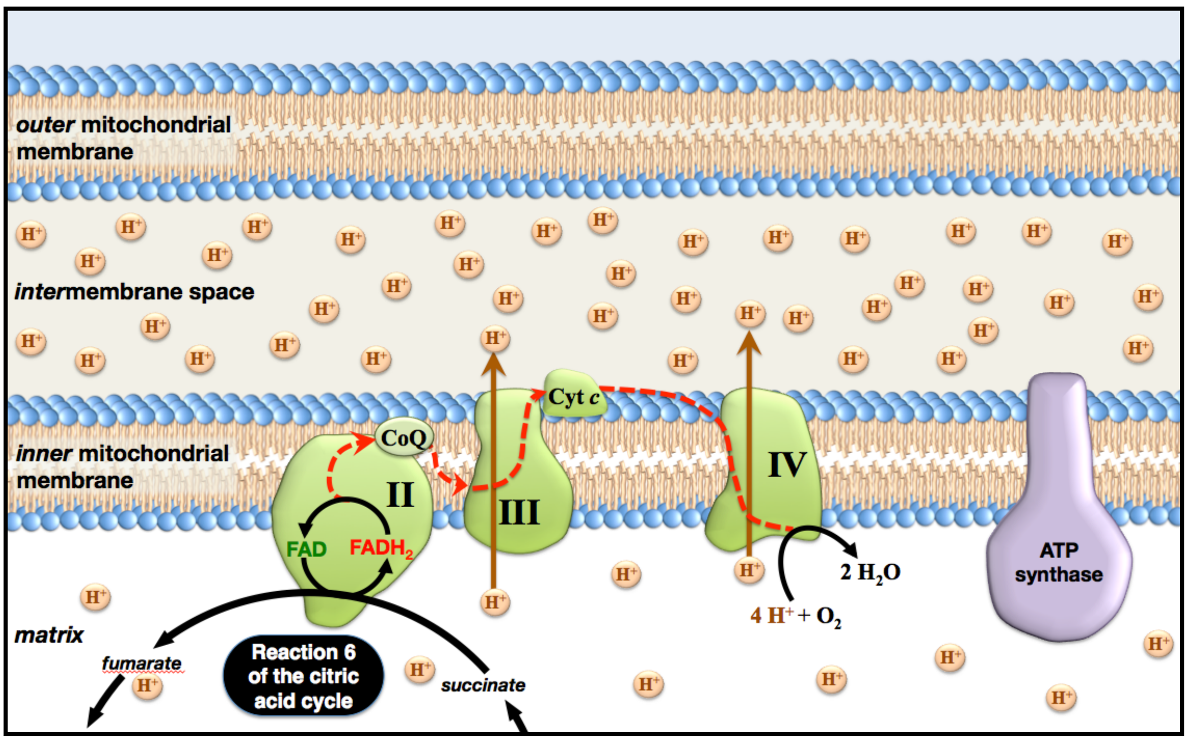
This energy is used by the complexes to __________ ____________ *hydrogen ions* from a region of ________ hydrogen ion concentration (the mitochondrial matrix) to a region of ________ hydrogen ion concentration (the *inter*membrane space), as indicated in the figure by the arrows in the figure on the previous page.

Electrons are ultimately transferred to, and thereby ***reduce*** O_2.

Electron Transfers and Hydrogen Ion Transport from $FADH_2$ Oxidation

$FADH_2$ is produced in _______________ of the *citric acid cycle*.

- The enzyme that catalyzes this reaction is part of an electron transfer intermediate called **complex II**.



In oxidative phosphorylation, **$FADH_2$** is ***oxidized*** and its electrons are sequentially passed between electron transfer intermediates, along the path that is indicated by the dashed curve, and then finally transferred to O_2.

The movement of electrons through protein complexes **III** and **IV** releases energy.

This energy is used by these complexes to *actively transport* hydrogen ions through the inner mitochondrial membrane into the intermembrane space.

Summary of the Oxidation of NADH and $FADH_2$ During Oxidative Phosphorylation

When **NADH** and **$FADH_2$** are oxidized, their electrons are transferred, through intermediates, to O_2.

As electrons move through complexes I, III, and IV, energy is released.

This energy is used by the complexes to **actively transport** hydrogen ions from a region of ***lower*** hydrogen ion concentration (the mitochondrial matrix) to a region of ***higher*** hydrogen ion concentration (the intermembrane space).

In doing so, the ***energy*** from **NADH** and **$FADH_2$** (that was originally in food) is converted to ***electrochemical energy*** within mitochondria.

This part of oxidative phosphorylation is often referred to as _____________ ________________.

The electron transfer intermediates (shaded green in the previous figures) that are involved in *electron transport* are sometimes called "***the electron transport chain***."

Next, you will learn how electrochemical energy within mitochondria is used to drive the production of **ATP**.

ATP Production in Oxidative Phosphorylation

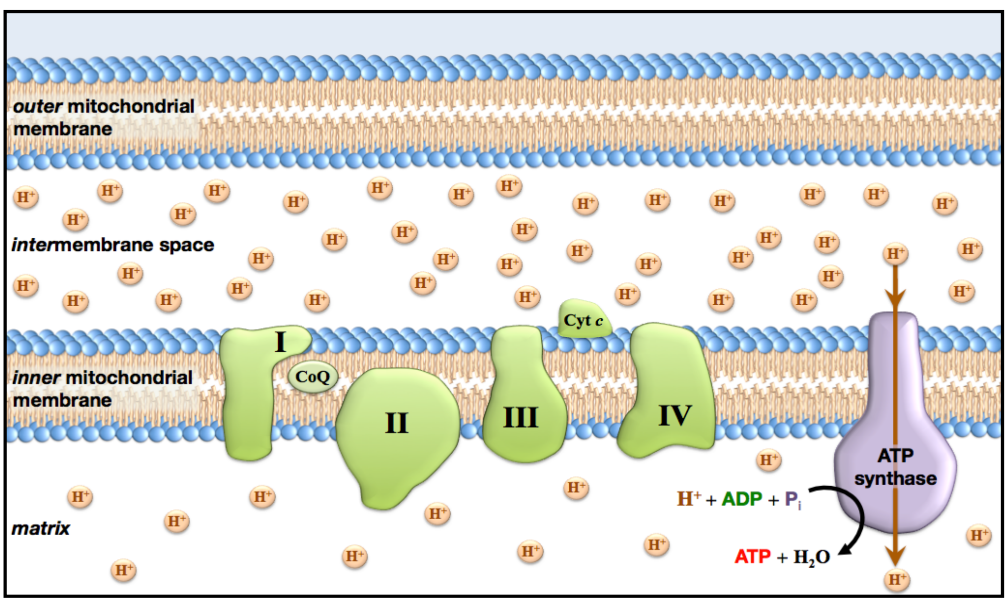
When there are *unequal* concentrations of a species on opposite sides of a membrane, we say that a "***concentration*** __________________" exists.

The creation of *electrochemical potential energy* in the form of an **H^+** concentration gradient was like charging a battery.

As with any dissolved species, hydrogen ions will ___________________ diffuse from areas of high concentration to areas of low concentration.

- It is lower in energy for the hydrogen ions to be in the matrix region (low concentration) than it is for them to be in the intermembrane space (higher concentration).

The **only** path between these regions in which hydrogen ions can passively diffuse is through the _____________________ enzyme, as illustrated below.



Much like electrical current passing through an electric motor does work, the passing of hydrogen ion current through an *ATP synthase* does work.

- This work is done by forcing the enzyme to change its shape and thereby supply the energy needed to form a bond between an inorganic phosphate (**P_i**) and **ADP**, to produce **ATP**.

The *ATP synthase* enzyme not only catalyzes the reaction for the synthesis of **ATP**, it also plays a role in delivering the energy needed to make **ATP** synthesis occur ***spontaneously***.

The number of **ATP** that can be produced from **NADH** or **$FADH_2$** depends on the cell and its current conditions.

The latest research indicates that, ***on average***,
one **NADH** produces about _________ **ATP**, and
one **$FADH_2$** produces about _______ **ATP**.

Let's calculate how many **ATP** can be produced from the catabolism of ***one glucose molecule***.

- For this calculation, we will assume that each **NADH** produces 2.5 **ATP**, and each **$FADH_2$** produces 1.5 **ATP**, and that **NADH** produced in glycolysis use the ***malate-aspartate shuttle***.

Solution:

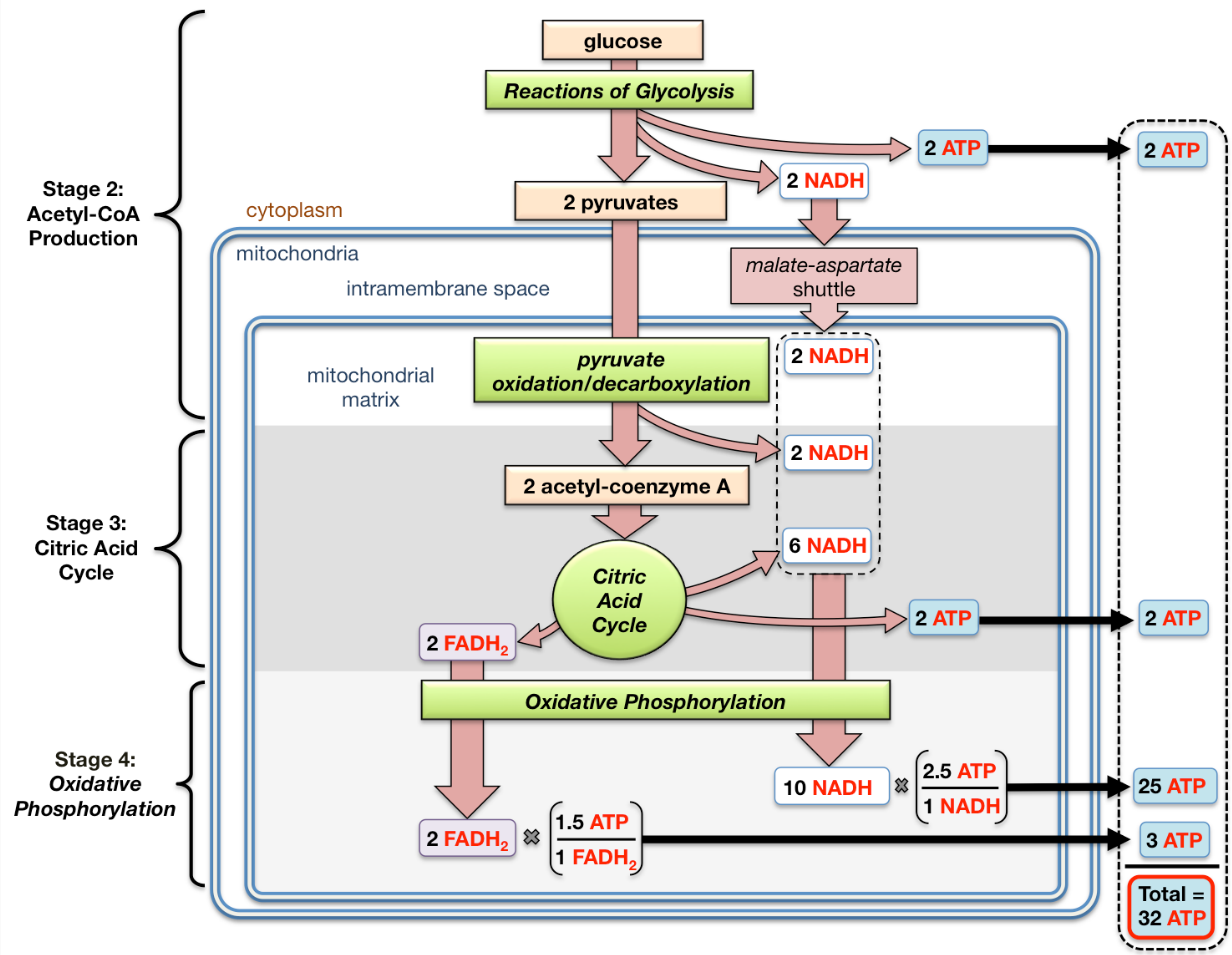
Stage 2: In *glycolysis*, glucose is converted to two pyruvate ions. In this process, two **NADH** and two **ATP** are formed. The two **NADH** undergo the ***malate aspartate shuttle*** and result in the formation of two **NADH** within the mitochondrial matrix.

The pyruvate ions can diffuse past both mitochondrial membranes, and enter the matrix region. There, the pyruvate ions undergo an oxidation/decarboxylation reaction. In this process, two **NADH** and two acetyl-CoA are formed.

Stage 3: In the c*itric acid cycle*, the two acetyl-CoA produce a total of six **NADH**, two **$FADH_2$**, and two **ATP**.

Stage 4: In *oxidative phosphorylation,* the ten **NADH** and two **$FADH_2$** produced in **stages 2** and **3** are oxidized in order to produce **ATP**.

This gives total of 32 ATP, as shown in the illustration below.



Understanding Check: Calculate how many **ATP** can be produced from the catabolism of **one glucose molecule** when the two NADH from glycolysis use the ***glycerol 3-phosphate shuttle***.

- Assume that each NADH that undergoes oxidative phosphorylation produces 2.5 ATP, and each $FADH_2$ produces 1.5 ATP.

Summary of Carbohydrate Catabolism

In the four stages of carbohydrate catabolism, chemical potential energy in carbohydrates is converted to chemical potential energy in **ATP**, a substance that can be used immediately by all cells to do cellular work.

The carbon, hydrogen, and oxygen atoms in carbohydrates, along with the oxygen we inhale, are converted to H_2O and CO_2.

Regulation of Blood Glucose Concentration

It is important for human **blood glucose concentration** (sometimes called blood sugar level) to remain within a "normal" range.

- The normal range of glucose concentration in the blood is about 80 to 110 mg per dL of blood.

Long term effects of having higher than normal blood glucose concentration (_____________) can include damage to kidneys, the neurological system, the cardiovascular system, eyes, feet, and legs.

Between meals or during starvation, blood glucose levels fall below the normal range (_____________).

- This can result in confusion, loss of coordination, difficulties in speaking, a loss of consciousness, seizures, and even death. Symptoms can come on quite quickly and include hunger, shaking, sweating, and weakness.

In the "***fed***" state, which occurs *soon after a meal* when blood glucose levels are high, ***liver*** and ***muscle cells*** (primarily) take in *extra* glucose and store it in the form of _______________.

- The chemical structure of glycogen is very similar to that of *amylopectin*; the only exception is that *glycogen* branches more frequently. For a review of glycogen and amylopectin structures, see chapter 12, section 6.
- The conversion of *glucose* to glycogen is called __________________.
- *Glycogenesis* is an *anabolic pathway* in which glucose residues, with the help of enzymes, are connected to each other through glycosidic bonds to form *glycogen*.

In the "***fasting state***," which occurs several hours after a meal, blood glucose levels become low, and glycogen is converted back to glucose in a process called ____________________.

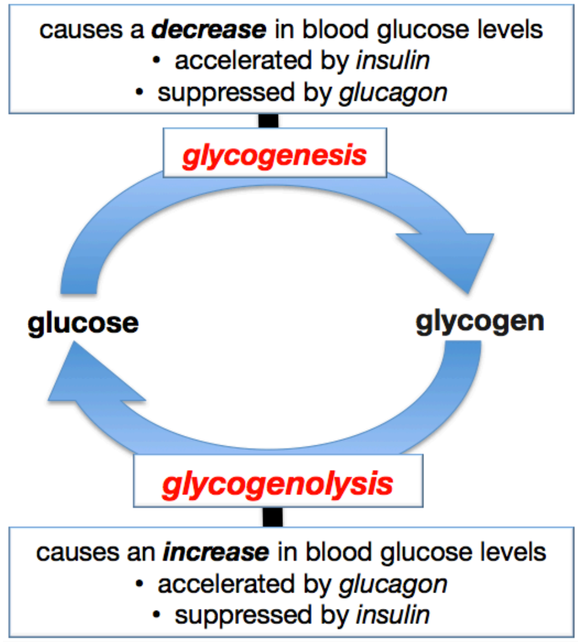
- ***Glycogenolysis*** occurs primarily in ***liver*** and ***muscle*** cells.
- It is the opposite of *glyco**genesis***. In *glyco**genolysis***, the glycosidic bonds between glucose residues are hydrolyzed.

Roles of Glycogenesis and Glycogenolysis in the Regulation of Blood Glucose Concentration

The body regulates blood glucose levels by releasing hormones that result in the production of compounds that ***inhibit and activate key enzymes in the glycogenesis and glycogenolysis pathways***.

In response to increased blood glucose concentration (in the fed state), the pancreas releases a protein hormone called ________________ into the blood stream.

- When insulin binds to liver and muscle cell receptors, it triggers a series of events that result in the ***activation*** of an enzyme in the *glyco**genesis*** pathway and the ***inhibition*** of an enzyme in the *glycogeno**lysis*** pathway.
  - *Accelerating glycogenesis* will result in **decreasing** the blood glucose concentration by increasing the rate of the conversion of glucose to glycogen.
  - *Suppressing glycogenolysis* helps in maintaining normal blood glucose concentration as the conversion of glycogen to glucose is inhibited.
- Another way that insulin is involved in lowering blood glucose concentration is by initiating a process that increases facilitated diffusion of glucose from the bloodstream into **all cell types**.



In response to decreased blood sugar levels (in the "fasting state"), the pancreas releases a protein hormone called ___________________ into the blood stream.

- Glucagon has the ______________ ***effect of insulin*** on liver cells; it *accelerates* glycogenolysis and *suppresses* glycogenesis.
  - *Accelerating glycogenolysis* will result in **increasing** the blood glucose concentration as glucose produced during glycogenolysis is transported from liver cells into the bloodstream.
  - *Suppressing glycogenesis* helps in maintaining normal blood glucose concentration by suppressing the conversion of glucose to glycogen.
- Glucagon also increases blood glucose concentration by accelerating ***gluconeogenesis*** (the production of glucose from non carbohydrate species).

Diabetes

Diabetes Mellitus (**DM**), commonly referred to as **diabetes**, is a disease caused by ***chronic*** ___________________________.

There are **three** types of **diabetes mellitus**: type I, type II, and gestational diabetes.

- In **diabetes type I**, also called ***insulin-dependent diabetes***, the pancreas produces too little __________. This can be a result of genetic disease, viral infection, or damage to the pancreas. Diabetes type I can be treated with insulin injections. Individuals must use a *glucometer* to frequently measure the concentration of glucose in their blood, and then inject insulin when elevated glucose levels are observed. Because diabetes type I often begins in childhood, it is sometimes referred to as ___________ ***diabetes***.

- ○ **Diabetes type II**, also called ***insulin-_______________ diabetes***, occurs when sufficient insulin is produced, however the insulin receptors are unable to respond appropriately. About 90% of diabetes cases are type II. This type of diabetes can be even more difficult to manage than type I diabetes because it does not respond to insulin injections. Diabetes type II occurs after childhood and is therefore sometimes referred to as ____________***-onset diabetes***.

- ○ **Gestational diabetes** occurs during ______________ in individuals without a previous diagnosis of diabetes. It is thought to be caused by pregnancy-related factors that affect insulin receptors. It is usually manageable with special diets and exercise; however, some individuals require antidiabetic drugs.

Triglyceride Metabolism

Dietary triglycerides, regardless of whether they came from plant or animal sources, are often referred to as ____________.

When triglycerides are catabolized, their chemical potential energy is converted to chemical potential energy in **ATP**.

- This process begins with the digestion of triglycerides.
- Triglycerides are also used in the formation of phospholipids and glycolipids, and as cellular signaling compounds.

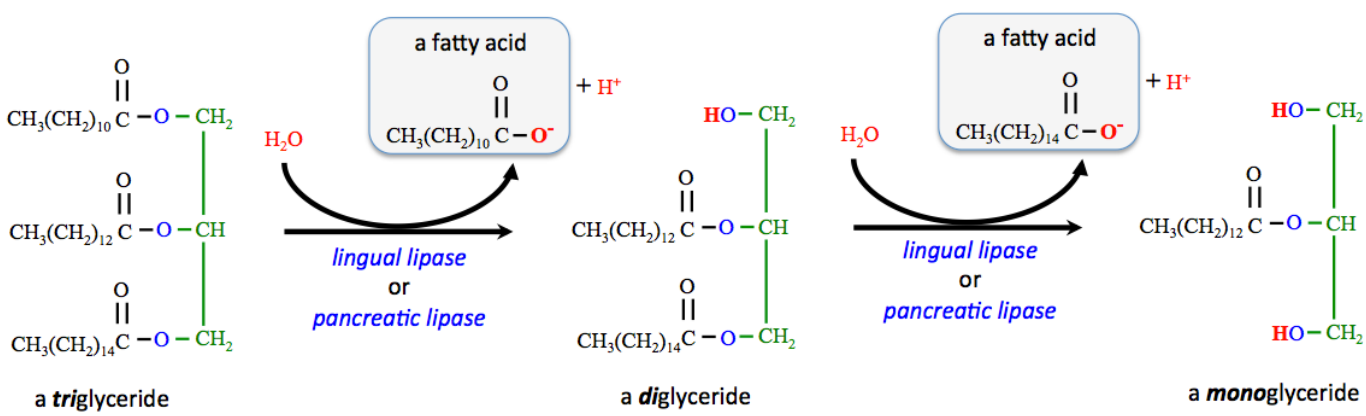
The body can store significant amounts of triglycerides, mostly in __________ **cells** (also called **fat cells**).

Digestion of Triglycerides

In order for triglycerides to pass through the intestine wall so that they can be used by the body, they must first undergo *partial* hydrolysis to produce ____________ __________ and ______________________.

Triglycerides are first hydrolyzed to ______________________, then to ________________________.

Each one of these reactions produces a ***fatty acid*** (as shown below).



This is referred to as " _______________ ***hydrolysis***" because one of the fatty acid residues *remains bound* to carbon number **2** of glycerol in the monoglyceride.

Triglyceride digestion begins in the ____________ where *lingual lipase* catalyzes the partial hydrolysis of a *very small percentage* of triglycerides.

The ***majority*** of dietary triglycerides are digested in the __________ _______________.

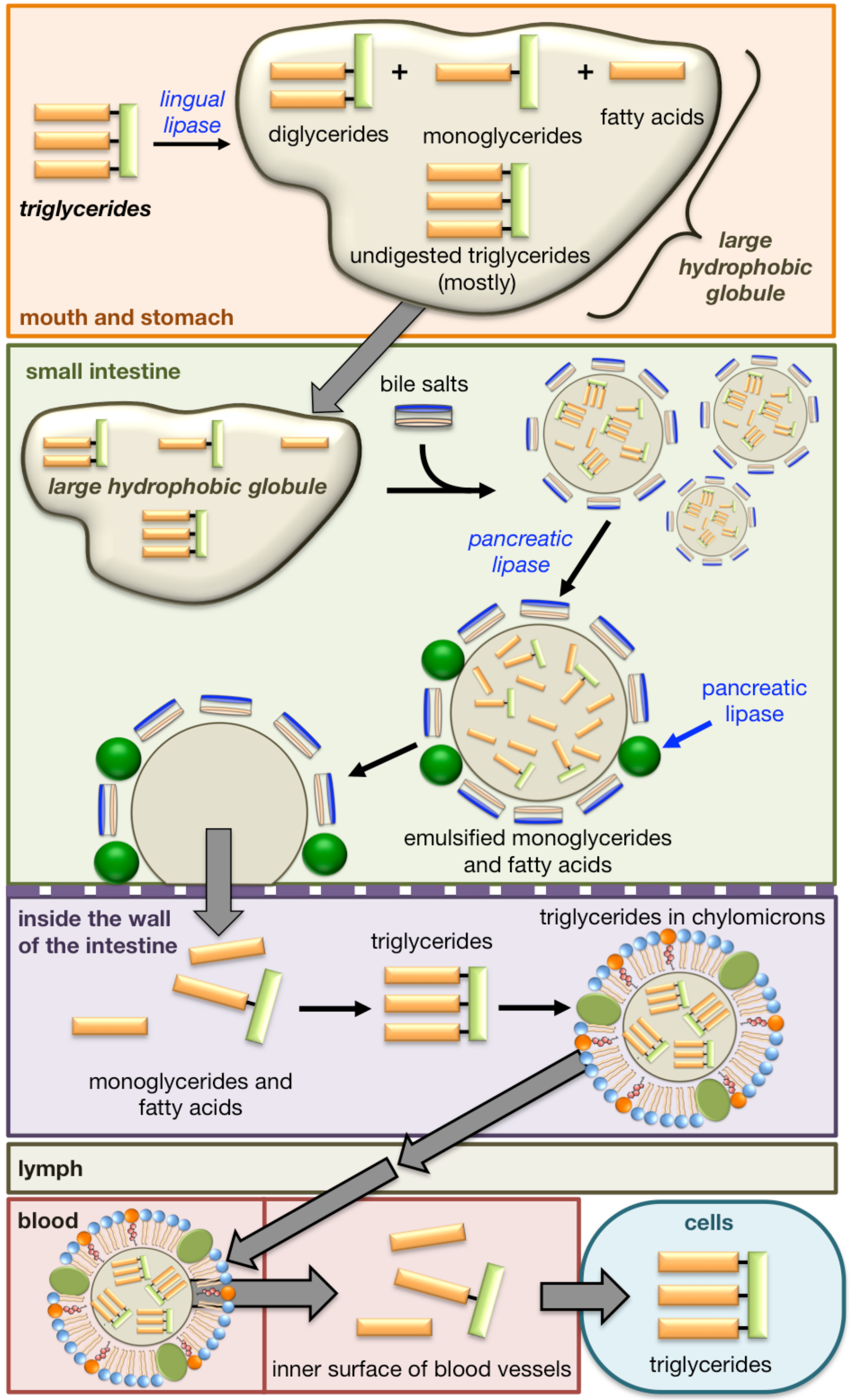
Large hydrophobic (insoluble) globules, that are composed mostly of triglycerides and a small amount of diglycerides, monoglycerides, and fatty acids, enter the ***small intestine***. In the small intestine, bile salts disassemble these large hydrophobic globules and emulsify them into small micelles.

When emulsified by bile salts, the ester bonds of the glycerides are oriented toward the surface of the micelle. This enables *pancreatic lipase* to catalyze the *partial* hydrolysis of emulsified triglycerides and diglycerides to produce ***fatty acids*** and ***monoglycerides***.

The fatty acids and monoglycerides that are formed inside the intestine can pass into the walls of the intestine. After being absorbed into the intestine walls, the fatty acids and monoglycerides are then re-assembled ***back into triglycerides***.

Since lymph, blood, and intercellular fluids are *aqueous mixtures,* and triglycerides are hydrophobic, the triglycerides must be ***emulsified*** in order to be transported throughout the body. This is done by ***chylomicrons***. Chylomicrons are small *lipoproteins* that are composed of a core that contains emulsified triglycerides (and some cholesterol and hydrophobic vitamins) surrounded by a lipid monolayer.

Triglycerides are emulsified in chylomicrons while in the wall of the intestine. The chylomicrons are then transferred into the lymph system, and then into the bloodstream. Triglycerides are released by the chylomicrons, and once again hydrolyzed to monoglycerides and fatty acids upon the inner surface of blood vessels. This occurs **primarily at blood vessels located in adipose (fat) tissue and muscles**. The monoglycerides and fatty acids can enter cells, where they are, once again, reassembled to triglycerides.



Adipose (fat) cells are the *major repository* for triglycerides; their primary function is to ______________ triglycerides.

Peripheral (other) cells/tissues can access this stored energy, as needed, when adipose cells ***completely*** *hydrolyze* the triglycerides to ***fatty acids*** and ***glycerol*** in a process called ________________.

The fatty acids are released from the adipose cells into the blood, and carried by *serum albumin protein* to other cells.

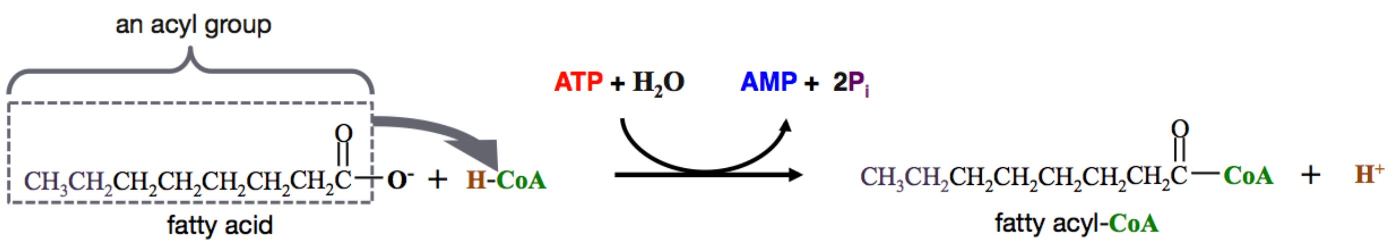
These **fatty acids** can then be _________________ to produce **ATP**.

Catabolism of Fatty Acids

Fatty acids are catabolized in order to convert their potential energy into potential energy in **NADH**, **$FADH_2$**, and acetyl-CoA.

The first reaction in the catabolism of fatty acids is called _________________.

- In this reaction, the _________ *group* of a fatty acid is transferred to *coenzyme* A.



The fatty acid is converted to a _________ ____________________.

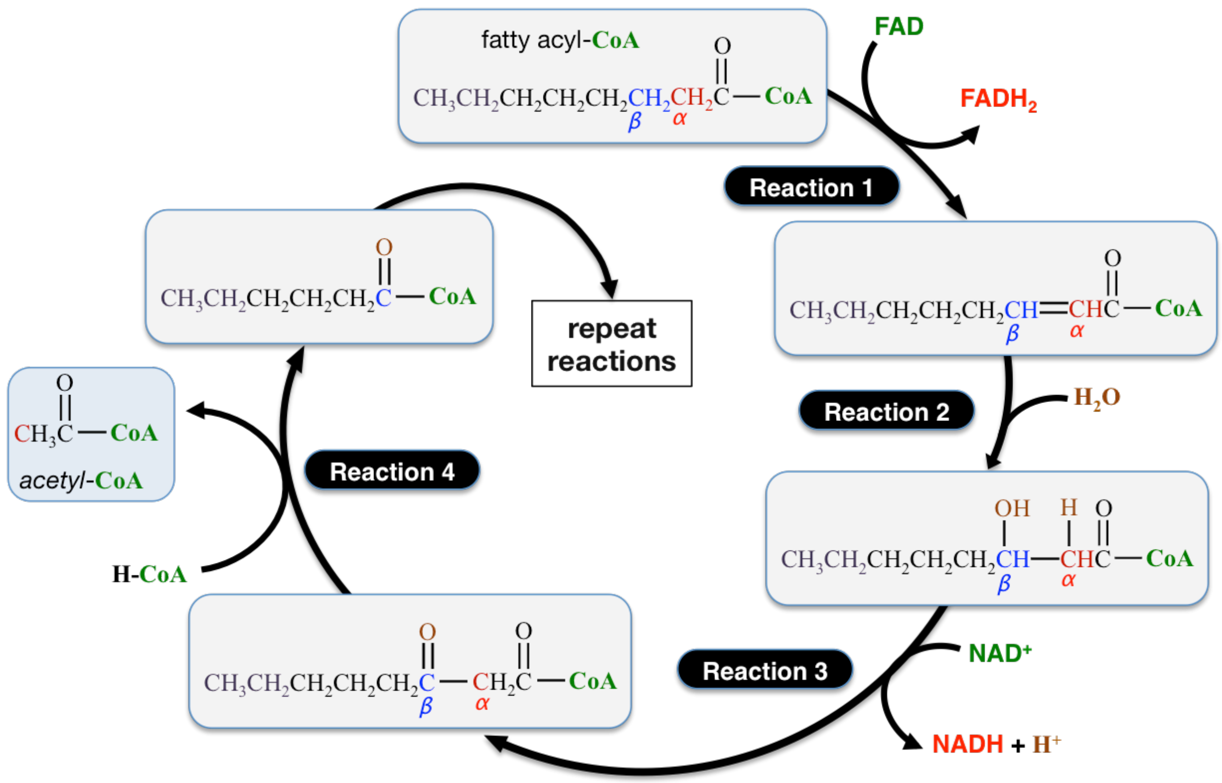
This reaction does not occur spontaneously without the external energy input provided from the hydrolysis of two inorganic phosphates from **ATP**.

- In this case, **ATP** is converted to **AMP** and two inorganic phosphate (**P_i**) ions.

The *activation* reaction is necessary in order for the acyl group from fatty acids to pass through the inner mitochondrial membrane and enter the matrix, where the subsequent reactions of fatty acid catabolism occur.

When fatty acyl-CoA enters the *mitochondrial matrix*, it undergoes a catabolic pathway called _______ - ________________ (***β*-oxidation**).

In ***β*-oxidation**, a fatty acyl-CoA, goes through a ***repeated*** series of *four* reactions, ***each time*** losing two of its _____________.



The carbon that is *next to* a fatty acyl's carbonyl group is designated as the "**α**-carbon," and the carbon that is two carbons away from the carbonyl group is designated as the "***β***-carbon."

In **reaction 1** of ***β***-oxidation, the **α**- and ***β***-carbons are ____________ (they lose hydrogens and electrons).

- The hydrogens and electrons are transferred to **FAD** to produce **$FADH_2$**.

In **reaction 2** the double bond between the **α**- and ***β***-carbons is *hydrated*.

In reaction 3, the ***β***-carbon is oxidized.

- In this oxidation, a hydrogen and electron are transferred to **NAD^+**, reducing it to **NADH**.

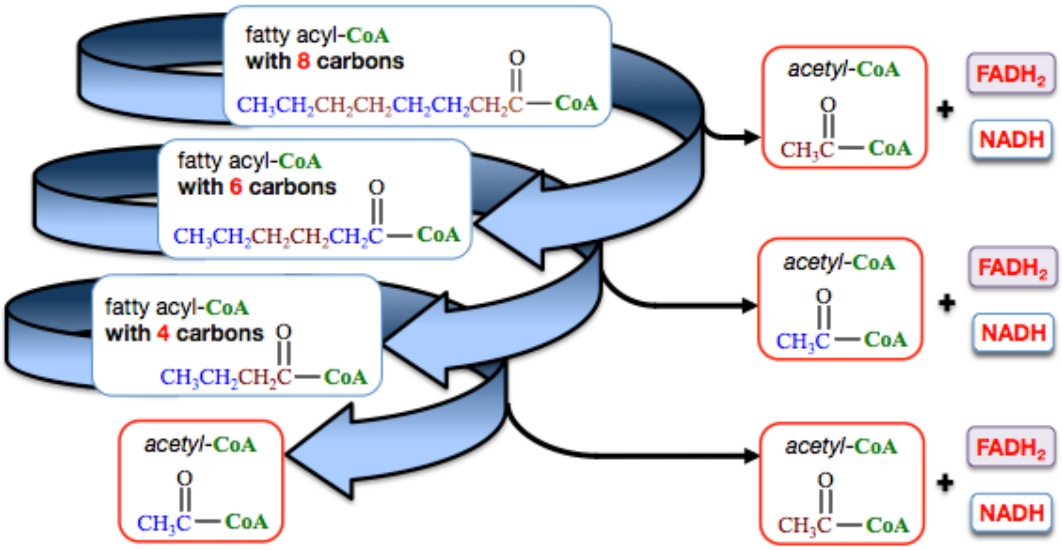
In **reaction 4**, the bond between the **α**- and ***β***-carbon is broken.

- A hydrogen forms a bond to what was formerly the **α**-carbon, **thereby** producing acetyl-CoA.
- The *acyl group*, containing what was formerly the ***β***-carbon, is transferred to coenzyme A, thereby forming a ___________ fatty acyl-CoA.

The *new* fatty acyl-CoA is _________ ***carbons shorter*** than the original one.

The *new* fatty acyl-CoA can undergo the ***β***-oxidation reactions.

For example, a*n eight-carbon* fatty acyl-CoA will undergo ***three*** cycles of the ***β-oxidation*** reactions.



When the *original* fatty acyl-CoA undergoes the ***β***-oxidation reactions series, one acetyl-CoA, one **NADH**, and one **FADH₂** are produced.

A ***new*** fatty acyl-CoA is also produced.

Each successive (new) fatty acyl-CoA undergoes the series of four reactions to produce more acetyl-CoA, **NADH**, and **FADH₂**.

The acyl group's length is decreased by ***two carbons*** with each successive ***β***-oxidation reaction series.

When the fatty acyl-CoA contains ________ carbons, then it will undergo the reaction series ***one final time***.

- In the final cycle, **reaction 4** produces two ***acetyl***-CoA.

If "**N**" equals the number of carbons that are contained in a fatty acyl-CoA, then it will undergo **[(N/2)-1]** ***β****-oxidation* cycles.

β- oxidation is classified a **"____________" metabolic pathway**.

- A **spiral pathway** is a metabolic pathway in which a ***series of repeated reactions*** is used to break down (or build up) a compound.

> **Understanding Check:** How many cycles of the ***β-oxidation*** spiral will occur for a **twelve-carbon** fatty acyl-CoA?

> **Understanding Check:** For the **twelve-carbon** fatty acyl-CoA in the previous problem:
> - How many acetyl-CoA are produced after all of the ***β-oxidation*** cycles?
> - How many NADH are produced after all of the ***β-oxidation*** cycles?
> - How many $FADH_2$ are produced after all of the ***β-oxidation*** cycles?

ATP Production from Fatty Acids

As was the case for carbohydrate catabolism, the catabolism of triglycerides converts potential energy in food into the form of chemical potential energy that is most useful in cells - **ATP**.

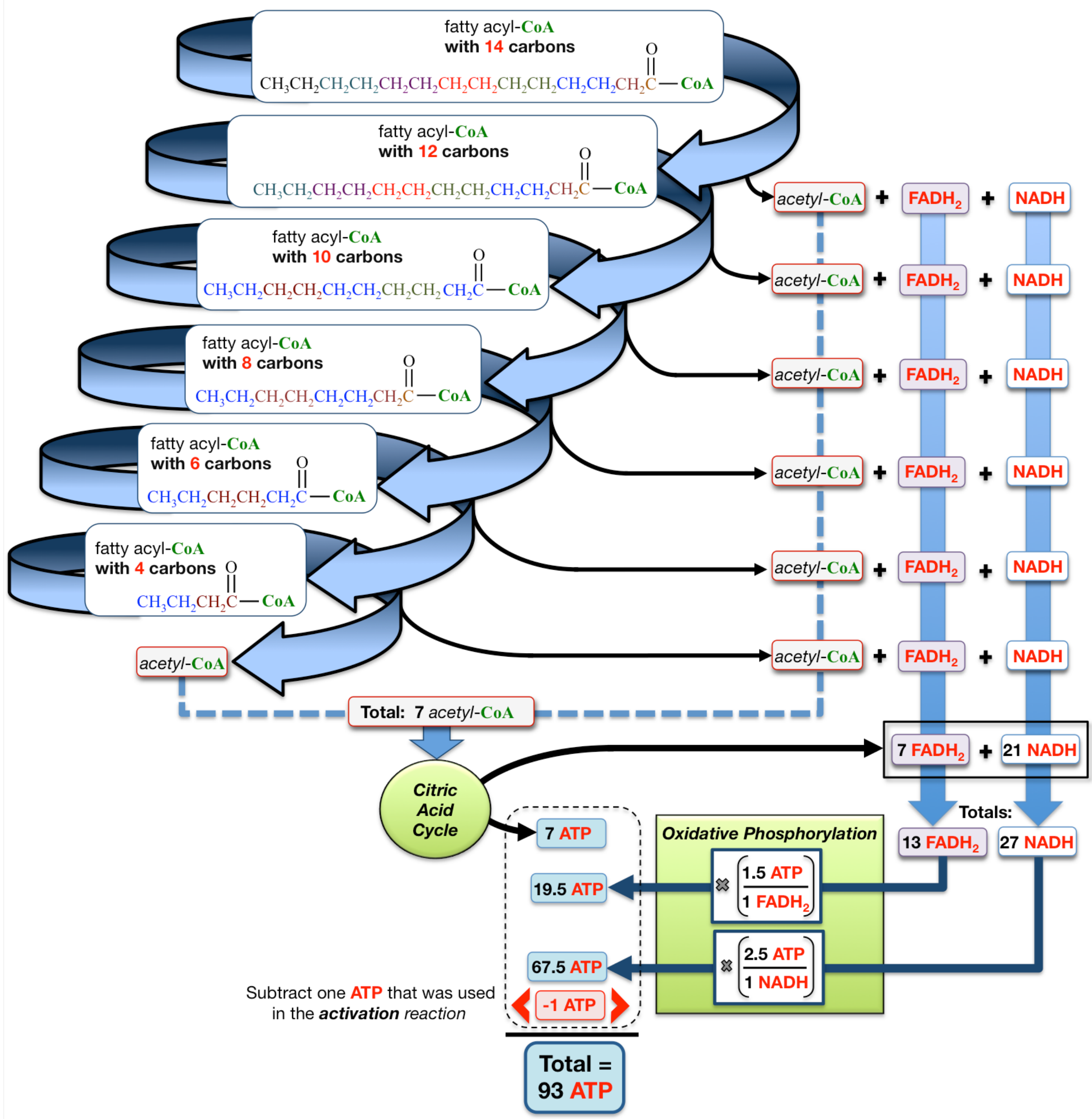
Because ***β***-oxidation occurs in the mitochondrial matrix, each acetyl-CoA that is produced can undergo the reactions of the citric acid cycle to produce an **ATP**, three **NADH**, and one **FADH₂**.

More **ATP** is produced when the **NADH** and **$FADH_2$** formed in the ***β***-oxidation cycles, along with the **NADH** and **$FADH_2$** formed in the citric acid cycle, undergo oxidative phosphorylation.

Let's consider how many **ATP** are produced from the catabolism of a typical fatty acid, *myristate*, which contains **14** carbon atoms (assume that *oxidative phosphorylation* produces, *on average*, 2.5 **ATP** per **NADH** and 1.5 **ATP** per **$FADH_2$**).

First, *myristate* is activated to produce a 14-carbon fatty acyl-CoA. The activation ***consumes*** one **ATP**.

The net gain of **ATP** from can be calculated as shown in the illustration below.



Each of the first *five* cycles of the ***β***-oxidation spiral produces one acetyl-CoA, one **NADH**, and one **$FADH_2$**. The *final cycle* of the spiral produces ***two*** acetyl-CoA, one **NADH**, and one **$FADH_2$**. The acetyl-CoA are processed through the citric acid cycle, producing **ATP** and *more* reduced coenzymes. The **NADH** and **$FADH_2$** formed in ***β***-oxidation and the **NADH**, and **$FADH_2$** formed in the citric acid cycle undergo oxidative phosphorylation. Since one **ATP** was consumed in the activation reaction, it is subtracted when calculating the *net gain* of **ATP**. ***β***-oxidation of myristate, *on average*, results in a net gain of **93 ATP**.

Understanding Check: What is the net gain in ATP for **β-*oxidation*** of a twelve-carbon fatty acid? Assume that *oxidative phosphorylation* produces, ***on average***, 2.5 ATP per NADH and 1.5 ATP per $FADH_2$.

Remember to subtract one ATP to account for the ATP that was consumed in the activation step.

Catabolism of Unsaturated Fatty Acids

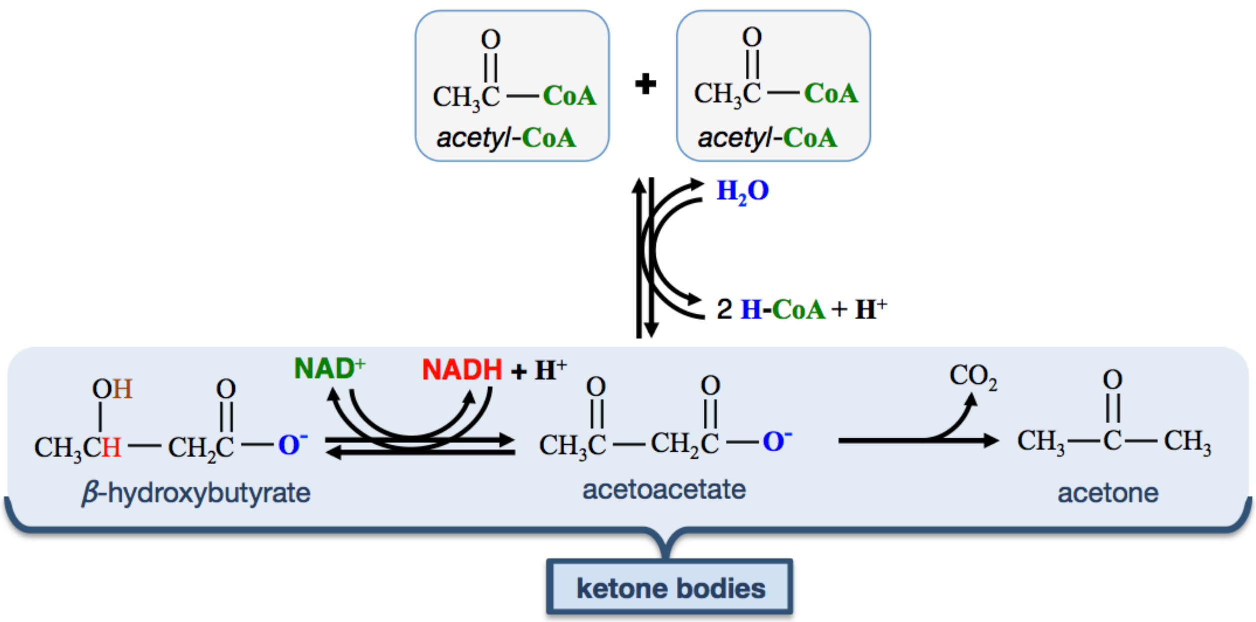
Unsaturated fatty acids (derived from unsaturated fat) have ***double bonds*** in their hydrocarbon tails. Depending on the location of these double bonds, extra steps may be required to transform the double bonds in order to produce fatty acyl-CoA that can undergo ***β***-oxidation.

Ketone Bodies

Catabolism of large quantities of triglycerides will result in high concentrations of acetyl-CoA.

Acetyl-CoA that is produced in excess of the amount that can be metabolized in the citric acid cycle results in a high concentration of acetyl-CoA in the mitochondrial matrix.

When this occurs, acetyl-CoA reacts with *other* acetyl-CoA to produce the three compounds that are referred to as _____________ ____________.



This process is referred to as ________________.

Ketone bodies are water-soluble, therefore easily dispersed from the liver to other parts of the body. Most cells, with liver cells being the notable exception, are capable of converting ketone bodies back into acetyl-CoA, and then metabolizing it in the citric acid cycle. Converting ketone bodies back to acetyl-CoA is the *reverse of ketogenesis* (different enzymes are involved). Some cell types rely on ketone bodies for **ATP** production more than others. Heart muscles and the renal cortex use ketone bodies more readily than glucose. The brain's primary energy source is glucose, but it is unable to store glucose and does not allow fatty acid salts (or amino acids) to enter. In the case of starvation, when there is very little glucose present, the brain gets 75% of its energy from ketone bodies.

When individuals diet, they begin to metabolize the triglycerides that are stored in fat cells. This leads to ***ketogenesis***.

In cases of starvation, poorly treated diabetes, and conditions related to alcoholic binge drinking, the cells cannot get glucose and extremely high rates of fatty acid salt catabolism results in dangerous, and even fatal levels of ketone bodies.

- ***β***-*hydroxybutyric acid* and *acetoacetic acid* (the acid forms of ***β***-*hydroxybutyrate* and acetoacetate, respectively) have significant acid strength.
- Their production results in a higher concentration of H_3O^+, which can overcome the blood's buffering capacity.
- When this occurs, the blood becomes acidic.

When blood pH is less than the normal range (7.35-7.45), the condition is called ______________.

- *Acidosis* can result in tissue dysfunctions and is especially damaging to the central nervous system.
- When *acidosis* is caused by excess *ketone bodies*, the condition is called _________________.

Fatty Acid Anabolism

Fatty acids are **produced** by a *spiral metabolic pathway* that operates in the **opposite** direction as ***β***-oxidation; it builds-up fatty acyl-CoA by a repeating series of reactions that **add** acetyl-CoA to a growing fatty acyl-CoA structure.

This ***anabolic*** process of synthesizing fatty acids from acetyl-CoA is called **fatty acid** _______________.

Fatty acid synthesis occurs primarily in adipose and liver cells.

The body can synthesize almost all of the fatty acids it needs ***except for linoleic and linolenic acid***.

- Linoleic and linolenic acid can ***only*** be obtained through dietary triglycerides, and are therefore classified as **essential fatty acids**.

Protein Metabolism

When ***dietary proteins*** are digested, they are converted to ***amino acids***. The *amino acids* are then used in various metabolic pathways.

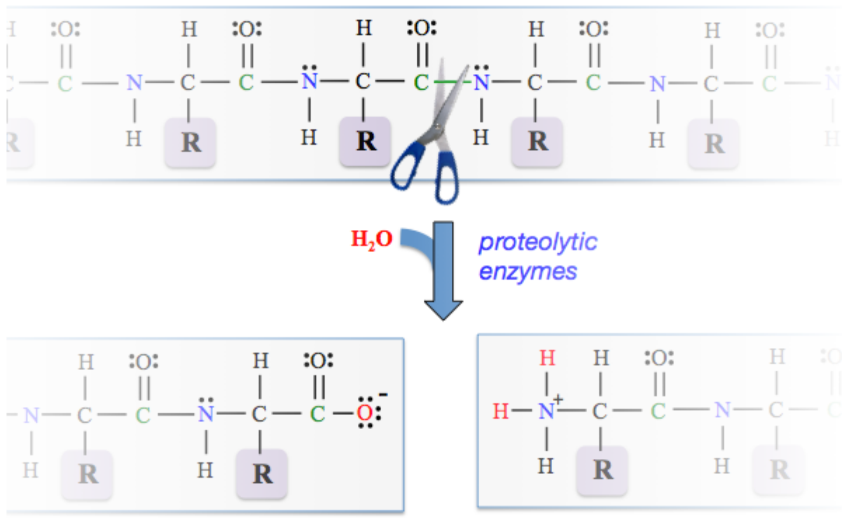
- In an *anabolic* process, they are used to build proteins and peptides according to the body's needs. You learned about this process in chapter 14 when I discussed how proteins are synthesized in the ***translation*** process.
- *Amino acids* are also used as nitrogen sources for the biosynthesis of other amino acids and other nitrogen-containing compounds, such as nucleotide bases.

Amino acids that are ingested in excess of what is needed for these biosynthesis needs are catabolized to produce **ATP**.

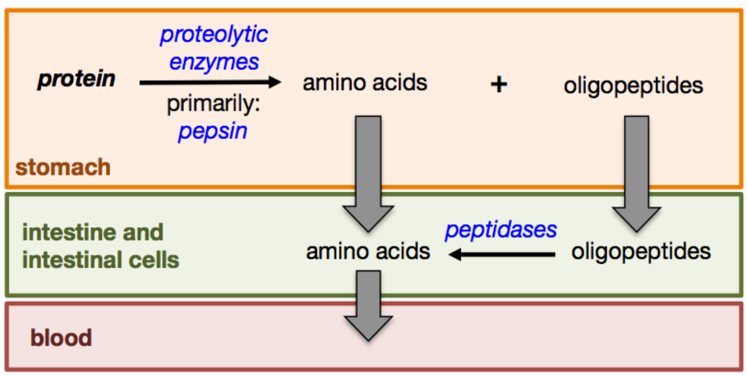
Digestion of Proteins

In the digestion process, dietary proteins are converted to ***amino acids*** by the *hydrolysis* of their _______________ ________________.

When a peptide bond is hydrolyzed, the peptide bond is broken and an oxygen is added to the carbonyl carbon and two hydrogens to the nitrogen.



Protein digestion begins in the ___________ and continues in the ***small intestine***.

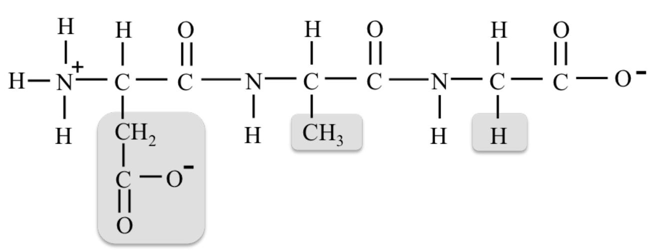


In the stomach, an acidic environment and proteolytic enzymes (primarily *pepsin*) catalyze the hydrolysis of proteins to *amino acids* and *oligopeptides*.

As these species move though the small intestine and enter the intestinal cells, the oligopeptides are further hydrolyzed to amino acids. This is done with the help of dietary enzymes called *peptidases*.

The amino acids are released from the intestinal cells into the blood stream, and then transported to other cells.

Understanding Check: Draw the structural formulas of the three amino acids that are produced when all of the peptide bonds in the tripeptide shown below are hydrolyzed.



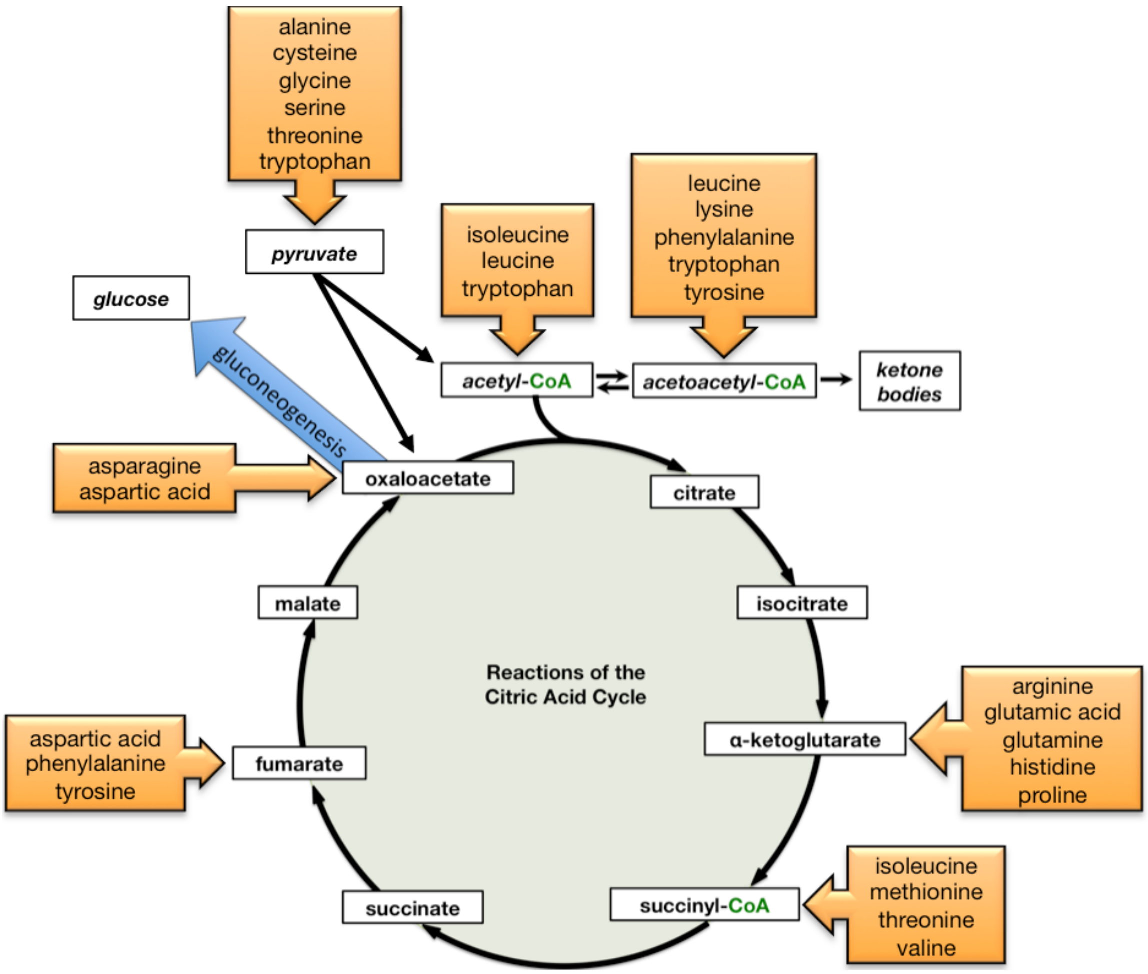
Catabolism of Amino Acids

Some of the amino acids produced in digestion are used for the synthesis of **proteins**, the synthesis of *other* **amino acids**, and the synthesis of *other* **nitrogen-containing compounds**.

Amino acids that are ingested in surplus of these biosynthesis needs are _______________ as fuel for the production of **ATP**.

This is done by transforming them into intermediate metabolites that can be converted to ____________, __________ ___________, ***or*** undergo the _________ _________ __________.

The entry points of amino acids into the various metabolic pathways are indicated in the figure below.



I do not expect students to memorize this table; however, there are a couple of important concepts that I want you to know:

1) Amino acids can be converted to pyruvate, acetyl-CoA, acetoacetyl-CoA, or some citric acid cycle intermediates. These compounds are then converted to glucose, ketone bodies, *or* undergo the citric acid cycle.
2) All ***twenty common amino acids*** can be converted into either pyruvate, acetyl-CoA, acetoacetyl-CoA, or a citric acid cycle intermediate.
   - The details of ***how*** the twenty common amino acids are converted into the metabolic intermediates are far beyond the scope of this course.
   - What is important to understand is that these conversions involve one or both of two important amino acid reactions: ____________________ and ______________ ____________________.

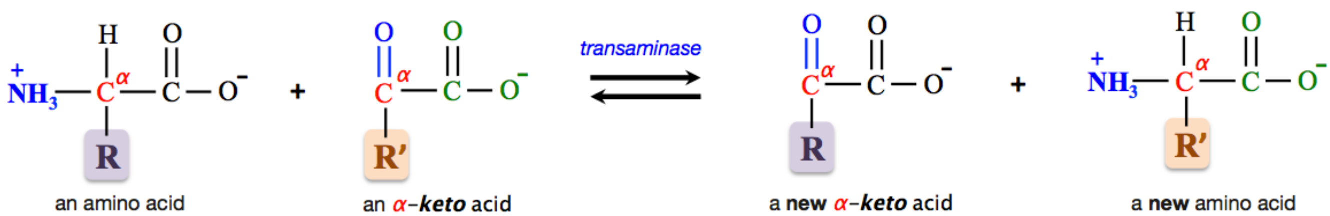
Transamination

Transamination involves the _______________ of a quaternary ammonium group (NH_3^+).

The NH_3^+ that is bound to the **α**-carbon of an amino acid is transferred to an ***α-keto* acid**.

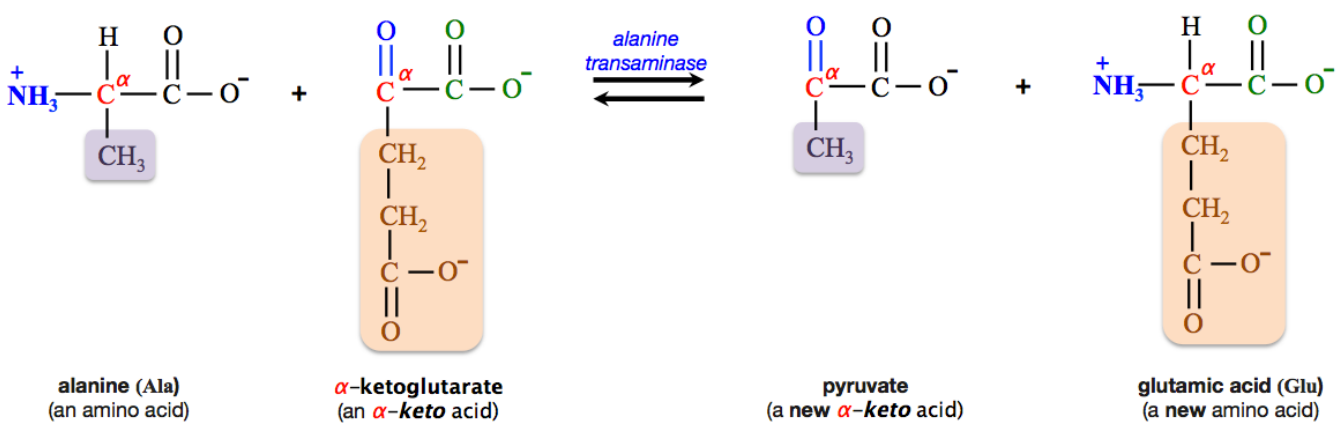
- An ***α***-keto acid is a *carboxylic acid* that has a ***carbonyl group*** (**C** = **O**) at the ***α***-carbon.

In a *transamination reaction*, an amino acid and an ***α***-keto acid are converted to a ***new*** amino acid and a ***new α***-keto acid. The general form of the transamination reaction is shown below.



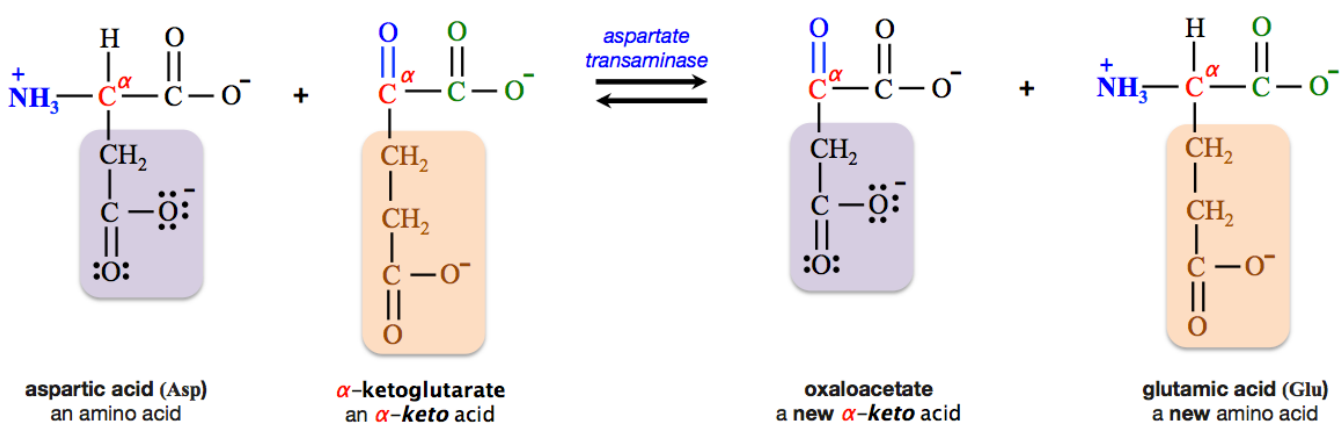
In *transamination reactions*, the NH_3^+ from an amino acid is ***usually*** transferred to ***α*-ketoglutarate** (an ***α***-keto acid).

Example:



In this reaction, alanine is converted to pyruvate.

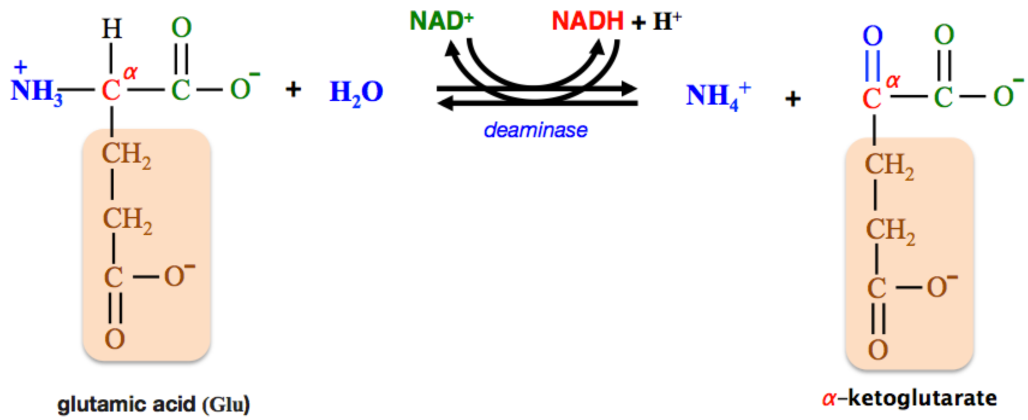
Another example of a *transamination reaction* is the conversion of aspartic acid to oxaloacetate, as shown below.



In transamination reactions, ***α***-ketoglutarate is converted to *glutamic acid*. We will now take a look at how *glutamic acid* is recycled back to ***α***-ketoglutarate in the ***oxidative deamination*** reaction.

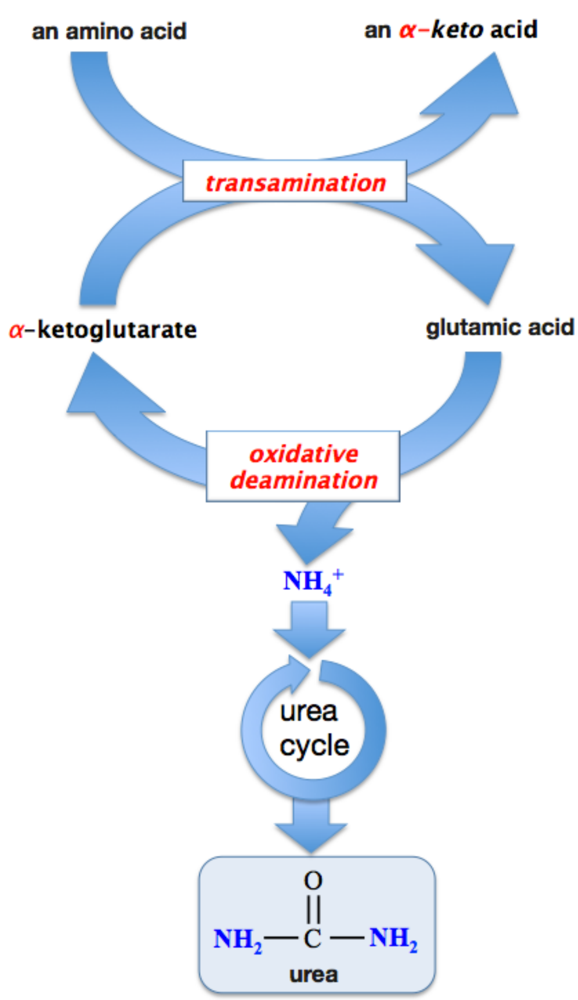
Oxidative Deamination

In *oxidative deamination*, a *quaternary ammonium group* (-NH_3^+) is ____________ from *glutamic acid*, thereby producing an ammonium ion (NH_4^+) and ***α***-ketoglutarate.



In addition to the removal of a *quaternary ammonium group*, *glutamic acid*'s ***α***-carbon is oxidized (gains an oxygen *and* loses a hydrogen). This oxidation is accompanied by the reduction of **NAD+**.

The ***α***-ketoglutarate that is produced in the reaction is now free to accept a _________ *quaternary ammonium group* from another amino acid in a *transamination reaction,* as illustrated below.



The free ammonium ions (NH_4^+) that are produced in oxidative deamination are ***toxic*** at elevated concentrations.

Humans and most other terrestrial vertebrates are capable of converting the ammonium ions to_________.

- This occurs in a series of reactions called the **urea cycle**.

Urea is filtered, by the ___________, into the urinary track and then removed from the body during urination.

Kidney disease can result in the build up of dangerous amounts of urea.

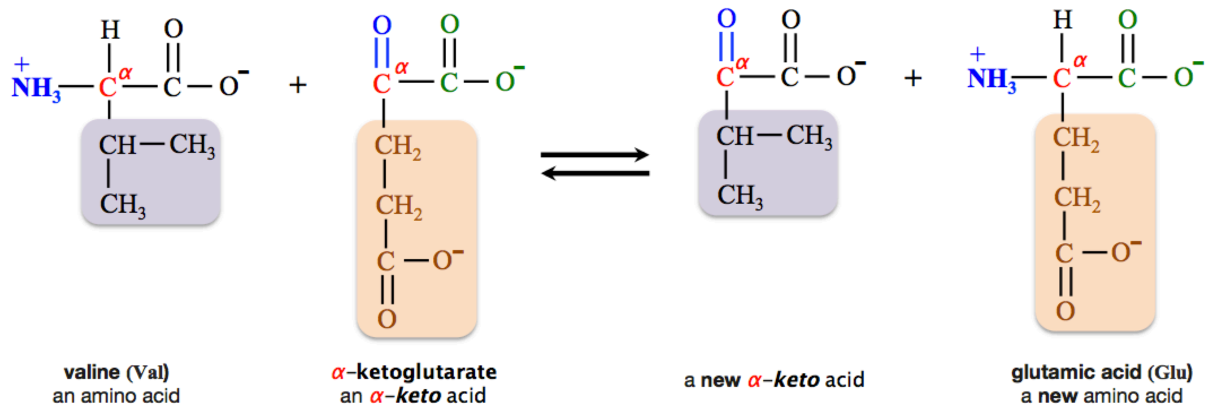
In cases of ***end-stage renal (kidney) failure***, safe blood urea levels are exceeded, and patients must undergo _______________ **treatments**.

Dialysis involves artificial methods of urea removal.

The most common of these is called **hemodialysis**. Hemodialysis takes several hours and is usually done multiple times per week. This process is not only time-consuming, but far from ideal because of many complications and side effects. Bedside nocturnal dialyzers are now available.

In otherwise healthy patients with kidney failure, kidney transplants are possible. Kidney donations are fairly common since most humans have two kidneys, and one kidney is usually sufficient to eliminate urea.

Understanding Check: Identify the following reaction as either a **transamination** ***or*** an **oxidative deamination** reaction.



Summary of Metabolism

The body is able to build proteins, carbohydrates, and triglycerides from smaller organic compounds in anabolic processes.

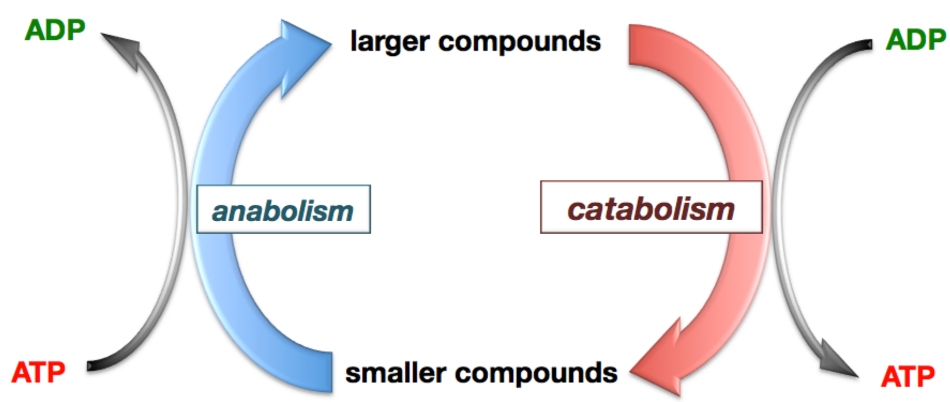
- Anabolic processes generally require the input of external energy.
- This energy often comes from chemical potential energy in **ATP**.

The body is able to break down proteins, carbohydrates, and triglycerides into smaller organic compounds in catabolic processes.

- Catabolic processes typically release energy.
- This energy is often used by the body to produce **ATP**.

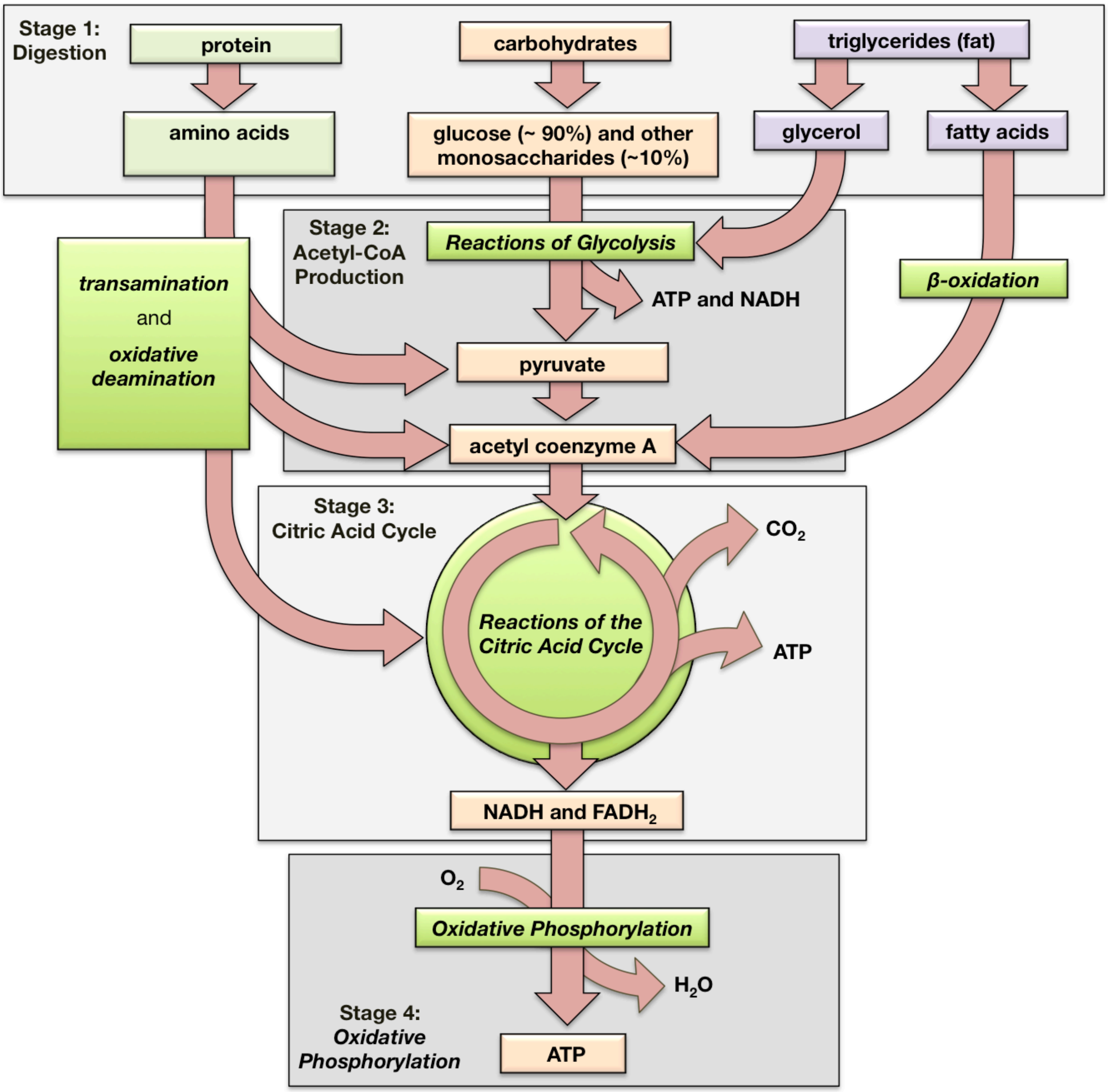
The metabolic strategy behind the production of **ATP** is that **ATP** is an energy source that can be instantaneously used by organisms to do cellular work and to provide the energy required for life-sustaining reactions that would otherwise not occur spontaneously.

The metabolic strategies of catabolism and anabolism are summarized in the illustration below.



Catabolism

The catabolism of food is summarized in the image below:



In the four stages of food catabolism, chemical potential energy in food is converted to chemical potential energy in ATP, NADH, and $FADH_2$.

- The NADH and $FADH_2$ can then be converted to electrochemical energy in the form of a hydrogen ion gradient.
- The electrochemical potential in this gradient is used to drive the production of ATP.

The ***catabolic processes*** discussed in this chapter are digestion, glycolysis, pyruvate oxidation/decarboxylation, the citric acid cycle, glycogenolysis, lipolysis, β-oxidation, and oxidative deamination.

These *catabolic processes* are listed and briefly described in the table below.

The Catabolic Processes in Chapter 15

Name	Description	Notes
digestion	***Carbohydrates*** are *hydrolyzed* to ***monosaccharides***. ***Triglycerides*** are "***partially***" *hydrolyzed* to ***fatty acid salts*** and ***monoglyceride***. ***Proteins*** are *hydrolyzed* to ***amino acids***.	
glycolysis	A ***linear metabolic pathway*** in which *glucose* is converted into **two** *pyruvate ions.*	**High** concentrations of **ATP**, *pyruvate*, or *other pathway products* suppress this process.
pyruvate oxidation/ decarboxylation	*Pyruvate* is oxidized and decarboxylated to produce *acetyl*-**CoA**.	
citric acid cycle	A ***circular metabolic pathway*** in which *acetyl*-**CoA** is metabolized to produce **ATP**, **NADH**, and **$FADH_2$**.	
glycogenolysis	*Glycogen* is converted to *glucose.* Glycogenolysis occurs primarily in ***liver*** and ***muscle*** cells. Liver cells will release the glucose into the bloodstream so that it can be taken in by other types of cells.	***Low blood glucose*** and ***glucagon*** accelerate this process. ***High blood glucose*** and ***insulin*** suppress this process.
β-oxidation	A ***spiral metabolic pathway*** in which *fatty acids are converted to acetyl*-**CoA, NADH** and **$FADH_2$**.	
lipolysis	*Triglycerides* that are stored primarily in adipose (fat) cells and muscle cells are broken down into *fatty acids* and *glycerol*. Liver cells can release the fatty acids and glycerol into the bloodstream so that they can be taken in by other types of cells.	
oxidative deamination	A *quaternary ammonium group* (-NH_3^+) is removed from *glutamic acid*, thereby producing ammonium (NH_4^+) and ***α***-ketoglutarate.	

Anabolism

The ***anabolic processes*** discussed in this chapter are gluconeogenesis, glycogenesis, fatty acid synthesis, and protein synthesis.

These *anabolic processes* are listed and briefly described in the table below.

The Anabolic Processes in Chapter 15

Name	Description	Notes
gluconeogenesis	The conversion of ***non-carbohydrate species into glucose***. This process is *similar* to the reverse of glycolysis. Gluconeogenesis occurs primarily in the liver. It increases blood glucose levels because liver cells can release the glucose that is produced into the bloodstream.	***Low blood glucose*** and ***glucagon*** accelerate this process.
glycogenesis	*Glucose* is converted to *glycogen.* Glycogenesis occurs primarily in ***liver*** and ***muscle*** cells. Glycogenesis lowers blood glucose levels because glucose is taken up by liver and muscle cells and then converted to glycogen.	***High blood glucose*** and ***insulin*** accelerate this process. ***Low blood glucose*** and ***glucagon*** suppress this process.
fatty acid synthesis	Fatty acids are produced by a spiral pathway that works in the opposite direction of ***β***-oxidation; it builds up fatty acyl-CoA by a repeating series of reactions that add acetyl-CoA to a growing fatty acyl-CoA structure. Fatty acid synthesis occurs primarily in adipose and liver cells.	
protein synthesis	*Amino acids* are converted to *proteins.*	This process was mentioned briefly in this chapter; however, it was ***thoroughly discussed chapter 14***.